Published in final edited form as:

Cell Mol Neurobiol. 2018 May ; 38(4): 777–782. doi:10.1007/s10571-017-0549-2.

Macrophages generate pericytes in the developing brain

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Abstract

Pericytes are defined by their anatomical location encircling blood vessels walls with their long projections. The exact embryonic sources of cerebral pericytes remain poorly understood, especially because of their recently revealed diversity. Yamamoto et al. (2017) using state-of-the-art techniques, including several transgenic mice models, reveal that a subpopulation of brain pericytes are derived from phagocytic macrophages during vascular development. This work highlights a new possible ancestor of brain pericytes. The emerging knowledge from this research may provide new approaches for the treatment of several neurodevelopmental disorders in the future.

Keywords

pericytes; brain; development; origin

Macrophages are phagocytic cells of the innate immune system that were originally described by the Russian Nobel Prize Elie Metchnikoff (Nathan 2008). These cells play central roles in homeostasis and pathology, including host defense, inflammation, metabolic functions, and tissue remodeling (Gordon and Martinez 2010; Biswas and Mantovani 2010; Sica and Bronte 2007). It is well known that macrophages display plasticity in their characteristics and can change phenotype and functions depending on the microenvironment

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AUTHOR CONTRIBUTIONS

P.H.D.M.P., A.E.P., V.M.A., L.L., J.P.A. and A.B. elaborated the figure. P.H.D.M.P., V.M.A., L.L., J.P.A., A.E.P., G.S.P.S., P.O.A., L.S., G.G.A., R.F., A.M., R.G. and A.B wrote the manuscript. All of the authors discussed the results in Yamamoto et al. (2017) and commented on the manuscript.

DISCLOSURES

The authors declare that there is no conflict of interests regarding the publication of this paper.

where they are located (Perry et al. 2010; Kigerl et al. 2009; Mosser and Edwards 2008). Nevertheless, whether macrophages can differentiate into another cell types remains elusive.

Pericytes are recognized by their anatomical perivascular location, embedded on the capillary walls in a shared basement membrane with endothelial cells (Armulik et al. 2011b; Winkler et al. 2011; Birbrair et al. 2015). The central nervous system has a 1:1 pericyte to endothelial cell ratio; higher than peripheral vascular beds in other tissues (Shepro and Morel 1993; Almeida et al. 2017). In the brain, these cells are uniquely positioned in close contact with neuronal and glial cells forming the neurovascular unit (Armulik et al. 2011b; Winkler et al. 2011). As vascular and neuronal functions are intimately entwined (Iadecola 2004), pericytes control pivotal neurovascular functions necessary for neuronal homeostasis (Winkler et al. 2011; Bell et al. 2010).

Pericytes are formed during both embryonic and postnatal period (Dias Moura Prazeres et al. 2017). Revealing the exact origin of pericytes is a central question in developmental biology. These cells have been shown to be heterogeneous with regard to their origin even within the same tissue (Sims 2000, 1991; Armulik et al. 2011a; Dias Moura Prazeres et al. 2017), and the ontogeny of pericytes subpopulations in distinct tissues continue being discovered. During early embryonic period, part of central nervous system pericytes derive from neuroectodermal neural crest as demonstrated by chimerization experiments (Etchevers et al. 2001; Trost et al. 2016). These initial findings were supported by more recent use of the lineage-tracing Cre/loxP mediated technologies (Simon et al. 2012). Nevertheless, whether all brain pericytes have the same ancestry remains unknown. In a recent article in *Scientific Reports*, Yamamoto and colleagues suggest that a subgroup of pericytes are derived from macrophages in the brain during vascular development (Yamamoto et al. 2017). The authors followed *in vivo* the fate of mature macrophages (F4/80⁺), and found that at E10.5 a subset of these cells associated with brain blood vessels and expressed several pericytic markers. Yamamoto and colleagues also analyzed the brains of lineage-tracing Vav-Cre/R26R^{EYFP} mice. These analyses revealed that cerebrovascular pericytes are labeled in those animals, suggesting Vav⁺ cells as a possible source of central nervous system pericytes. Interestingly, Vav-Cre strains have been shown to target both hematopoietic and endothelial lineages (Crocker et al. 2004; de Boer et al. 2003; Georgiades et al. 2002), thus these results suggest that brain pericytes may be derived from any cell of these lineages. Importantly, recently, Chen and others demonstrated that endothelial cells give rise to one fifth of cardiac pericytes in the embryonic heart (Chen et al. 2016). As neural crest cells do not express recombinase in Vav-Cre mice, these results suggest that the developmental sources of brain pericytes are heterogeneous.

Furthermore, Yamamoto and colleagues found that in Csf1^{op/op} mice, deficient in macrophages, the pericytes number was decreased in the brain, suggesting that macrophages contribute to pericyte coverage during neurovascular development in the brain. Nonetheless, CSF1 and its receptor CSF1R are expressed by multiple cell types besides macrophages (Pixley and Stanley 2004; Chitu and Stanley 2006; Hamilton 2008), including neurons (Luo et al. 2013). Thus, the use of CD169-Cre/iDTR mice, in which tissue-macrophages can be specifically genetically ablated (Chow et al. 2013), will be more appropriate to study the influence of macrophages on pericytes coverage in the developing brain.

Interestingly, the authors showed that not all hematopoietic cells contribute to cerebrovascular pericyte development. Yamamoto and colleagues analyzed pericytes coverage in the embryonic brain of a mouse model with deficiency in cells from the lymphoid lineage (Rag2 knockout). These experiments revealed that NG2+ pericytes are not affected in those mice. This data suggests that, in contrast to F4/80+ macrophages, lymphoid cells do not contribute to pericytes development in the brain.

This study provides a new possible role of macrophages in the developing brain, besides a new unexpected origin for central nervous system pericytes.

PERSPECTIVES / FUTURE DIRECTIONS

Pericytes have been shown to be heterogeneous in their ontogeny (Dias Moura Prazeres et al. 2017). The possible pericytic developmental sources include sclerotomal compartment (Winkler 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; Yamanishi et al. 2012), neuroectoderm (Simon et al. 2012), endothelial cells (Chen et al. 2016), and others (Armulik et al. 2011b). Strikingly, another recent study has shown that some pericytes also derive from the hematopoietic lineage (Yamazaki et al. 2017). To demonstrate this, Yamazaki and colleagues used *in vivo* fate-tracing technologies to track specifically myeloid lineage-derived cells (Yamazaki et al. 2017), suggesting that myeloid lineage progenitor cells originate pericytes. Interestingly, Yamamoto and colleagues show that a subgroup of pericytes derive from F4/80+ mature macrophages. Whether those mature macrophages correspond to all myeloid lineage-derived pericyte-forming cells or whether some myeloid progenitors form pericytes without previously becoming phagocytes remains unknown.

Pericytes are also heterogeneous in their distribution, phenotype and function (Sims 2000, 1991; Armulik et al. 2011a; Birbrair and Delbono 2015; Birbrair and Frenette 2016; Birbrair et al. 2013a; Birbrair et al. 2013d, 2014c; Birbrair et al. 2014d; Coatti et al. 2017), and several subpopulations have been characterized in various tissues (Asada et al. 2017; Khan et al. 2016; Birbrair et al. 2013c; Göritz et al. 2011; Stark et al. 2013), including the central nervous system (Göritz et al. 2011; Birbrair et al. 2014b). In the spinal cord, pericytes that express α SMA and desmin are different from the ones that express the Glutamate aspartate transporter GLAST in phenotype and function (Goritz et al. 2011). In the brain, we identified two pericyte subtypes, type-1 (NG2+/Nestin-GFP-) and type-2 (NG2+/Nestin-GFP+), using a double-transgenic Nestin-GFP/NG2-DsRed mouse (Birbrair et al. 2014b). The cerebral pericyte subsets differ in their functions, as i.e. after brain injury, only type-1 pericytes participate in the scar tissue formation (Birbrair et al. 2014b). Whether the same pericyte subpopulations are present during brain embryogenesis remains unknown. And, more interestingly, which pericyte subset correspond to the ones derived from macrophages should be explored in future studies.

Importantly, not all perivascular cells are pericytes. Other cellular populations have been shown to be located in the same anatomical position: i.e. smooth muscle cells, fibroblasts (Soderblom et al. 2013), adventitial cells (Crisan et al. 2012), and even macrophages (Bechmann et al. 2001; Guillemin and Brew 2004). The key difference between pericytes

and other perivascular cells is the vascular basal lamina covering pericytes (Allsopp and Gamble 1979). As none of pericytic markers are specific, and could be expressed by other cells (Armulik et al. 2011a), the perivascular cells expressing NG2 proteoglycan could be i.e macrophages, not pericytes. As it has already been shown that NG2 could be expressed in those cells (Yotsumoto et al. 2015). Thus, whether the perivascular cells analyzed in the embryonic brain by Yamamoto et al. are pericytes still needs to be clarified. The combination of pericytic molecular markers with immunolabeling of the vascular basal lamina, genetic cell fate mapping, transcriptomic and single cell analysis will confirm the nature and exact origin of those cells in the future.

Notably, the myeloid populations hosted in the brain are also heterogeneous, including parenchymal microglia, perivascular myeloid cells, choroid plexus macrophages, and meningeal macrophages, and they do not respond uniformly to tissue microenvironmental changes (Gordon et al. 2014). The macrophage marker used by Yamamoto and colleagues, F4/80 [also known as EMR1 in humans (Hamann et al. 2007)], is expressed in all these cellular populations (Gordon et al. 2014; Yamamoto et al. 2017). Thus, whether the differentiation capacity to form pericytes is specific to a unique myeloid population, or whether all these cells may become pericytes remains to be elucidated.

Genetically modified mice have been widely applied to study the fate of several cell types within diverse tissues microenvironments (Sena et al. 2017a; Sena et al. 2017b; Andreotti et al. 2017; Borges et al. 2017; Paiva et al. 2017). The ability to follow specific cell populations in mice of different ages including embryos has allowed us to answer specific questions regarding the origins of different cell populations in various organs (Lousado et al. 2017). Yamamoto and colleagues used Vav-Cre/R26R^{EYFP} mice (Yamamoto et al. 2017), in which the whole hematopoietic lineage gets labeled. Future studies should use a macrophage specific Cre-line, such as CD169-Cre/R26R^{EYFP}, to demonstrate that brain macrophages originate a subgroup of pericytes.

In recent years, pericytes' potential to contribute to the formation of several other cell types has been established by numerous studies; and the general consensus holds that pericytes are cells with high plasticity, and could be used for regenerative medicine (Birbrair et al. 2017a; Birbrair et al. 2015). However, there is no evidence whether pericytes can differentiate into the hematopoietic lineage. As a subset of brain pericytes possible derive from hematopoietic cells (Yamazaki et al. 2017), it will be interesting to test whether the reverse also may occur. Are pericytes also able to form hematopoietic cells under certain pathophysiological conditions?

In conclusion, understanding the origin and the cellular processes that drive pericyte formation in the brain is a central question in developmental neuroscience. Whether all cerebral pericytes from the same tissue have the same ancestry remains unknown. Yamamoto and colleagues provide a new and unexpected source for a brain pericyte subpopulation: phagocytic macrophages (Yamamoto et al. 2017). This new knowledge advances our comprehension of brain pericytes biology, which in the future will help us to understand the pericytes roles in several neurodevelopmental disorders.

ACKNOWLEDGMENTS

Alexander Birbrair is supported by a grant from Pro-reitoria de Pesquisa/Universidade Federal de Minas Gerais (PRPq/UFMG) (Edital 05/2016); Akiva Mintz is supported by the National Institute of Health (1R01CA179072-01A1) and by the American Cancer Society Mentored Research Scholar grant (124443-MRSG-13-121-01-CDD).

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Figure 1. Macrophages form pericytes in the developing brain.

Pericytes are present around the brain blood vessels. The study of Yamamoto and colleagues now suggests that macrophages present in the dorsal midbrain of E10.5 embryos may differentiate into pericytes (Yamamoto et al. 2017). Future studies will reveal the origins of other pericyte subpopulations, and whether a specific macrophage subtype have plasticity to differentiate into pericytes.

Table 1.

A Summary of molecular markers discussed in this article

Markers	Description	Reference
Vav1	Expressed in hematopoietic stem cells, endothelial cells, cells in the ovaries and testes and few other lineages.	(Ogilvy et al. 1998; Joseph et al. 2013)
Csf1	Expressed by multiple cell types besides macrophages, including neurons.	(Tushinski and Stanley 1983; Pixley and Stanley 2004; Chitu and Stanley 2006; Hamilton 2008; Luo et al. 2013)
CD169	Specific tissue resident macrophage marker.	(Ohnishi et al. 2013; Chow et al. 2013)
Rag2	Rag2 expressed in lymphoid lineage cells.	(Shinkai et al. 1992)
F4/80	F4/80 is a well-known macrophage marker, although it may be also expressed in other hematopoietic cells.	(Austyn and Gordon 1981)
NG2	It is a membrane proteoglycan found in several cell types, including, oligodendrocyte progenitors and pericytes.	(Birbrair et al. 2014a; Birbrair et al. 2013b)
Nestin	Expressed in several stem cells, including neural stem cells. It is also present in a pericytes' subset.	(Birbrair et al. 2014a; Birbrair et al. 2011; Birbrair et al. 2017b)