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Pericytes modulate myelination in the central nervous system

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Abstract

Multiple sclerosis is a highly prevalent chronic demyelinating disease of the central nervous system. Remyelination is the major therapeutic goal for this disorder. The lack of detailed knowledge about the cellular and molecular mechanisms involved in myelination restricts the design of effective treatments. *De La Fuente et al.* (2017) by using state-of-the-art techniques, including pericyte-deficient mice in combination with induced demyelination, reveal that pericytes participate in central nervous system regeneration. Strikingly, pericytes presence is essential for oligodendrocyte progenitors differentiation and myelin formation during remyelination in the brain. The emerging knowledge from this research will be important for the treatment of multiple sclerosis.

Keywords

pericytes; multiple sclerosis; myelination; central nervous system

Multiple sclerosis is the leading cause of neurological disability, most prevalent in young adults, affecting more than two million people worldwide (Compston and Coles, 2008; Lublin and Reingold, 1996; Milo and Kahana, 2010). Symptomatically, multiple sclerosis patients present fatigue, cognitive deficits, pain, depression, mobility and balance impairment, reduced cardiovascular fitness, weakness, ataxia, bladder dysfunction, pseudobulbar affect, and spasticity (Feinstein et al., 2015). Multiple sclerosis is characterized by demyelination and irreversible axonal damage in the central nervous system (Trapp et al., 1998). Remyelination becomes inefficient and ultimately fails with disease development (Franklin and Ffrench-Constant, 2008). All the current treatments have mainly anti-inflammatory effects and increasing evidence indicates that these therapies are more effective in the early phases of disease progression (Imitola et al., 2006). Due to our

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restricted knowledge about the underlying molecular changes involved in multiple sclerosis progression, these treatments fail to promote remyelination and central nervous system repair. The primary goal to treat these patients with a mechanism-based approach is to reveal the cellular and molecular mechanisms involved in this disability. As remyelination protects against axonal damage and restores axonal conduction in mouse models of multiple sclerosis (Irvine and Blakemore, 2008), therapies inducing remyelination should be beneficial for patients with this disorder. Nevertheless, the lack of a detailed knowledge about the biology of remyelination in the central nervous system restricts the design of effective treatments.

Pericytes are cells defined based on their anatomical location around blood vessel walls (Dias Moura Prazeres et al., 2017). They communicate with endothelial cells along the length of the vasculature by physical contacts and paracrine signaling (Birbrair et al., 2013c). In the central nervous system, the ratio of pericytes to endothelial cells is approximately 1:1 (Shepro and Morel, 1993), indicating the enormous importance of pericytes in the central nervous system physiology. Novel approaches which combine anatomical location with expression of multiple molecular markers, and with genetic lineage tracing became available recently, contributing to the progress in the understanding of pericytes function in health and disease (Birbrair et al., 2015). Besides stabilizing blood vessels, pericytes play important roles in vascular development, maturation, permeability and remodeling (Enge et al., 2002; Hellstrom et al., 2001; Leveen et al., 1994; Lindahl et al., 1997; Soriano, 1994). Moreover, they regulate the blood flow (Pallone et al., 2003), and collaborate with astrocyte to regulate the maintenance of functional integrity of the blood-brain, blood-retinal, and blood-spinal cord barriers (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; Thanabalasundaram et al., 2011). Additionally, pericytes show immune functions by regulating lymphocytes activation (Balabanov et al., 1999; Fabry et al., 1993; Tu et al., 2011; Verbeek et al., 1995), and by attracting innate leukocytes that exit through the sprouting vessels (Stark et al., 2013). Also, they contribute to the clearance of toxic cellular byproducts, can affect blood coagulation, and have direct phagocytic activity (Balabanov et al., 1996; Bouchard et al., 1997; Castejon, 2011; Fisher, 2009; Hasan and Glees, 1990; Jaynes, 1985; Kim et al., 2006; Thomas, 1999). Furthermore, pericytes' capacity to behave as stem cells, forming other cell types, and to regulate other stem cells' activity has been recently demonstrated (Asada et al., 2017). Nevertheless, the pericytes role in myelination either by supplementation of important factors for this process to occur or by differentiation into myelinating cells remains poorly defined.

Now, in a recent article in *Cell Reports*, De La Fuente and colleagues show that pericytes modulate oligodendrocyte progenitors involved in central nervous system regeneration (De La Fuente et al., 2017). Interestingly, following white matter demyelination, pericytes activate and reside near differentiating oligodendrocyte progenitors. The authors used a mouse model of central nervous system demyelination combined with genetic depletion of pericytes to study the role of pericytes during remyelination. Strikingly, their results demonstrated that oligodendrocyte progenitors differentiation and myelin formation are delayed during remyelination in pericytes-deficient mice (De La Fuente et al., 2017). Furthermore, pericytes-derived conditioned medium promotes oligodendrocyte progenitors

differentiation *in vitro*. Also, by using cerebellar slice cultures exposed to pericytes-derived conditioned medium, De La Fuente and colleagues demonstrated that pericyte produced factors enhance remyelination *ex vivo*. Finally, by the use of blocking antibodies and small interfering RNA, the authors identified $\alpha 2$ -chain of laminin (Lama2) as a key pericyte-derived molecule promoting oligodendrocyte differentiation. This work provides a novel role for central nervous system pericytes in myelination. Here, we discuss the findings from this study, and evaluate recent advances in our understanding of the roles of pericytes in multiple sclerosis.

PERSPECTIVES / FUTURE DIRECTIONS

Although pericytes are defined by their anatomical perivascular location, not all perivascular cells are pericytes. Several cells that may share molecular markers with pericytes have been described as perivascular: e.g. i.e. macrophages (Bechmann et al., 2001; Guillemin and Brew, 2004), adventitial cells (Crisan et al., 2012), smooth muscle cells (Asada et al., 2017), and fibroblasts (Soderblom et al., 2013). De La Fuente and colleagues based their pericyte identification on platelet-derived growth factor receptor beta (PDGFR β) expression. Nevertheless, this marker could refer to other cell populations. For instance, PDGFR β is a known marker of fibroblasts in the central nervous system (Soderblom et al., 2013; Spitzer et al., 2012). Although none of brain pericyte markers are specific, when used in combination they clearly distinguish pericytes from other cell types. Recently new molecular markers were described for pericytes, such as Gli1 (Sena et al., 2017) and Tbx18 (Birbrair et al., 2017). Future studies will need to clarify whether the perivascular population of cells activated after demyelination in the brain *in vivo* are pericytes. Also, the combination of immunolabeling of the vascular basal lamina with pericyte molecular markers will confirm the exact nature of those cells.

De La Fuente and colleagues examine pericytes as a homogeneous cell population in their study. Nevertheless, pericytes are heterogeneous in their morphology, distribution, origin, molecular markers, and function (Dias Moura Prazeres et al., 2017). Pericytes associated with different blood vessel types differ in their morphology, markers, and function (Asada et al., 2017; Kunisaki et al., 2013; Morikawa et al., 2002; Nehls et al., 1992). At least two pericyte subpopulations have been described in the central nervous system. Type-1 and type-2 pericytes were distinguished based on the presence or absence of Nestin-GFP expression (Birbrair et al., 2014). Another group identified type-A and type-B pericytes based on their heterogeneous expression of desmin, α smooth muscle actin, and glutamate aspartate transporter (Glast) (Goritz et al., 2011). ATP sensitive potassium channel Kir6.1 only labels a subset of pericytes in the brain (Bondjers et al., 2006). Thus, whether only a fraction of pericytes promote myelination after demyelination still needs to be elucidated. It would be interesting to evaluate whether distinct pericytes' subsets behave differently during myelination. Furthermore, the precise identity of oligodendrocyte progenitors is poorly defined. In a recent study, phenotypically distinct subsets of oligodendrocyte progenitors were identified in the brain (Leong et al., 2014). Whether these oligodendrocyte progenitors subpopulations interact differently with pericytes could be an interesting topic to be explored.

The findings from De La Fuente et al. (2017) are based on the data obtained from $\text{Pdgfr}^{\text{ret/ret}}$ mice, which have altered tissue distribution of PDGFR β protein due to loss of a proteoglycan binding motif, as a genetic model for pericyte deficiency to study toxin-induced demyelination (Armulik et al., 2010; De La Fuente et al., 2017). However, some abnormalities were previously described in those mice not necessarily pericyte absence-related, such as retarded growth (Lindblom et al., 2003), and progressive brain calcification (Keller et al., 2013). PDGFR β may be important also for other cell types, as during embryogenesis, PDGFR β is broadly expressed in multiple cellular lineages throughout the embryo (Guimaraes-Camboa et al., 2017). Thus, it is possible that $\text{Pdgfr}^{\text{ret/ret}}$ mice are deficient in several other cell populations important in the remyelination process, besides pericytes. This should be explored in future studies.

De La Fuente and colleagues used toxin-induced demyelinating mouse models. These models provide clues for the understanding of molecular mechanisms of remyelination. To determine the extent, to which these factors or mechanisms are relevant for multiple sclerosis requires analysis of respective lesions in other mouse models of multiple sclerosis and in human patients. Several animal models currently available have provided indispensable contribution to our understanding of mechanisms relevant for multiple sclerosis pathogenesis (Steinman, 1996). For instance, experimental autoimmune encephalomyelitis is thought to model the mechanisms involved in multiple sclerosis (Gold et al., 2006; Rivers et al., 1933). Future studies should explore the role of pericytes in these models combined with genetic ablation, and lineage-tracing of pericytes. Additionally, it will be interesting to explore whether pericytes stimulate myelination during embryonic development in the brain in physiologic conditions.

Pericytes are highly plastic, and have the ability to differentiate into different cell types, including osteoblasts (Khan et al., 2016), myoblasts (Birbrair et al., 2013d), adipocytes (Birbrair et al., 2013a), fibroblasts (Birbrair et al., 2014), smooth muscle cells (Birbrair et al., 2013c), and chondrocytes (Asada et al., 2017). Due to this multipotency, pericytes are potential targets for tissue repair and regenerative medicine (Birbrair et al., 2015). Recent studies suggest that pericytes also have the ability to differentiate into neural and glial cells (Dore-Duffy et al., 2006; Karow et al., 2012; Nakagomi et al., 2015; Paul et al., 2012). Interestingly, pericytes differentiate into oligodendrocyte progenitors *in vitro* (Birbrair et al., 2013b). Nevertheless, cell culture systems are characterized by high concentration of mitogens and artificial conditions which may induce differentiation ability that could not be shared by the corresponding endogenous cells *in vivo*. Genetic fate-tracing mouse models are the most reliable tools for assessing cell plasticity *in vivo*. Thus, it will be interesting to evaluate whether brain pericytes have the ability to differentiate into the oligodendrocyte lineage *in vivo* under physiologic conditions as well as during remyelination after central nervous system damage.

Cell therapy remains a promising, but still challenging, treatment for different central nervous system disorders (Martinez-Morales et al., 2013). Multiple cell types from a variety of sources have been proposed to treat multiple sclerosis (Rice et al., 2013). De La Fuente and colleagues offer a new candidate and renewed hope for cell therapy in multiple sclerosis: the pericyte (De La Fuente et al., 2017). Nonetheless, proposed novel treatments must

achieve more than just the replacement of lost oligodendrocytes, as several other alterations occur in the central nervous system during multiple sclerosis progression. Thus, future studies should explore whether pericytes have other abilities in addition to their production of bioactive molecules that promote myelination. For instance, can pericytes exert immunomodulatory and neuroprotective effects? Do they interact with other central nervous system cells, such as resident neural stem cells? If they do, beyond multiple sclerosis, pericytes properties could be exploited to contribute to the treatment of other neurodegenerative diseases.

Pericytes release multiple bioactive molecules able to regulate proliferation and migration of central nervous system progenitor cells (Choe et al., 2014; Maki et al., 2015). Thus, pericytes can induce a regenerative milieu in the brain. De La Fuente and colleagues show that *in vitro* and *ex vivo* pericyte-derived Lama2 mediate oligodendrocyte progenitor differentiation. Transgenic mice have been widely applied to study distinct cell types within tissues microenvironments. The ability, not only to ablate cells, but also to delete single genes in specific cellular populations in adult mice has allowed us to answer specific questions regarding the roles of different cell subsets in the regulation of several physiologic processes. The exact molecular mechanism of oligodendrocyte progenitors differentiation *in vivo* is yet unclear, and will need to be revealed in future studies. Lama2 has not been conditionally deleted from pericytes or from other possible sources, so there is no direct evidence that pericytes are the only/main functionally important source of Lama2 for oligodendrocyte progenitors differentiation. The generation of Lama2 floxed mice to be crossed with pericyte-specific inducible CreER driver will allow us to specifically delete Lama2 in pericytes *in vivo*. In addition to studies in genetic mouse models, transcriptomic and single cell analysis represent fundamental tools that will help us understand the role of pericytes in multiple sclerosis.

Multiple sclerosis is presumed to be an inflammatory disease, characterized by autoimmune attack against the myelin components (Nylander and Hafler, 2012). Thus, extensive efforts have been done to characterize the peripheral immune cells that become mobilized to enter the central nervous system in this disorder. These experiments have provided the rationale for multiple sclerosis treatment through immunomodulation (Dendrou et al., 2015). Recent studies suggest that pericytes display a variety of immune properties (Stark et al., 2018). For instance, pericytes overexpress essential adhesion molecules, such as VCAM-1 and ICAM-1, involved in the control of immune cell trafficking across the vasculature (Guijarro-Munoz et al., 2014), and secrete a big repertoire of chemokines (Asada et al., 2017). Nevertheless, pericytes roles are complex, and our understanding of the crosstalk of pericytes with immune cells is still limited. Thus, what is the relationship between distinct immune cell populations involved in multiple sclerosis and brain pericytes remains to be studied.

Demyelination is a pathologic process of destruction of myelin-supporting cells not only in the central nervous system, as the primary site of demyelination could be in the peripheral nervous system (Lampert, 1978). In the periphery, Schwann cells produce the myelin sheath insulating neuronal axons (analogous to oligodendrocytes in the central nervous system) (Lousado et al., 2017). It will be interesting to explore whether pericytes also affect

Schwann cells myelination in demyelinating disorders that affect the peripheral nervous system, such as Guillain-Barré syndrome (Burns, 2008), chronic inflammatory demyelinating polyradiculoneuropathy (Hughes and Mehndiratta, 2012), paraproteinemic demyelinating neuropathy (Mehndiratta et al., 2004), copper deficiency (Narayan and Kaveer, 2006), and Charcot marie tooth type 1 and type X (Mehndiratta and Gulati, 2014).

In conclusion, the study by De La Fuente and colleagues reveal a novel important role of pericytes in central nervous system myelination. However, our understanding of pericytes biology in multiple sclerosis still remains limited, and the complexity and interactions of different cellular components of the brain microenvironment during this disease progression should be elucidated in future studies.

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Figure 1. Pericytes activate oligodendrocyte progenitor differentiation through Lama2 production.

Pericytes are present around the brain blood vessels. The study of De La Fuente and colleagues now reveals a novel very important function for pericytes in the central nervous system remyelination (De La Fuente et al., 2017). Pericyte-derived Lama2 mediate oligodendrocyte progenitors differentiation, and absence of pericytes leads to reduction in remyelination after toxin-induced demyelination in the brain.