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PERICYTES ARE HETEROGENEOUS IN THEIR ORIGIN WITHIN THE SAME TISSUE

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Abstract

Pericytes heterogeneity is based on their morphology, distribution, and markers. It is well known that pericytes from different organs may have distinct embryonic sources. *Yamazaki et al.* (2017) using several transgenic mouse model reveal by cell-lineage tracing that pericytes are even more heterogeneous than previously appreciated. This study shows that pericytes from within the same tissue may be heterogeneous in their origin. Remarkably, a subpopulation of embryonic dermal pericytes derives from the hematopoietic lineage, an unexpected source. Reconstructing the lineage of pericytes is central to understanding development, and also for the diagnosis and treatment of diseases in which pericytes play important roles.

Keywords

pericytes; stem cells; origin; embryonic; plasticity

Approximately one hundred years ago, Karl Wilhelm Zimmermann named a population of contractile cells *pericytes* because they were primarily located around blood vessels

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DISCLOSURES

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(Zimmermann, 1923). The word *pericyte* derives from the Greek *kytos*, a hollow vessel, appropriately describing a cell surrounding a blood vessel. Back then, these cells were identified mainly by their anatomical location and morphology. Pericytes have long projections that encircle the vessel walls which are widely scattered in all tissues (Hirschi and D'Amore, 1996). They surround endothelial cells and communicate with them along the length of the blood vessels by physical contact and paracrine signaling (Diaz-Flores et al., 1991).

Defining a specific molecular marker for pericytes has been challenging. Until recently, light and electron microscopy were the only techniques able to visualize them, thus limiting the knowledge acquired from those studies. In the last years, with the advent of fluorescent and confocal microscopy, technologies combining anatomical location, expression of surface markers, and genetic lineage tracing enabled the discovery of pericytes' varying, sometimes unexpected, roles in health and disease (Birbrair et al., 2015). It is already known that pericytes stabilize blood vessels and participate in vascular development, maturation, remodeling, architecture, and permeability (Enge et al., 2002; Hellstrom et al., 2001; Leveen et al., 1994; Lindahl et al., 1997; Soriano, 1994). Additionally, they regulate blood flow (Pallone and Silldorff, 2001; Pallone et al., 1998; Pallone et al., 2003), and, in the central nervous system, collaborate with astrocytes to maintain the functional integrity of the blood brain barrier (Al Ahmad et al., 2011; Armulik et al., 2010; Bell et al., 2010; Cuevas et al., 1984; Daneman et al., 2010; Dohgu et al., 2005; Kamouchi et al., 2011; Krueger and Bechmann, 2010; Nakagawa et al., 2007; Nakamura et al., 2008; Shimizu et al., 2008). Pericytes also may affect immune function by regulating lymphocyte activation and by phagocytic activity (Balabanov et al., 1999; Balabanov et al., 1996; Bouchard et al., 1997; Castejon, 2011; Fabry et al., 1993; Fisher, 2009; Hasan and Glees, 1990; Jeynes, 1985; Kim et al., 2006; Thomas, 1999; Tu et al., 2011; Verbeek et al., 1995). Interestingly, strong evidence identified pericytes as stem cells capable to form several other cell types (Birbrair et al., 2017a; Birbrair and Delbono, 2015; Birbrair et al., 2017b; Birbrair et al., 2014a; Birbrair et al., 2013a, b, c; Birbrair et al., 2013d, 2014b, 2015; Birbrair et al., 2014c; Brighton et al., 1992; Collett et al., 2003; Crisan et al., 2008; Davidoff et al., 2004; Dellavalle et al., 2011; Dellavalle et al., 2007; Diaz-Flores et al., 1992; Doherty et al., 1998; Dore-Duffy et al., 2006; Farrington-Rock et al., 2004; Feng et al., 2011; Olson and Soriano, 2011; Richardson et al., 1982; Tang et al., 2008).

Pericytes differ in their embryonic origin between tissues (Armulik et al., 2011; Sims, 1991, 2000). Very little is known about the exact identity of pericyte ancestors within developing tissues, and there is evidence for numerous distinct developmental sources (Armulik et al., 2011). Lineage tracing studies indicate that pericytes in the cephalic region and thymus are of neuroectodermal origin (Foster et al., 2008; Muller et al., 2008; Simon et al., 2012; Trost et al., 2013; Zachariah and Cyster, 2010); while in lung, heart, liver and gut, the mesothelium is the main source of perivascular cells (Armulik et al., 2011; Asahina et al., 2011; Cai et al., 2008; Khan et al., 2016; Mellgren et al., 2008; Que et al., 2008; Zhou et al., 2008). In most other organs, pericytes derive from the mesoderm; specifically, the sclerotomal compartment (Armulik et al., 2011; Asahina et al., 2011; Bergwerff et al., 1998; Etchevers et al., 2001; Korn et al., 2002; Que et al., 2008; Wilm et al., 2005; Winkler et al., 2011; Yamanishi et al., 2012).

Understanding the origin and the processes that drive pericyte formation is a central question in developmental biology. Whether all pericytes from the same tissue have the same ancestry remains unknown. Nevertheless, in a recent article in *Cell Reports*, Yamazaki and colleagues showed that a pericyte subpopulation within the embryonic skin derives from an unexpected source (Yamazaki et al., 2017). The authors used *in vivo* lineage-tracing technologies to track specifically neural crest-, endothelial-, and hematopoietic-derived cells. These experiments suggested that during development the sources of tissue pericytes are heterogeneous. Strikingly, some of the pericytes in the embryonic skin and brain had hematopoietic origin (Yamazaki et al., 2017). Furthermore, the authors showed defective pericyte development in a mouse model with a known impairment of the myeloid lineage, suggesting that cells from this lineage contribute to pericyte formation in ectodermal organs (Yamazaki et al., 2017). Additionally, this study unravels an important signal (TGFβ) necessary for hematopoietic progenitors to differentiate into pericytes (Yamazaki et al., 2017). This study brings a new possible ancestor for pericytes, and reopens the discussions about pericytes' heterogeneity. These cells are heterogeneous not only in their morphology, distribution, molecular markers and function, but also in their origin even within the same tissue.

Pericytes have been anatomically defined by their perivascular location in the blood vessel wall in close contact with endothelial cells (Feng et al., 2011; Sa-Pereira et al., 2012). However, not all perivascular cells are pericytes. Besides smooth muscle cells, other cellular types have been described as perivascular: i.e. adventitial cells (Crisan et al., 2012), fibroblasts (Soderblom et al., 2013), and macrophages (Bechmann et al., 2001; Guillemin and Brew, 2004). Classical electron microscopy studies of pericytes reveal their location under the vascular basal lamina (Allsopp and Gamble, 1979), in contrast to other perivascular cells. None of pericyte markers are specific, since they are also expressed by other cell types; and their expression in pericytes is highly dependent on the developmental stages (Armulik et al., 2011). Thus, pericitic markers used in this study could refer to other cell populations. For instance, PDGFRβ is a known marker of other cell types, such as fibroblasts (Soderblom et al., 2013; Spitzer et al., 2012); while NG2 proteoglycan could be expressed in macrophages (Yotsumoto et al., 2015). Additionally, pericytes that do not express NG2 were also recently described (Stark et al., 2013). Recent studies discovered new molecular markers for pericytes, such as Gli1 (Kramann et al., 2015; Kramann et al., 2017) and Tbx18 (Guimaraes-Camboa et al., 2017). Whether the perivascular cells derived from hematopoietic progenitors in the embryonic skin are pericytes still needs to be clarified. The combination of pericyte molecular markers with immunolabeling of the basal lamina in genetic lineage tracing models will confirm the nature of those cells.

Surprisingly, Yamazaki and colleagues found that perivascular cells were labeled in Vav-Cre/R26R^{EYFP} mice, but not in Tie2-Cre/R26R^{EYFP} mice (Yamazaki et al., 2017). It is known that Tie2 gene is expressed by endothelial cells (Maisonpierre et al., 1997; Schnurch and Risau, 1993). However, hematopoietic cells also express Tie2 (Arai et al., 2004; Takakura et al., 1998). Consistent with this, Tie2-Cre mice display Cre recombinase in both endothelial cells and hematopoietic cells, especially in hematopoietic stem cells (HSCs) (Constien et al., 2001; de Lange et al., 2008; Kisanuki et al., 2001; Tang et al., 2010). During development, both endothelium and definitive HSCs which form all hematopoietic cells,

arise from a shared precursor, the hemogenic endothelium (Chen et al., 2009; Hirschi, 2012; Medvinsky and Dzierzak, 1996; Nguyen et al., 2014; Rafii et al., 2016). Due to this, it is virtually impossible to avoid some Cre recombinase activity in hematopoietic cells when using endothelial specific promoters with constitutively active Cre recombinase. Similarly, Vav-Cre strains have been shown to target both hematopoietic and endothelial cells (Croker et al., 2004; de Boer et al., 2003; Georgiades et al., 2002). It will be interesting to explore whether the embryonic hematopoietic cells that originate dermal pericytes derive from a different source than the hemogenic endothelium.

Interestingly, a recent study shows that cardiac endothelial cells give rise to ~20% of pericytes in the murine embryonic heart (Chen et al., 2016). Thus, the developmental sources of pericytes are more heterogeneous than previously appreciated. These surprising findings raise the possibility that distinct subsets of pericytes, depending on their developmental origin, could differentially contribute to different pathological conditions.

Additionally, to examine which specific hematopoietic cells form pericytes, CD11b-Cre/TdTomato mice were analyzed (Yamazaki et al., 2017). Nevertheless, pericytes may express CD11b in culture (Balabanov et al., 1996), as well as after stroke (Ozen et al., 2014). Thus, although pericytes in the skin vasculature are labeled in this genetic tracing mouse model (Yamazaki et al., 2017), whether dermal pericytes express CD11b earlier during development or if they derive from non-pericyte CD11b+ cell populations remains to be elucidated.

Although the authors show that dermal myeloid progenitors differentiate into pericytes in culture (Yamazaki et al., 2017), recent studies have shown that cells' behavior *in vitro* could be completely different from their functionality *in vivo* (Guimaraes-Camboa et al., 2017; Snippert and Clevers, 2011; van Berlo et al., 2014). Artificial conditions in the dish which characterize cell culture systems may activate differentiation potential that could be not shared by these same endogenous cells *in vivo* under physiological conditions (Guimaraes-Camboa et al., 2017; Snippert and Clevers, 2011; van Berlo et al., 2014).

Thus, the plasticity observed *in vitro* might be simply a consequence of the artificial cell culture microenvironment. Based on this, a recent study has challenged the current view about pericytes' capacity to differentiate into other cell types and reopened the discussion about pericytes' plasticity (Birbrair et al., 2017a; Guimaraes-Camboa et al., 2017).

Furthermore, Yamazaki and colleagues used a transgenic mouse model (PU.1 knockout) in which severe impairment of the myeloid lineage was previously reported (McKercher et al., 1996; Scott et al., 1994). In those mice, F4/80+ macrophages were absent from the skin. Although the vascular network covered by endothelial and smooth muscle cells appeared normal, these vessels had a reduction in pericytes (Yamazaki et al., 2017). Interestingly, the reduction in the number of pericytes was approximatelly 50%, while the proportion of dermal pericytes derived from the hematopoietic lineage seems to correspond to approximately one fourth of all pericytes in the skin. It will be interesting to explore whether the absence of one pericyte subpopulation may influence the development of other pericitic subtypes in the same tissue but of different origin.

PERSPECTIVES/FUTURE DIRECTIONS

Pericytes development and survival are regulated by several signals coming from other cells, i.e. platelet-derived growth factor-β (PDGF-β) (Leveen et al., 1994), transforming growth factor-β1 (TGFβ) (Gaengel et al., 2009), heparin-binding epidermal growth factor (HB-EGF)(Stratman et al., 2010); stromal-derived factor 1-a (SDF-1α)(Song et al., 2009); Sonic hedgehog (Shh)(Nielsen and Dymecki, 2010); Jagged-1 (Jag-1)(Liu et al., 2009); Ephrin (Salvucci et al., 2009). Macrophages produce several of these molecules (Arango Duque and Descoteaux, 2014; Coulthard et al., 2012; Edwards et al., 2009; Goh et al., 2009; Heldin and Westermark, 1999; Pereira et al., 2013). Future studies will address whether the lack of macrophage-derived signals may affect pericytes survival.

Also, it remains unknown whether pericytes at early stages of skin development express PU.1 gene; and whether the absence of pericytes in PU.1 knockout mice is due to autonomous efect on pericytes. These issues may be addressed by using pericyte-specific inducible CreER driver, such as Tbx18-CreERT2 recently described (Guimaraes-Camboa et al., 2017), crossed to PU.1 floxed mouse (Iwasaki et al., 2005). In the resulting mice, Tbx18-CreERT2/PU.1fl/fl, PU.1 could be deleted specifically in pericytes at different developmental stages.

Mukouyama group found that TGFβ signaling is required for the differentiation of hematopoietic cells into pericytes in the embryonic skin, by deleting the gene for TGFβ receptor specifically in hematopoietic cells (Yamazaki et al., 2017). The primary sources of TGFβ in the skin remains unknown. Blood vessels form highly branched and ramified networks with nerves extending into almost every part of our body (Carmeliet and Tessier-Lavigne, 2005). The functional interdependence between the two systems is reflected in their close anatomic apposition (Bates et al., 2003; Lewis, 1902; Quaegebeur et al., 2011). The nervous system provides precise control of vascular diameter and blood flow. Blood vessels and nerves can crosstalk to one another and stimulate each other's growth by neurotrophic or angiogenic guidance signals, respectively (Butler et al., 2010). Ingrowth of nerves precedes arterial formation, which follows axons branching pattern in the embryonic skin (Li et al., 2013; Mukouyama et al., 2002). The most prevalent cell type in peripheral nerves is the Schwann cell. In the bone marrow, Schwann cells maintain HSCs in the quiescent state through the production of activated TGFβ. It remains unknown whether during embryonic skin development perineural cells (Schwann cells) regulate the formation of perivascular cells (pericytes) through TGFβ production.

Within the same tissue, pericytes were characterized as heterogeneous based on their phenotype, molecular markers, distribution, and function (Armulik et al., 2011; Sims, 1991, 2000; Stark et al., 2013). For instance, in the adult skeletal muscle, two pericyte subtypes were identified based on their expression of Nestin-GFP. They differ in their differentiation potential; while type-1 pericytes (Nestin GFP−/NG2 DsRed+) can form fat and fibroblasts, type-2 pericytes (Nestin GFP+/NG2 DsRed+) have myogenic, neurogenic and angiogenic potential (Birbrair et al., 2014a; Birbrair et al., 2013a, c; Birbrair et al., 2014b, 2015; Birbrair et al., 2014c). Whether those same subtypes are present during embryogenesis

remains unknown. And, more interestingly, further studies will reveal the origin of skeletal muscle pericytes subpopulations.

Two varieties of bone marrow pericytes were distinguished according to their location in the blood vessels: arteriolar and sinusoidal (Birbrair and Frenette, 2016). Arteriolar and sinusoidal pericytes can be separated in Nestin-GFP transgenic mice according to Nestin-GFP transgene expression level (Birbrair et al., 2011; Kunisaki et al., 2013). Sinusoidal pericytes express low levels of the Nestin-GFP transgene, thus are denominated Nestin-GFP dim cells. Arteriolar pericytes express high levels of the Nestin-GFP transgene, thus are denominated Nestin-GFP bright cells. Additionally, arteriolar pericytes express the pericytic marker NG2 proteoglycan, and do not express leptin receptor; while sinusoidal pericytes express leptin receptor, but lack NG2 expression (Kunisaki et al., 2013). Interestingly, although both pericyte subtypes produce the chemokine C-X-C motif ligand 12 (CXCL12), only Cxcl12 derived from arteriolar pericytes is importante for HSC maintenance (Asada et al., 2017). The embryonic origin and the developmental relationship of bone marrow pericyte subpopulations remain to be elucidated.

In the spinal cord, pericytes that express the glutamate aspartate transporter Glast differ from those that express desmin and αSMA (Goritz et al., 2011). After spinal cord injury, only Glast+ pericytes increase in number and form the core of the scar, suggesting that the role of spinal cord pericytes' subpopulations differ in tissue repair after CNS injury (Goritz et al., 2011). Nevertheless, whether spinal cord pericytes have distinct origins is still unknown.

Pericytes' potential to differentiate into several cell types has been established by numerous studies; and the general consensus holds that pericytes are cells with high plasticity; although a recent study challenges this concept (Birbrair et al., 2017a; Guimaraes-Camboa et al., 2017). Future studies should address whether this hematopoietic lineage-derived pericyte subpopulation vary in its differentiation capability in comparison to other pericytes from the same tissue. Pericyte-intrinsic changes may be reversible or not but, either way, represent another source of heterogeneity; a pericyte subpopulation could be more prone to differentiate or to enter apoptosis than another.

Furthermore, it will be interesting to test whether this differentiation from hematopoietic cells into pericytes during development could be reversed under certain pathological circumstances; are pericytes able to form hematopoietic cells?

In addition to genetic cell fate mapping, transcriptomic and single cell analysis represent fundamental tools that will help us understand the roles and the origins of pericyte subpopulations within the same tissue. This understanding may bring new approaches for several pathologic conditions as pericytes are present in all tissues and play important roles related to tissue turnover and regeneration. Taking their diversity into account, pericytes will be crucial in advancing our understanding of development, disease and aging.

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Highlights

- Pericytes from within the same tissue may be heterogeneous in their origin.
- A subpopulation of embryonic dermal pericytes derives from the hematopoietic lineage.

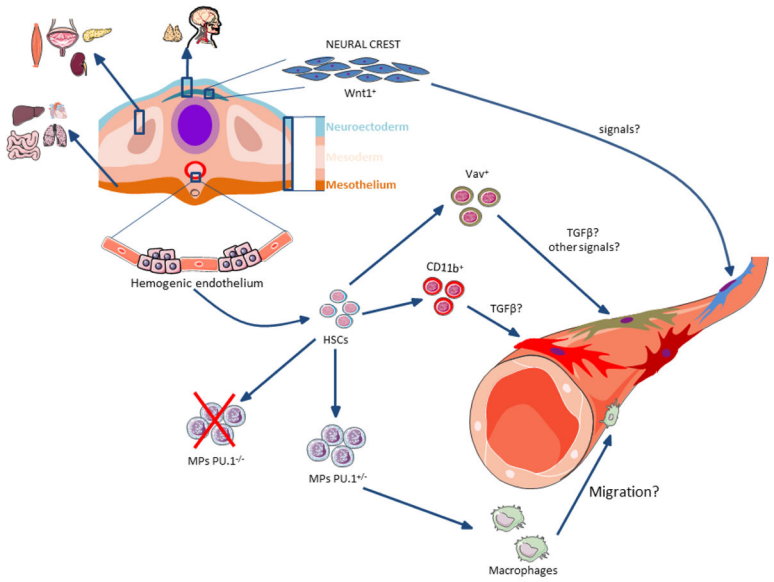

Figure 1. Heterogeneity in the pericytes origins

Pericytes are present around blood vessels in several tissues, such as brain, heart, lungs, skeletal muscle, pancreas, intestine, bone marrow, kidney, and others. During the embryonic development, pericytes in the head, cephalic region and thymus originate from the neuroectodermis, the ones found in gut, liver, lungs and heart are derived from the mesothelium, while the mesoderm gives rise to pericytes in other organs (such as kidneys, liver and pancreas). The study of Yamazaki and colleagues now suggests that surprisingly a subgroup of pericytes may derive from the hematopoietic lineage (Yamazaki et al., 2017). With the appearance of state of art technologies, such as new pericyte-lineage tracing mouse models, the true origin of pericytes subgroups will likely be revealed with much greater details in future studies.