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How Plastic Are Pericytes?

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Pericytes are defined by both their anatomical location and molecular markers. Numerous publications have reported their role as stem cells, contributing to the formation of tissues other than blood vessels. However, using cell-lineage tracing in a new transgenic mouse model, a recent study shows that in the context of aging and some pathologies, Tbx18+ pericytes do not function as stem cells in vivo. This study challenges the current view that pericytes can differentiate into other cells and reopen questions about their plasticity. This emerging knowledge is important not only for our understanding of development but may also inform treatments for diseases.

Keywords: pericytes, stem cells, regeneration, plasticity

In the late 1800 s, the French physiologist, Charles-Marie Benjamin Rouget, described a population of contractile cells in the capillaries, named *Rouget cells* after him [1]. German anatomist and histologist Karl Wilhelm Zimmermann (1861–1935) renamed them *pericytes* due to their predominant location around blood vessels [2], and more than 100 years later, they were still identified mainly by location.

Now, approaches that consider anatomical location, the expression of several molecular markers, and genetic lineage are advancing our understanding of pericytes' roles in health and disease [3]. In addition to physically stabilizing blood vessels, pericytes contribute to their normal architecture; vascular development, maturation, and remodeling; and regulate permeability and blood flow [4–11]. They collaborate with astrocytes to maintain the functional integrity of the blood–brain barrier [12–23], can affect blood coagulation [24–26], and play a role in immune function by regulating lymphocyte activation [27–30]. Evidence for phagocytic properties has been reported [31–35].

In the last 10 years, numerous studies have established pericytes' potential to contribute to the formation of various tissues; and the consensus holds that they have high plasticity. However, in a 2017 article in *Cell Stem Cell*, Guimarães-Camboa et al. challenge the current view of endogenous pericytes as tissue-resident progenitors with the capacity to differentiate into other cell types in vivo [36]. In this study, we discuss these findings and evaluate recent advances in our understanding of pericytes' contribution to tissue regeneration/homeostasis as tissue-resident progenitors in vivo.

The Guimarães-Camboa group performed an exhaustive analysis of cell fate tracing to study pericyte plasticity. First, they generated a new mouse model (Tbx18H2B-GFP) that can be used to label pericytes and smooth muscle cells in several adult organs based on their expression of the transcription factor Tbx18. Based on this knowledge, the group created another mouse model in which the fate of Tbx18+ pericytes and Tbx18+ smooth muscle cells could be tracked in vivo (Tbx18-CreERT2/tdTomato mice).

After following these animals for 2 years, they found that Tbx18-derived cells maintain their mural identity in the heart, muscle, fat, and brain, suggesting that perivascular cells do not originate other cell types as these organs age. To test whether their plasticity arises after tissue injury, the authors fate traced Tbx18-derived cells after brain and muscle damage. Surprisingly, under the tested conditions, pericytes did not contribute to the formation of other cell types. The study strongly suggested that, in vivo, pericytes do not behave as stem cells.

According to the International Society for Cellular Therapy (ISCT), adult stem cells were initially defined by three criteria: (1) adherence to plastic [37]; (2) expression of specific surface antigens; and (3) multipotent differentiation potential in vitro [38]. These criteria are now unanimously

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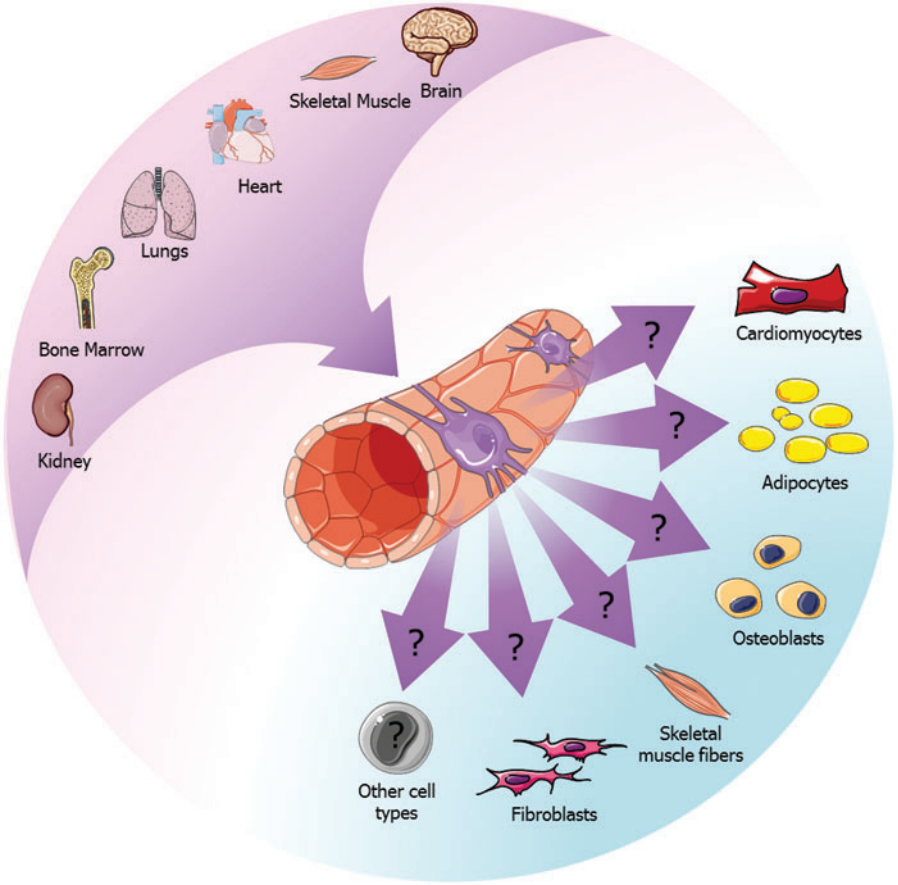

FIG. 1. Pericytes behave like stem cells: true or false? Pericytes are present around blood vessels in several tissues, such as brain, heart, lungs, skeletal muscle, bone marrow, and kidneys. Previous in vivo studies demonstrated that, under certain physiological and/or pathological conditions, pericytes may differentiate into other cell types: adipocytes, cardiomyocytes, osteoblasts, skeletal muscle fibers, fibroblasts, and others. Guimarães-Camboa et al. now suggest that pericytes do not behave as stem cells [36]. Future studies using state-of-the-art technologies, such as new pericyte lineage-tracing mouse models, may reveal the true potential of pericytes in much greater detail. Color images available online at www.liebertpub.com/scd

considered too minimal since practically every nonclonal culture of cells from any tissue could be classified as stem cells under the right culture conditions [39]. Additionally, the definition did not encompass a cell's behavior in vivo. These criteria will have to be restated.

Genetic fate-tracing mouse models are the most reliable tools for assessing cell plasticity in vivo, but they are highly dependent on the mouse model used. The inconsistencies between the Guimarães-Camboa group study and previous work may be due to the specificity of the transgenic mouse models used to mark pericytes in vivo.

While the new data may have an important impact on the field of pericyte biology, they also raise concerns. The authors showed the in vitro capacity of Tbx18H2B-GFP+ cells to differentiate into adipocytes, osteoblasts, and chondrocytes, but they did not show whether Tbx18-CreERT2/tdTomato+ cells can do so as well. Future studies should address this question, which would clarify whether inserting the CreERT2 cassette alters function in those cells, especially because Cre may be toxic under certain conditions [40].

Another open question is whether the pericytes labeled in Tbx18-CreERT2/tdTomato mice show stem cell activity in vivo under conditions not explored in this study. Other studies using different genetic lineage-tracing models under different conditions have shown that pericytes can form several cell types; for instance, odontoblasts (in NG2creER/Rosa26R mice) [41], scar-forming stromal cells (in Glast-CreER/R26R-YFP mice) [42], and follicular dendritic cells (in PDGFRβ-Cre/Rosa26R mice) [43].

To determine whether pericytes form fibroblasts, Guimarães-Camboa et al. used a transgenic mouse in which GFP is expressed under the control of the type I collagen promoter (Col1α1-GFP mice) [36,44] because there is no single marker for all fibroblasts. They performed brain injury in Tbx18-CreERT2/tdTomato/Col1a1-GFP mice and found that pericytes do not form Col1a1-GFP+ fibroblasts [36]. Nevertheless, after injury, the number of cells producing type I collagen was very small. Note that, along with fibronectin and laminin, the major extracellular matrix molecule produced in the fibrotic scar after central nervous system (CNS) lesion is type IV collagen [45–47], whereas very little type I collagen is produced. Thus, future studies should analyze which cells contribute to type IV collagen production after CNS injury, rather than type I, which seems less relevant in this type of scar. They might resolve the controversy with another group, which found that, using Glast-CreER mice, GLAST+ pericytes are the main source of fibrotic scar tissue after CNS injury [42].

Several in vivo studies using lineage-tracing technologies have demonstrated that pericytes from several tissues may contribute to fibroblast formation in other tissues in some pathologies. For instance, Dulauroy et al. showed that pericytes expressing ADAM12 during development give rise to most of the collagen-producing cells during skeletal muscle injury [48]. Mederacke et al. generated pericyte-specific lecithin retinol acyltransferase Cre mice, which marked nearly all liver pericytes, and confirmed that in models of cholestatic, toxic, and fatty liver disease, pericytes are the

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main collagen-producing cells [49]. Humphreys et al. found evidence that pericytes give rise to fibroblasts during experimentally induced fibrosis in mice [50]. Given pericyte heterogeneity within the same and between different tissues [3,51–65], the exact contribution of pericytes to fibrosis may vary by organ and pathophysiological condition [66].

Guimarães-Camboa et al. also performed a transaortic constriction in Tbx18-CreERT2/tdTomato mice and found a few examples of pericyte-derived ventricular cardiomyocytes [36]. This result is not surprising as the rate of cardiomyocyte regeneration in adult heart is very low [67,68]. The fact that they found labeled cardiomyocytes supports another study that showed the capacity of pericytes to differentiate into cardiac cells [69].

Although pericytes and vascular smooth muscle cells are both mural cells, they occupy different locations in the vasculature and are defined as two distinct cell types. Since both are labeled in Tbx18-CreERT2/tdTomato mice, determining whether pericytes differentiate into smooth muscle cells in this mouse model is impossible. In the heart, pericytes are the second largest cell population [70], and a recent study showed that during development, they generate smooth muscle cells [71]. Whether they do so in the adult heart remains unknown.

Interestingly, Guimarães-Camboa et al. did not test whether pericytes from Tbx18CreERT2 mice could give rise to osteoblasts, chondrocytes, or odontoblasts in vivo as other studies have reported [36,41,72–74].

Future studies should resolve this controversy. Guimarães-Camboa et al. showed that Pdgfrb-Cre transgenic mice are unsuitable for specific lineage tracing of pericytes because PDGFRβ is expressed throughout the embryo during development. Since its expression is more restricted in adult animals, why did they not use PDGFRβ-CreERT2 mice instead [36,75]? Future work should compare the reported results to results using PDGFRβ-CreERT2, which should mark pericytes in all tissues in Tbx18-CreERT2 mice.

The conclusion that vascular cells do not form adipocytes is very startling; other recent studies in vivo using specific vascular cell-lineage tracing have shown opposite results [73,74,76]. Future studies should be designed to explain these differences. When their vascular cells are labeled, why can Myh11-CreERT2, NG2-CreER, Lepr-cre, and NG2-Cre transgenic mice form fat-storing cells, whereas Tbx18CreERT2 mice cannot? As bone marrow pericytes are labeled in Tbx18-CreERT2/tdTomato mice, future studies should expose them to sublethal irradiation, which induces fat formation in the marrow.

Using Tbx18CreERT2 mice, the authors also conclude that resident pericytes do not form skeletal muscle fibers. However, under the same experimental conditions, but using other mice, several groups came to different conclusions about the in vivo myogenic capacity of skeletal muscle pericytes. Using Alkaline Phosphatase-CreERT2 transgenic mice, Dellavalle et al. demonstrated that pericytes residing in postnatal skeletal muscle differentiate into skeletal muscle fibers and, furthermore, generate satellite cells, the skeletal muscle-specific progenitors [77]. Using NG2-Cre mice, Kostallari et al. demonstrated that pericytes can form myofibers and are indispensable for postnatal skeletal muscle growth. Using a transgenic mouse model for selective diphtheria toxin-induced depletion of NG2+ pericytes, they found that pericyte ablation led to myofiber hypotrophy. This report was the first to show that skeletal muscle formation in vivo depends on myogenic cells other than satellite cells [78]. Future studies should test whether Tbx18+ pericyte depletion in Tbx18-CreERT2/iDTR mice affects the regenerative potential of the skeletal muscle and other organs.

Several studies of pericyte biology focused on developmental events and times when the basement membrane around blood vessels is not fully developed, when pericytes may be more exposed to differentiation cues from their surroundings. Might pericytes exhibit stem cell behavior only when they are removed from their niche and exposed to artificial conditions? Future studies should explore the pericyte response in Tbx18CreERT2 mice at different developmental stages and in tissues like bone marrow, where periendothelial cells are not embedded in a basement membrane.

Note that pericytes from the kidneys, liver, lungs, gastrointestinal tract, and pancreas were not labeled in Tbx18H2B-GFP mice. Why? Given their heterogeneity, do pericytes in these different tissues share specific capabilities? Liver pericytes have been shown to form other cells in vivo using lineage fate tracing specific to hepatic pericytes [49]. What are their origins? Do they develop from a different source than pericytes that express Tbx18? For instance, during development, the origins of pericytes from the liver, lung, and gut have been mapped to the mesothelium [79–81]. In sharp contrast, lineage-tracing studies indicate that forebrain pericytes have a neuroectodermal origin [82]; whereas endothelial cells give rise to cardiac pericytes in the murine embryonic heart [83].

Interestingly, Xu et al. showed the importance of Tbx18 in the normal development of the vasculature in mammalian kidneys, when it is expressed by pericytes. Moreover, they observed a reduction of the number of pericytes around blood vessels in Tbx18-/- mice [84]. Future studies will address when renal pericytes stop expressing Tbx18.

Not all perivascular cells are pericytes, and the expression of Tbx18 in other perivascular cells (i.e., adventitial perivascular cells [85], perivascular fibroblasts [86], perivascular macrophages [87,88]), has not been investigated. Furthermore, vascular smooth muscle cells are also labeled using Tbx18CreERT2/TdTomato mice, perhaps obscuring rare events, such as differentiation to other cell lineages. Flow-cytometric characterization of freshly dissociated cells using this and other genetic lineage-tracing models will provide an accurate quantification of cell fates.

Finally, pericytes have been shown to be heterogeneous even within the same tissue as demonstrated in skin, spinal cord, brain, skeletal muscle, heart, kidney, lung, and bone marrow [42,66,89–94]. According to Guimarães-Camboa et al., $\sim$10% of pericytes were not labeled in the Tbx18CreERT2/TdTomato model, which suggests that a subpopulation of pericytes were not analyzed in their study. Does a rare population of Tbx18$^-$PDGFRβ$^-$ pericytes exist, and can they behave as stem cells? In addition to genetic cell fate mapping, transcriptomic and single-cell analysis represent fundamental tools that will help us to understand the roles of pericytes within the same tissue.

In conclusion, Guimarães-Camboa et al. provide a new and important insight into pericyte biology: pericyte plasticity is limited, and they do not behave as stem cells under

certain conditions [36]. This new concept challenges several studies, not only in vitro, but also in vivo, with other lineage-tracing transgenic mice (Fig. 1). The potential for unraveling whether and how pericytes form other cell types in normal and diseased physiology is limited only by the precision of the distinct Cre alleles that are available. Are pericytes unable to behave like stem cells only in the Tbx18-CreERT2 mouse model? In the coming years, studies defining whether pericytes can act as stem cells and under what conditions may spark new approaches to several pathological conditions. Present in all tissues, pericytes may play important roles in tissue turnover and regeneration.

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Author Disclosure Statement

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