STEM CELLS AND DEVELOPMENT
Volume 25, Number 20, 2016
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DOI: 10.1089/scd.2016.0177

Not All Pericytes Are Born Equal: Pericytes from Human Adult Tissues Present Different Differentiation Properties

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Pericytes (PCs) have been recognized for a long time only as structural cells of the blood vessels. The identification of tight contacts with endothelial cells and the ability to interact with surrounding cells through paracrine signaling revealed additional functions of PCs in maintaining the homeostasis of the perivascular environment. PCs got the front page, in the late 1990s, after the identification and characterization of a new embryonic cell population, the mesoangioblasts, from which PCs present in the adult organism are thought to derive. From these studies, it was clear that PCs were also endowed with multipotent mesodermal abilities. Furthermore, their ability to cross the vascular wall and to reconstitute skeletal muscle tissue after systemic injection opened the way to a number of studies aimed to develop therapeutic protocols for a cell therapy of muscular dystrophy. This has resulted in a major effort to characterize pericytic cell populations from skeletal muscle and other adult tissues. Additional studies also addressed their relationship with other cells of the perivascular compartment and with mesenchymal stem cells. These data have provided initial evidence that PCs from different adult tissues might be endowed with distinctive differentiation abilities. This would suggest that the multipotent mesenchymal ability of PCs might be restrained within different tissues, likely depending on the specific cell renewal and repair requirements of each tissue. This review presents current knowledge on human PCs and highlights recent data on the differentiation properties of PCs isolated from different adult tissues.

A Historical Introduction

Pericytes (PCs) were initially described by the French scientist Charles-Marie Benjamin Rouget as a population of perivascular contractile cells surrounding the endothelial cells (ECs) of small blood vessels. They were named Rouget cells after their discoverer, but later the term ''pericytes,'' which refers to their location around small vessels, was introduced [1,2].

PCs, surrounded by the basal membrane, establish intimate contacts, called peg-and-sockets, with ECs. These contacts are composed of cytoplasmic elongations of PCs (pegs), invaginated into the ECs membrane (sockets) [3–5]. Interactions between PCs and ECs take place through tight and gap junctions rich in connexin 43 that are present at the contact sites [6–8] and are stabilized by adhesion plaques between these cells and fibronectin in the extracellular matrix [8–10]. These multiple interactions have the role of reinforcing the communication between PCs and ECs and contribute to the correct distribution of the mechanical contractile force generated by vascular smooth muscle cells (VSMCs) [11–14].

In the past years, different names, such as mural cells, PCs, and VSMCs, have been used interchangeably to refer to all the perivascular cells that support microvasculature and establish intimate cell-to-cell contacts [15]. However, more recently, differences between PCs and VSMCs have been recognized, indicating that despite sharing common markers, they represent two distinct cell populations that can be distinguished depending on their specific localization and functional role [2,11,15,16]. Indeed, PCs are predominantly localized around small vessels, whereas VSMCs are mainly positioned around larger vessels. In the latter anatomical location, VSMCs are wrapped in multiple layers perpendicularly distributed along the axis of vessels, thus providing structural support in regulating blood flow and in controlling, especially in arterioles, the diameter of the vessels. In contrast, PCs are longitudinally oriented with respect to the axis of vessels and are generally organized in a single cell layer [11,16,17].

Another distinctive feature of PCs and VSMCs is their relative abundance around the vasculature. In fact, the number of VSMCs and PCs may vary depending on of the caliber of the vessel and among different tissues. For instance, in retinal capillaries, VSMCs and PCs are present in a 1:1 ratio, whereas in other tissues VSMCs are usually more represented than PCs [18,19]. Moreover, VSMCs, at variance with PCs, do not establish direct contacts with ECs, as they are separated

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from the endothelium by the basal membrane or, in case of larger arteries, by the intima layer [11].

Based on this evidence, PCs, although considered for many years the microvascular counterpart of VSMCs, are now recognized as a well-defined perivascular cell population that plays a role in regulating homeostatic processes between the ECs and surrounding tissue [20–22]. This function is of increased significance in tissues, like the central nervous system, where PCs contribute to form a functional barrier with the blood stream [23].

A novel interest in PCs was stimulated by studies that revealed that PCs are capable of differentiating into several mesodermal cell lineages, thus revealing additional and unexpected properties of these cells that have opened a new area of research oriented toward a possible use of PCs in the regenerative medicine field [21,24–26]. These properties of PCs should not surprise, as we are aware now of the contribution provided by a number of stem/progenitor cells, including multipotent or more lineage-restricted cells, associated with blood vessels in maintaining the homeostasis of tissues [27]. Furthermore, the cellular dynamics of blood vessels have attracted increasing interest over the past years since, in addition to their physiological role, they are also involved in pathological conditions such as atherosclerosis and cancer [19,28,29].

Recognition of the ability of PCs to differentiate into different mesodermal lineages has also opened new questions about their relationships with others stem/progenitor cells associated with the vascular compartment and more, in general, with mesenchymal stem cells (MSCs) derived from connective tissue [30].

PCs: From the Developing Embryo to the Perivascular Compartment of Adult Tissues

Studies based on chimeras and cell-fate mapping indicated that VSMCs arise from distinct embryonic compartments. In fact, lineage-tracing experiments of VSMC progenitors in the embryo and in the adult organism revealed that VSMCs might derive from neural crest, proepicardium, mesothelium, the secondary heart field, and somitic and splanchnic mesoderm [17,31,32]. In a similar manner, PCs found in the head and thymus are apparently also derived from the cranial neural crest, whereas PCs residing in other anatomical regions of the adult body are likely derived from the mesoderm [2,16,31].

In 1999, Cossu and collaborators reported the characterization of a novel cell population following in vitro culture of E9.5 mouse dorsal aorta explants. These cells coexpressed early endothelial and myogenic markers. After the initial association of mesoangioblasts with the embryonic dorsal aorta, additional experiments based on lineage tracing indicated that these cells can originate from the hemogenic endothelium [33]. In addition, these cells were capable of giving rise to multiple differentiated cells of mesodermal derivatives, after both in vivo transplantation and in vitro culture [24]. Due to their capacity to originate both vascular and extravascular mesodermal derivatives, this cell population of embryonic aorta-associated multipotent progenitors was named mesoangioblasts [34].

However, much of the interest on mesoangioblasts, and later on adult PCs, was triggered by the initial evidence that transplant of murine mesoangioblasts contributed to the growth and regeneration of muscle fibers in vivo [24]. Additional experiments elegantly demonstrated also the ability of systemically transplanted mesoangioblasts to reach the developing skeletal muscle fibers through the circulation [35].

Notably, the in vivo potential of mesoangioblasts was not limited only to skeletal myogenesis. Experiments on chimeric embryos, where embryonic aorta-derived cells from quail or mouse were grafted into chick embryo, revealed that mesoangioblasts initially integrated into the vasculature of the host, actively concurring to the generation of chimeric microvasculature in different tissues. Grafted mesoangioblasts were finally found as a fully differentiated cell component in a broad range of mesodermal tissues [34]. The ability of mesoangioblasts to travel through the bloodstream led to the hypothesis that, during embryonic development, they could migrate from the dorsal aorta along the forming blood vessels, contributing to the perivascular cell compartment of postnatal tissues [36].

On this basis, it is evident that adult PCs have some of the functional properties observed in mesoangioblasts, including the mesenchymal, endothelial, and vasculogenic abilities [21,37].

Stem and Progenitor Cells Associated with the Wall of Blood Vessels

Regardless of their likely relationship with the embryonic mesoangioblasts, PCs present in adult tissues represent a population of cells of the perivascular compartment that can differentiate into different mesodermal cell types [37,38].

A well-studied cell population that shares several properties with adult PCs is represented by the adventitial reticular cells present in the wall of the sinusoids of bone marrow tissue. Adventitial reticular cells form a layer on the abluminal side of ECs of the sinusoids, which is therefore not different from the relationship that PCs establish with ECs in capillaries and small vessels [39]. A number of studies have associated adventitial reticular cells with the stromal cells of bone marrow from which the so-called bone marrow MSCs/stromal stem cells are derived [40]. The ability of these cells to generate progenitors that can differentiate in cartilage, bone, and adipocytes closely resembles the properties of PCs.

Actually, both cell types express a set of common markers [41]. Adventitial reticular cells and the stromal cells of bone marrow have been shown to represent a specific cell population of skeletal stem cells devoted to bone growth and renewal as well as to participate in the establishment of the hematopoietic stem cell niche [39,42].

Over the years, a number of studies have indicated that, in addition to PCs and to adventitial reticular cells/stroma cells of bone marrow, a number of multipotent or lineage-restricted progenitor cell populations are present in the wall of postnatal vessels, where they are essentially mainly associated with the function of maintaining the structural integrity of the vascular system. Lineage-specific progenitors mainly dedicated to the replacement of ECs or to the generation of new smooth muscle cells have been identified in the arteries of adult tissues [19,43,44].

In addition to lineage-restricted progenitors, a number of studies have also identified multipotent stem/progenitor cells present in the wall of blood vessels. Most of these cell

populations are generically defined as MSCs, yet their characterization is still lagging behind given the inherited difficulties to distinguish MSCs from PCs [29,37,45–48]. Other studies have resulted in the initial characterization of additional multipotent cell populations of the vascular wall that bear some relationships with PCs: adventitial cells and myogenic ECs. Of note, these two cell populations share with PCs both the ability to differentiate into some mesodermal lineages and the expression of several MSC markers [28].

Adventitial cells, which are different from the ''adventitial reticular cells'' of bone marrow, were first isolated from the adipose stromal vascular fraction as $CD34^+$ $CD31^-$ $CD45^-$ $CD146^-$ expressing cells [49,50] with a lower efficiency to differentiate into adipocytes when compared with isogenic PCs [50]. Their localization in the adventitia can easily distinguish them from typical $CD34^+$ ECs [47]. Intriguingly, adult adipose-derived adventitial cells appear to represent a source of MSCs clearly distinct from PCs [29].

Myogenic ECs have been identified in vessels from skeletal muscle where they can be identified by the expression of different myogenic markers, such as CD56 and PAX7, but also of endothelial markers, such as CD34, CD144, and von Willebrand factor (vWF) [51]. Myogenic ECs are currently defined as $CD56^+$ $CD34^+$ $CD144^+$ $CD45^-$ cells and are able to differentiate into skeletal muscle cells, chondrocytes, osteocytes, and adipocytes [52,53].

Altogether, adventitial cells and myogenic ECs have the capacity to proliferate and the potential to give rise to endothelial, smooth muscle, and additional mesenchymal cell types. Accordingly, the vascular wall appears to possess the characteristic of a niche-like environment, a concept of high relevance considering the involvement of the vascular compartment in physiological and pathological conditions [2,15,45,54,55].

PCs, MSCs, and the Perivascular Compartment

The term MSCs was introduced by Caplan to define cells derived from bone marrow that were able to differentiate in different mesenchymal lineages, including adipocytes, osteocytes, and chondrocytes [56]. After the original isolation from human bone marrow [57], MSCs have also been isolated from a wide variety of adult human organs and tissues by exploiting an isolation procedure based on the enzymatic digestion of the stromal vascular fraction of bioptic specimens [58–63].

In analogy to other adult stem cells, we still need to identify unique markers for recognizing MSCs, since all surface antigens routinely used to characterize MSCs are also expressed by a variety of unrelated cells (see Murray et al. [41] for a compelling list of MSCs and perivascular cells markers). Accordingly, MSCs are currently defined based on both operational and functional criteria: MSCs must be adherent to plastic, must possess self-renewing ability, and must be able to differentiate into at least adipogenic, osteogenic, and chondrogenic lineages, to express CD105, CD73, and CD90 while being negative for the expression of CD45, CD34, CD14 or CD11b, CD79α, or CD19 and human leukocyte antigen (HLA)-DR surface molecules [64].

Despite extensive studies aimed to better define the in vitro properties of MSCs, once isolated from tissues, their localization and physiological role in vivo still remain to be clarified. Based on their nearly ubiquitous presence, it has been proposed that in vivo MSCs might reside within the perivascular compartment of adult connective tissues [36,65,66].

Indeed, the identification of the multipotent properties of PCs supported the hypothesis that also MSCs might have a perivascular origin [30,65]. Studies of lineage tracing, based on neural-glial-2 (NG2), peroxisome proliferator-activated receptor gamma (PPARγ), alkaline phosphatase (AP) and GLI1 expression, indicated that progenitors capable of differentiating in vivo into either osteogenic, adipogenic, or myogenic cells (ie, mesodermal progenitors) are localized in the perivascular niche of incisors, fat, and skeletal muscle, respectively [67–70]. However, the relationship between these progenitors from the perivascular niche and PCs is not yet completely determined.

Evidence supporting the association of in vivo multipotent MSCs with the perivascular compartment has been provided in bone marrow. Here, the adventitial reticular cells that surround bone marrow sinusoids are considered, along with bone marrow stromal cells, the endogenous progenitor of MSCs, given their ability to self-renew and to fully organize the complete hematopoietic environment of bone marrow [40,43]. Culture of adherent cells derived from adventitial reticular and stromal cells is referred to as bone marrow stromal cells or bone marrow MSCs.

Results from several laboratories have reported that MSCs isolated from different tissues displayed properties similar to bone marrow MSCs in terms of surface marker expression and growth rate. However, the multipotent and clonogenic abilities of MSCs from other tissues are less efficient with respect to those derived from bone marrow [71]. In this context, Peault's group reported that in vivo PCs, identified as such by the coexpression of known perivascular markers such as NG2, CD146, and PDGF-Rβ, when purified from various adult tissues and cultured in vitro, retain the expression of perivascular and mesenchymal markers and also express additional MSCs markers, suggesting that the intimate connection between PCs and MSCs appears to be more than a hypothesis [37,46,72].

A comparison between MSCs from various sources, including bone marrow, and retinal cultured PCs initially indicated that also MSCs and PCs were similar in terms of immunophenotype and differentiation abilities, although they reported that CD146 was expressed only by PCs [73]. Other studies have shown that CD146 is expressed also by MSCs isolated from tissues other than bone marrow, although at variable levels with respect to PCs [74,75], as also discussed later. A more recent compelling comparison between bone marrow MSCs and PCs has revealed that MSCs and PCs share several immunophenotypic markers and are both able to differentiate toward adipogenic, osteogenic, and chondrogenic lineages, although their multipotent abilities were differentially dependent on the culture conditions [74].

Additional differences between MSCs and PCs were also observed in the analysis of the transcriptome of MSCs and PCs [74]. Evidence of differences between MSCs and PCs should not surprise, considering that MSCs are obtained without a prospective isolation and therefore represent a highly heterogeneous cell population containing progenitors with distinct differentiation abilities that vary depending on the tissue of origin [58,76–79]. Further differences between PCs and MSCs are also supported by the evidence that cultured PCs from skeletal muscle, but not MSCs from the same tissue, were able to fuse and form myotubes in vitro,

suggesting that PCs from skeletal muscle present a broader range of differentiation abilities than MSCs.

In line with this finding, a more recent comparison between isogenic MSCs and PCs from adipose tissue revealed that PCs are endowed with more efficient differentiation abilities than their MSCs counterparts, although both cell populations were nearly identical in terms of surface marker expression [75]. Opposite evidence in terms of differentiation abilities has been obtained in the myometrium, where PCs can only differentiate toward smooth muscle cells [80], whereas MSCs are able to differentiate toward adipogenic, osteogenic, and chondrogenic lineages [81]. Experiments with MSCs isolated from dental pulp and adipose tissue indicate that not all MSCs isolated from those tissues are derived from PCs [29,68].

Based on this evidence, we can conclude that, although the perivascular compartment contains mesodermal precursors such as PCs and MSCs, a direct relationship between PCs and MSCs, although possible, still remains to be formally proved in most tissues.

PCs: Surface Marker Expression and Procedures for Isolation and In Vitro Culture

PCs are currently isolated from human adult tissues using two different procedures: selection of perivascular cell populations by fluorescent-activated cell sorting (FACS) or selection of weakly adhering cells that emerge from culture of explants of biopsies enriched in small blood vessels. In some cases, these two approaches have been combined. Several markers associated with cells present in the perivascular compartment are currently known (see Murray et al. [41] for a compelling list of perivascular cells markers). Nevertheless, markers that can be univocally associated with PCs are still missing.

Studies performed on tissue biopsies have shown that PCs in vivo can be identified by three main markers. A widely used marker for characterization of PCs is the cell adhesion molecule CD146, which also recognizes adventitial reticular cells of the bone marrow [40] and is also present on cell surface of additional cell populations such as endothelial progenitors of the VSMC lineage [82], but also mature ECs [83]. A second marker is NG2, a proteoglycan also expressed by progenitors of oligodendrocytes and chondrocytes [84,85] and that is present on mural cells during vascular morphogenesis [86]. The last marker used for identification of PCs is the platelet-derived growth factor receptor beta (PDGFRβ), the receptor for a powerful mitogen of cells of mesenchymal origin that also plays a pivotal role in vessel formation, being involved in differentiation and proliferation of both PCs and VSMCs [87,88].

In situ PCs also express α-smooth muscle actin and desmin, in addition to other mesodermal markers such as CD73, CD90, and CD105. Finally, in vivo PCs can be identified as they do not express endothelial and hematopoietic markers such as CD31, vWF, CD34, and CD45 [37,38]. PCs also express AP, although its expression has been formally observed in vivo only in skeletal muscle PCs [88]. Based on the combination of markers expressed by PCs in vivo, these cells have been purified from the stromal vascular fraction of adipose tissue as a population of cells positive for CD146 and negative for CD34, CD45, and CD31 by using multicolor FACS. After expansion in vitro, purified PCs also express NG2, PDGFRβ, and other mesodermal markers leading to the definition of a compelling PCs molecular signature based on the expression of CD146, NG2, PDGFRβ, and AP and the absence of CD34, CD45, vWF, and CD144 [37]. Cell sorting based on these markers has also been exploited to isolate PCs from human fetal tissues, endometrium, heart, and also from skeletal muscle [37,89].

PCs from adult human skeletal muscle tissue are usually isolated following the technique of culture of explants starting from tissue biopsies. Nearly 2 weeks after the initial plating, small round-refractile cells start to emerge from the cultured explants. These cells are then harvested and expanded to obtain cultured PCs [38]. PCs derived by explant culture from skeletal muscle or from other adult tissues share the known surface marker profile identified in vivo and on FACS-purified cells [75,80,90]. A combination of the explant-culture protocol and FACS selection has been more recently introduced to isolate skeletal muscle PCs. This approach is based on the selection of AP-expressing cells from the population of weakly adhering cells emerging from skeletal muscle explant culture. Of note, this isolation procedure generates a population of cultured PCs again expressing the same molecular signature already reported [88,91].

PCs from Skeletal Muscle

The increased attention on the multipotent properties of PCs stems from the seminal work on embryonic mesoangioblasts [24,34]. The characterization of mouse embryo mesoangioblasts and later of postnatal adult PCs provided solid evidence that these cells, even when delivered systemically, are able to colonize skeletal muscle and to differentiate in healthy muscle fibers resulting in a significant functional recovery in dystrophic mice [92]. Mesoangioblasts, in fact, express a subset of integrins and receptors that efficiently allow migration through both the blood stream and vascular wall crossing [35,93].

In the following years, cell populations endowed of myogenic potential have also been isolated from canine's postnatal skeletal muscle biopsies. In analogy with previous results obtained in dystrophic mice, systemic delivery of healthy donor dog mesoangioblasts resulted in the improvement of muscle function in dystrophic dogs [94].

Finally, Cossu and coworkers used explant cultures of adult skeletal muscle biopsies to isolate human adult PCs [90]. Cultured PCs from human skeletal muscle, in line with mouse and dog adult cells, displayed a strong spontaneous myogenic potential in vitro and were also able to fuse with mouse muscle fibers once injected into the femoral artery of scid-mdx immunodeficient mice. In addition, cultured PCs differentiated in vitro also toward adipogenic and osteogenic lineages, thus combining biological properties of original mesoangioblasts [90].

The therapeutic potentials of PCs in contributing to skeletal muscle tissue regeneration when injected into preclinical models of muscular dystrophy reflect a physiological role of these cells. In fact, recent work by several groups has shown that in skeletal muscle tissue, PCs are part of a pool of cells that, in addition to the ''proper'' myogenic precursors (ie, satellite cells), can directly [88,95] or indirectly [96,97] contribute to the process of muscle repair and

regeneration. Indeed, lineage tracing of skeletal muscle PCs showed that these cells are able to enter the skeletal muscle niche compartment in the early stages of postnatal growth and to contribute to the formation of the adult satellite cell compartment. These PC-derived satellite cells can fuse into developing skeletal muscle fibers and contribute to normal muscle growth in unperturbed conditions during adult life and, even more, participate in regeneration of skeletal muscle tissue after injury [88]. Altogether, these data indicate that the observed ability of isolated and cultured PCs to enter the myogenic cell fate, when used for therapeutic protocols, reflects a tissue-specific commitment of these cells.

Based on the results obtained in murine and canine preclinical models of muscular dystrophy, a phase I/IIa clinical trial using cultured PCs was recently started. This trial aimed to treat pediatric patients affected by Duchenne muscular dystrophy with the intraarterial infusion of HLA-matched allogeneic PCs obtained from adult skeletal muscle of healthy donors. Unfortunately, the engraftment of the transplanted PCs was minimal and the overall efficacy of this treatment was negligible in terms of functional recovery, as compared with results obtained in preclinical models. Nevertheless, this study indicated that a cell therapy approach based on infusion to each patient of hundreds of millions PCs can be considered safe, providing an encouraging outcome for future improvements of the procedure [98].

PCs from Other Adult Human Tissues

The identification of multipotent PCs in skeletal muscle, the encouraging outcomes obtained in preclinical animal models, and the emerging role of PCs in tissue regeneration in physiological and pathological conditions inspired additional studies aimed at the isolation of PCs from other human adult tissues.

PCs have been isolated by FACS as $CD146^+ CD34^- CD56^- CD45^-$ cells from the stromal vascular fraction of adipose tissue from where a large number of PCs can be obtained [37,72]. Adipose tissue PC-derived cells are clonal cells able to give rise to adipocytes, osteocytes, and chondrocytes. When injected into skeletal muscle of cardiotoxin-treated mice, they are also able to contribute to fiber regeneration, although evidence for spontaneous skeletal muscle differentiation has not been provided. A more compelling analysis on adipogenic potential of distinct stromal cell populations revealed that PC-derived cells display a stronger tendency to differentiate into multilocular adipocytes than endothelial progenitors, supra adventitial cells, and mature ECs [50].

More recently, Lauvrud et al. further confirmed that adipose PC-derived cells expressing CD146 are endowed with a more robust adipogenic potential than their CD146 negative counterpart [99]. Interestingly, FACS-sorted adipose PC-derived cells improved fracture healing when percutaneously injected into an atrophic nonunion rat model [100], giving promising results also for future clinical exploitation of the osteogenic potential of adipose PCs. In this context, the sorting procedure proposed by Crisan et al., which is considered the most accurate approach to isolate adipose PCs by FACS [46], has been slightly improved to obtain a clinically relevant number of cells without the need of expansion in culture.

PCs from adipose tissue have also been isolated as floating cells outgrowing from explant culture of fat tissue biopsies, in strict analogy with the procedure used to isolate PCs from skeletal muscle. These cultured PCs express the classical pericytic markers, including CD146, AP, and NG2, whereas they do not express the endothelial markers CD31 and CD34. They are able to differentiate into adipocytes, osteocytes, and smooth muscle cells, whereas they are unable to spontaneously differentiate into skeletal muscle cells unless when cocultured with an established myogenic cell line [75]. As a matter of fact, PCs from adipose tissue either isolated through FACS selection or explant culture appear to possess comparable characteristics.

Interest in identifying cardiac stem cells also triggered studies on the isolation of human PCs from heart. Resident microvascular heart PCs were identified as cells surrounding microvessels and capillaries, which coexpressed CD146, NG2, and PDGFRβ and were negative for endothelial markers. These cells were further isolated by FACS starting from the myocardium using a positive selection for CD146 and a negative selection for CD34, CD45, CD56, and CD117, in strict analogy with PCs from adipose tissue. Cultured heart PCs displayed null skeletal myogenic potential and limited cardiomyogenic capacity, being only committed to an immature cardiomyocitic phenotype. In contrast, heart PCs could be robustly differentiated toward adipogenic, osteogenic, and chondrogenic lineages [101].

Murine heart cell populations, endowed with strong cardiomyogenic ability, have been isolated by FACS as CD34 and NG2 positive cells or, after colony-forming assay, as colony-forming unit fibroblasts (CFU-Fs). Of note, $CD34^+ NG2^+$ cardiomyogenic cells failed to differentiate toward additional mesenchymal lineages, whereas cardiac CFU-Fs displayed adipogenic, osteogenic, and chondrogenic potentials [102,103]. These data indicate that, although homologous cell populations have not been isolated yet from human heart, distinct progenitors with different differentiation potentials can be found in the perivascular compartment of the heart. Intriguingly, heart cell populations that expressed pericytic markers appear to be selectively committed toward the cardiac phenotype.

A tissue characterized by the presence of a predominant smooth muscle tissue component is the uterus. The presence of PCs around microvessels in biopsies of endometrium has been revealed by immunostaining for CD146 and PDGFRβ. Accordingly, these cells have been isolated by FACS, using CD146 and PDGFRβ as selection markers, starting from the enzymatic digestion of endometrial biopsies. Endometrial PCs were capable of differentiating into multiple mesenchymal lineages, including smooth muscle. A comparative transcriptomic analysis between endometrial PCs, endometrial fibroblasts, and endometrial ECs revealed that freshly isolated PCs express genes involved in smooth muscle differentiation at higher levels with respect to the other cell populations [104].

PCs from uterus have been more recently isolated by explant culture of myometrial biopsies. These PCs from myometrium are similar to those isolated from the endometrium in terms of morphology and surface marker expression [80,104]. Nevertheless, myometrial PCs can readily differentiate only into smooth muscle cells, whereas they were totally incapable of differentiating into other mesenchymal lineages, including skeletal muscle differentiation. Both myometrial and endometrial PCs express notch receptors [80,105], whose activation is known to be involved in the

development of endometrium as well as in PCs differentiation [21,106,107]. However, inhibition of notch signaling had no effect on the properties of myometrial PCs, whereas it affected both gene expression and proliferation of PCs from the endometrium [80,108].

Based on the reported evidence, it appears that PCs from distinct tissues are endowed with different mesodermal potentials, although they are virtually indistinguishable in terms of morphology and marker expression. In addition, when considering adipose tissue, skeletal muscle, heart, and uterus, PCs appear to retain a preferential commitment toward the main cell type of the tissue where they reside. Intriguingly, this aspect has also been observed in bone marrow, where in situ adventitial reticular cells, which can be considered the bone marrow equivalent of PCs, showed a preferential tendency to differentiate into bone [40].

Very recently, Sacchetti et al. performed a compelling comparison between $CD146^+/CD34^-/CD45^-$ cells isolated from different human tissues [109]. These authors reported that, in addition to marked differences between the cell populations analyzed in terms of transcriptomic signature, bone marrow-derived cells were skeletogenic but neither myogenic nor chondrogenic, whereas skeletal muscle-derived cells were myogenic, but not skeletogenic. Additional analysis of the differentiative properties of perinatal cord blood-derived cells indicated that these cells were chondro-osteogenic but not myogenic, further supporting the idea that perivascular/MSCs progenitors can be endowed with differentiation abilities closely related to the tissue of origin.

However, it should be noted that cell populations used by Bianco and collaborators were obtained using a prospective isolation protocol slightly different from that described by Peault's group [37,46]. In addition, previous studies based on different isolation strategies, culture conditions, and differentiation assays have provided results that differ from those reported by Sacchetti et al. [109–111]. Indeed, we should always be aware that even minimal changes in isolation and culture protocols might induce small variations in the cell populations obtained, which might then cause differences in the observed properties of the resulting cells. Nonetheless, even when using the same prospective isolation protocol, Sacchetti et al. [109] noted that only PCs from skeletal muscle were capable of spontaneously differentiating into skeletal muscle cells.

In this context, it is worth noting that induced pluripotent stem cells (iPSCs) obtained by reprogramming skeletal muscle PCs are endowed with better skeletal muscle differentiation efficiency than iPSCs obtained by fibroblasts reprogramming [112,113]. However, contrasting evidence on the ability of PCs and related cell populations from brain to spontaneously differentiate into neuronal lineages has been reported [114–117]. Altogether, currently available data on PCs isolated from adipose and cardiac tissues, endometrium, myometrium, bone marrow, and skeletal muscle appear to be more prone to differentiate toward the cell type specific of the tissue from where they were isolated.

Concluding Remarks

In this review, we attempted to describe the state of the art on PCs from adult human tissues with respect to their identification and their differentiation properties. Cells capable of differentiating into different lineages of mesodermal origin have been isolated from several tissues of mice and humans. Among these cells, PCs have recently attracted the interest of several research teams because of their potential applications in cell therapy protocols and also for representing a potential source for MSCs. However, despite the high interest and of intensive investigation, we are still far from having attained a unique idea on the overall identity of PCs.

Despite the lack of specific surface markers that would allow to unambiguously label homogeneous populations of PCs, these cells can be identified in vivo as non-ECs ($CD34^-$ and $CD31^-$ cells) that natively express perivascular and mesenchymal markers (NG2, AP, PDGFRβ, CD44, CD73, CD90, CD105, and CD146) [37,38,72,91]. However, these markers are not always all present on PCs from adult human tissues [41,72,118].

Prospective isolation of PCs can be obtained selecting for $CD146^+$ $CD34^-CD45^-CD56^-$ cells [37,46]. Once in culture, these cells retain the above-mentioned markers, but also express additional mesenchymal markers [37,67]. Nevertheless, these markers do not allow establishing a clear relationship between PCs and MSCs, and between PCs and the numerous progenitor cell populations found in the perivascular compartment or in the connective tissue of the different organs of the adult organism.

Initial results indeed claimed that PCs isolated from various tissues might share common traits, including growth properties, surface marker expression, and differentiation potencies. This initial enthusiasm has been tempered by more recent data obtained by different groups, which although contribute to expand our knowledge on biology of PCs, also have added additional information, suggesting that PCs may significantly differ from MSCs [29,68]. Furthermore, evidence has been provided indicating additional variability among populations of PCs. In this context, recent data suggest that even within the same tissue, PCs may differ on the basis of specific properties that include the type and size of blood vessels of residence and the interactions that they establish with other cells [28,72,118]. In addition, PCs within a given tissue may functionally behave differently under pathological conditions [119–121].

In conclusion, work from several laboratories during the past few years has provided a large body of information on the properties of PCs. Noteworthy, converging evidence derived from studies mainly performed on PCs isolated from skeletal muscle, bone marrow, and adipose tissue and new results obtained from additional tissues including endometrium, myometrium, and cardiac tissue suggest that PCs isolated from different tissues, even if they might present a varied range of differentiation properties, appear to have a characteristic preference to differentiate toward the specific cell type of the tissue from where they have been isolated. This is likely due to the local cues imposed by the environment where PCs reside, which might reflect the cell renewal and repair processes required for maintenance of the ''tissue homeostasis'' of each specific tissue.

Acknowledgments

This work was supported by a PAR FAS 2007–2013 grant, ToRSADE, from Regione Toscana to Vincenzo Sorrentino, and a MIUR-FIR 2013 RBFR13A20K grant to Enrico Pierantozzi.

Author Disclosure Statement

The authors declare no competing financial interests.

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Received for publication June 19, 2016
Accepted after revision August 22, 2016
Prepublished on Liebert Instant Online August 22, 2016