Pericytes Stimulate Oligodendrocyte Progenitor Cell Differentiation during CNS Remyelination

Graphical Abstract

Highlights
- CNS-resident PCs react to demyelination and are found close to differentiating OPCs
- PC-deficient mice show delayed OPC differentiation during CNS remyelination
- PC-conditioned medium accelerates OPC differentiation and enhances remyelination
- PC-derived LAMA2 induces OPC differentiation

In Brief
Following toxin-induced demyelination in PC-deficient mice and using a number of in vitro approaches, Guzman de la Fuente et al. show that CNS pericytes (PCs) respond to demyelination and, through Lama2 secretion, stimulate oligodendrocyte progenitor cell differentiation during remyelination. These findings extend PC function beyond vascular homeostasis toward regeneration.

Authors
Alerie Guzman De La Fuente, Simona Lange, Maria Elena Silva, ..., Ludwig Aigner, Robin J.M. Franklin, Francisco J. Rivera

Correspondence
francisco.rivera@uach.cl

Report
De La Fuente et al., 2017, Cell Reports 20, 1755–1764
August 22, 2017 © 2017 The Authors.
http://dx.doi.org/10.1016/j.celrep.2017.08.007
Pericytes Stimulate Oligodendrocyte Progenitor Cell Differentiation during CNS Remyelination

Alerie Guzman De La Fuente,1,17 Simona Lange,2,17 Maria Elena Silva,1,2,3,4,5,6 Ginez A. Gonzalez,1 Herbert Tempfer,3,7,8 Peter van Wijngaarden,1,9 Chao Zhao,1 Ludovica Di Canio,1 Andrea Trost,2,3,10 Lara Bieler,3,11 Pia Zaurnair,10 Peter Rotheneichner,5,11 Anna O’Sullivan,11 Sebastien Couillard-Despres,3,11 Oihana Errea,1 Maarja A. Mäe,12 Johanna Andrae,12 Liqun He,13 Annika Keller,14 Luis F. Bátiz,4,15 Christer Betsholtz,5,16 Ludwig Aigner,7 Robin J.M. Franklin,1,18 and Francisco J. Rivera1,2,3,4,5,16,19,18

1Wellcome Trust and MRC Cambridge Stem Cell Institute, University of Cambridge, Cambridge CB20AH, UK
2Institute of Molecular Regenerative Medicine, Paracelsus Medical University Salzburg, 5020 Salzburg, Austria
3Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TRECS), Paracelsus Medical University Salzburg, 5020 Salzburg, Austria
4Laboratory of Stem Cells and Neuroregeneration, Institute of Anatomy, Histology and Pathology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile
5Center for Interdisciplinary Studies on the Nervous System (CISNe), Universidad Austral de Chile, Valdivia, Chile
6Institute of Pharmacy, Faculty of Sciences, Universidad Austral de Chile, Valdivia, Chile
7Institute for Tendon and Bone Regeneration, Paracelsus Medical University Salzburg, 5020 Salzburg, Austria
8Integrated Cardio Metabolic Center (ICMC), Karolinska Institutet Novum, 141 57 Huddinge, Sweden
9Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Ophthalmology, Department of Surgery, University of Melbourne, Australia
10Ophthalmology/Optometry and Research Program for Experimental Ophthalmology, Paracelsus Medical University Salzburg, 5020 Salzburg, Austria
11Institute of Experimental Neuroregeneration, Paracelsus Medical University Salzburg, 5020 Salzburg, Austria
12Department of Immunology, Genetics and Pathology, Rudbeck Laboratory, Uppsala University, 751 85 Uppsala, Sweden
13Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin Neurological Institute, Key Laboratory of Post-Neuroinjury Neuro-Repair and Regeneration in Central Nervous System, Ministry of Education and Tianjin City, Tianjin 300052, China
14Division of Neurosurgery, Zürich University Hospital, Zürich University, 8091 Zürich, Switzerland
15Centro de Investigación Biomédica (CIB), Facultad de Medicina, Universidad de los Andes, Santiago, Chile
16Integrated Cardio Metabolic Center (ICMC), Karolinska Institutet Novum, 141 57 Huddinge, Sweden
17These authors contributed equally
18Senior author
19Lead Contact

Correspondence: francisco.rivera@uach.cl
http://dx.doi.org/10.1016/j.celrep.2017.08.007

SUMMARY

The role of the neurovascular niche in CNS myelin regeneration is incompletely understood. Here, we show that, upon demyelination, CNS-resident pericytes (PCs) proliferate, and parenchymal non-vessel-associated PC-like cells (PLCs) rapidly develop. During remyelination, mature oligodendrocytes were found in close proximity to PCs. In Pdgfβ+/ret/ret mice, which have reduced PC numbers, oligodendrocyte progenitor cell (OPC) differentiation was delayed, although remyelination proceeded to completion. PC-conditioned medium accelerated and enhanced OPC differentiation in vitro and increased the rate of remyelination in an ex vivo cerebellar slice model of demyelination. We identified Lama2 as a PC-derived factor that promotes OPC differentiation. Thus, the functional role of PCs is not restricted to vascular homeostasis but includes the modulation of adult CNS progenitor cells involved in regeneration.

INTRODUCTION

Although the adult mammalian CNS has a limited capacity for regeneration, lost oligodendrocytes and the myelin they produce are restored during remyelination. In response to demyelination, oligodendrocyte progenitor cells (OPCs) proliferate and migrate to the lesion, where they differentiate into remyelinating oligodendrocytes (Franklin and Ffrench-Constant, 2008; Zawadzka et al., 2010). Remyelination restores saltatory conduction and ensures axonal survival, and its impairment renders demyelinated axons vulnerable to irreversible degeneration (Franklin et al., 2012). Thus, promoting remyelination is a major therapeutic objective in chronic demyelinating diseases such as multiple sclerosis, where remyelination becomes increasingly inefficient with disease progression (Goldschmidt et al., 2009).

Myelination during development is strictly coupled to angiogenesis (Yuen et al., 2014), where OPCs use the vasculature as scaffolds for migration (Tsai et al., 2016). Similarly, regeneration in the CNS is coupled to the vascular niche (Manavski et al., 2012). The CNS vascular niche consists of endothelial cells (ECs), vasculature-associated cells such as perivascular cells, astrocytes, neurons, OPCs, molecules derived from these cells, and blood-derived elements. Pericytes (PCs), which are located
Figure 1. Pericytes React to Demyelination
(A) Ethidium bromide-induced demyelinated lesion in the CCP of adult rats.
(B) PDGFRb expressing PC and RECA-1+ ECs in NAWM.

(legend continued on next page)
RESULTS

Pericytes Respond to CNS Demyelination

We first analyzed the proliferative response and localization of ECs and PCs following induction of white matter demyelination upon injection of ethidium bromide into the caudal cerebellar peduncles (CCPs) of adult rats (Figure 1A). In this model, demyelination occurs within 24 hr of injection and induces OPC proliferation and migration, which peaks at 5 days post-lesion induction (dpl), followed by OPC differentiation, which is ongoing at 14 dpl. Remyelination is completed by 21 dpl. There was a significant increase in proliferating (Ki67-positive) rat endothelial cell antigen 1 (RECA-1)-expressing ECs and a robust proliferative response of platelet-derived growth factor receptor beta (PDGFRb)-expressing cells to regulation of OPC migration during cortical development (Choe et al., 2014). Here we analyzed PCs, their response to a demyelinating lesion, and their functional role in oligodendrocyte differentiation during remyelination. In vivo relevance was studied through a genetic mouse model with reduced pericyte coverage. Moreover, molecular and cellular analysis identified the PC-derived factor modulating OPC differentiation.

Impaired Oligodendrocyte Differentiation during Remyelination in PC-Deficient Mice

To determine whether CNS-resident PCs influence remyelination, we used Pdgfbret/ret mice, in which a mutation in the retenit motif of the Pdgfb gene causes a 75%–85% reduction in capillary PC coverage compared with heterozygous littermates (Figure 2A; Armulik et al., 2010; Lindblom et al., 2003). PDGFRb was still expressed in these mice and can still be used as a marker for residual pericytes.

We first examined myelination in Pdgfbret/ret mice and found that, on post-natal day 12 (P12), the density of mature oligodendrocytes (Olig2+/APC+) was lower and the density of OPCs (Olig2-/APC-) higher than in control mice. However, on P17, no differences were observed in OPC differentiation and myelination (Figure S2).

Following lysolecithin-induced demyelination in the ventral spinal cord white matter (WM), the number of PDGFRb+ cells at 5 dpl was less than in control mice, and there were fewer PLCs. However,
Figure 2. OPC Differentiation Is affected during Remyelination in Pdgfb<sup>ret/ret</sup> Mice

(A and B) Illustrations of decreased PC coverage in Pdgfb<sup>ret/ret</sup> mice (A) and of lysolecithin-induced demyelination (B).

(C and J) Mature oligodendrocytes (Olig2+/APC+) and OPCs (Olig2+/APC−) in lesions of control and Pdgfb<sup>ret/ret</sup> mice at 14 dpl (C) and 21 dpl (J).

(D–G and K–N) Quantitative analyses of oligodendroglia at 14 dpl (D–G) and 21 dpl (K–N).

(H and I) In situ hybridization and quantification for PLP of control and Pdgfb<sup>ret/ret</sup> mice at 14 dpl.

(O and P) Toluidine blue staining of remyelination in control and Pdgfb<sup>ret/ret</sup> mice at 21 dpl (O) and its quantification by relative ranking analysis (P).

Means ± SEM are shown. Data were analyzed by Student’s t test or Mann-Whitney U test. *p < 0.05, **p < 0.01, ***p < 0.001. Scale bars, 100 μm.
by 14 dpl, the density of PDGFRb+ cells was the same in both groups because of a higher proliferative response of these cells in the Pdgfb0/0 mice (Figures S3A–S3F). No differences were detected in the astrocyte or in the macrophage/microglial response between Pdgfb0/0 mice and control mice (Figures S3G–S3I). Microglia/macrophages showed the same pro-inflammatory and anti-inflammatory cell profile distribution in both groups (Figures S3J–S3L), and no differences were detected in BBB stability in the lesion area (Figures S3M–S3Q).

The total number of Olig2+ cells within the lesion was reduced in Pdgfb0/0 mice compared with controls at 14 dpl. There was no significant difference in the number of Olig2+/APC– OPCs between Pdgfb0/0 and control mice (Figures 2C and 2E). However, the number of Olig2+/APC+ mature oligodendrocytes was significantly reduced in Pdgfb0/0 mice (Figures 2C, 2F, and 2G).

In situ hybridization for proteolipid protein (PLP), a major myelin component, generated consistent results (Figures 2H and 2I). However, the densities of Olig2+ cells and Olig2+/APC+ oligodendrocytes were the same in both groups by 21 dpl (Figures 2J–2N). No differences were detected in the extent of remyelination, as assessed by ranking analysis of toluidine blue-stained resin sections in which demyelinated and remyelinated axons were discernable (Figures 2O and 2P).

These data indicate that Pdgfb0/0 mice show a delay in OPC differentiation because of the decreased numbers of PDGFRb+ cells at the earlier stages following demyelination. However, because the PDGFRb+ cell numbers normalize by 14 dpl, this delay does not translate into a decrease in remyelination.

PCs Promote OPC Differentiation and Enhance Remyelination Ex Vivo

We next examined how PCs might directly influence OPC function. We therefore exposed cultured OPCs to PC-conditioned medium (PC-CM) and evaluated the rate of differentiation. MSC-conditioned medium (MSC-CM), previously identified as a strong inducer of OPC differentiation (Jadasz et al., 2013), was used as a positive control. Primary PCs exhibiting MSCs features, including mesenchymal differentiation potential, were isolated from adult rat brains (Figure 3A; Figures S4B–S4D).

Upon incubation with PC-CM, a higher proportion of OPCs had acquired 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNP) and myelin basic protein (MBP) expression at 2 days in vitro (DIV) compared with those exposed to non-conditioned control medium (Figures 3B–3D). We also found a significantly higher proportion of NG2+/Olig2+ OPCs in the PC-CM-treated cultures (Figures 3B and 3E). This effect was likely due to an anti-apoptotic effect of the PC-CM because PC-CM significantly decreased the proportion of caspase-3-positive OPCs compared with control conditions (Figure 3F). Proliferation, assessed by Ki67 staining, was not affected by PC-CM (Figure 3G).

We next examined whether PCs can enhance remyelination. We used postnatal rat-derived cerebellar organotypic slice cultures as an ex vivo model of remyelination (Yuen et al., 2013; Zhang et al., 2011). In this model, P10 rat cerebellar slices were demyelinated using lysolecithin (Birgbauer et al., 2004) and then exposed to PC-CM or control medium (Figure 3H). Remyelination was analyzed at 0, 2, 4, 6, and 8 days after lysolecithin treatment by immunohistochemical staining for MBP and neurofilament heavy chain (NFH). PC-CM significantly enhanced the remyelination rate after lysolecithin-induced demyelination (Figures 3I and 3J).

PC-Induced OPC Differentiation Is Mediated through Lama2

We have previously shown that Lama2 mRNA expression is decreased in the microvessels of Pdgfb0/0 mice compared with control mice (Armulik et al., 2010; Figure 4B). The Lama2 gene product is highly expressed during remyelination (Zhao et al., 2009) and has been shown to modulate OPC function (Relucio et al., 2012). Given that the main source of Lama2 within the microvessels is PDGFRb+ cells, as shown by RNA sequencing (RNA-seq) (He et al., 2016; Figure 4A), we investigated whether Lama2 is a mediator of the PC-induced effect on OPC differentiation. RNA in situ hybridization of healthy brain sections revealed a specific expression of Lama2 in cells expressing the PC markers PDGFRb and CD13 (Figure 4D). In control mice, Lama2 was mainly detected around cell bodies and processes of PCs, whereas Pdgfb0/0 mice had less Lama2 protein expression that, when present, was always associated with residual PCs (Figure 4E). Cultured PCs also expressed Lama2 (Figure 4C). Pre-incubation of PC-CM with an anti-Lama2 antibody resulted in a significant decrease in the Olig2+/CNP+ and Olig2+/MBP+ populations compared with PC-CM pre-incubated with a general immunoglobulin G (IgG), reducing OPC differentiation to a level indistinguishable from control conditions (Figures 4F and 4G). These results were replicated in OPCs exposed to PC-CM harvested from PCs treated with either non-targeting or Lama2 small interfering RNA (siRNA) for 48 hr (Figures 4H and 4I). Taken together, these data identify Lama2 as a PC-derived molecule that promotes OPC differentiation.

DISCUSSION

This work reveals an unidentified role of PCs in CNS regeneration. We show that PCs in the vessel walls respond to...
demyelination by proliferation. We describe a parenchymal cell population expressing PC markers such as PDGFRb and desmin that appears soon after the induction of demyelination. Although these cells express PC markers, we cannot be certain of their origin, and, therefore, we refer to them as PLCs. Upon demyelination, both PCs and PLCs have a high proliferative response; however, mature oligodendrocytes are preferentially located in higher frequency close to PCs. These data suggest that, even though both populations respond to demyelination, they may have differential roles in their interaction with OPCs during remyelination, which will require further investigation. In mice with a reduced PC density, OPC differentiation is delayed in the demyelinated lesion, resulting in fewer mature oligodendrocytes at 14 dpl. Moreover, exposure to PC-CM accelerated OPC differentiation and enhanced ex vivo remyelination. We identified Lama2 as a key factor responsible for the effect of PCs in promoting OPC differentiation.

In humans, loss of LAMA2 gene expression causes WM abnormalities, manifested at an early postnatal age, when developmental myelination occurs (Allamand and Guicheney, 2002). Similarly, a mouse model for Lama2 deficiency (Lama2<sup>−/−</sup>) shows developmental delays in oligodendrocyte differentiation and the accumulation of OCPs, leading to defects in myelination in the corpus callosum (Chun et al., 2003; Relucio et al., 2012). Lama2 regulates OPC function through its interaction with dystroglycan (Leiton et al., 2015). In the CNS, Lama2 is expressed by PCs and upregulated during OPC differentiation (14 dpl) in a toxin-induced demyelination model (Zhao et al., 2009). Lama2 seems to be relevant for PC function because Lama2<sup>−/−</sup> mice have decreased microvascular PC coverage associated with BBB defects (Menezes et al., 2014). Our data suggest that PC-derived Lama2 has a key role in promoting OPC differentiation because the PC-CM effect in OCPs was inhibited when exposed to an anti-Lama2 antibody or when PCs were treated with Lama2 siRNA. Consistent with this, we observed that OPC differentiation was delayed in adult Pdgfb<sup>ret/ret</sup> mice after lyssolecithin-induced demyelination. These findings indicate that PCs provide an appropriate milieu for differentiating OPCs through Lama2.

This study indicates that PC functions are not restricted to vascular homeostasis but, rather, extend to CNS regeneration. This is supported by studies illustrating that PCs respond with high proliferation to acute lesions such as stroke or spinal cord injury (SCI), where they modulate inflammation or the formation of fibrotic scar tissue (Göritz et al., 2011; Özen et al., 2014).

There we show that, besides stabilizing CNS vasculature and regulating EC function, pericytes also have a high proliferative response following CNS demyelination and directly influence CNS-resident progenitor cell differentiation during remyelination, most likely by secretion of Lama2.

**EXPERIMENTAL PROCEDURES**

**Animal Work**

Animal experiments within this research have been regulated under the Animals (Scientific Procedures) Act 1986 Amendment Regulations 2012 following ethical review by the University of Cambridge Animal Welfare and Ethical Review Body (AWERB) in accordance with United Kingdom Home Office regulations (Project License 70/7715) and in accordance with Austrian laws on animal experimentation and were approved by Austrian regulatory authorities (Permit No. BMWF-66.012/0001-Ii/3b/2014; license codes BMWF-66.012/0037-WF/V/3b/2014 and BMWF-66.012/0032-WF/V/3b/2015). During this study, 2- to 3-month-old Sprague Dawley rats and 12-week-old Pdgfb<sup>ret/ret</sup> mice (hetero- and homozygous), which were previously described by Armulik et al. (2010) and Lindblom et al. (2003), were used for toxin-induced demyelination.

**Cell Culture**

Preparation of CNS pericytes was performed following the Dore-Duffy protocol (Dore-Duffy et al., 2008) with modifications. Rat bone marrow-derived MSCs were prepared as described previously by Rivera et al. (2006). OCPs were prepared from neonatal P0–P2 Sprague-Dawley rats, cortices and hippocampi were digested with papain solution, and dissociated cells were seeded into poly-D-lysine-coated T75 flasks. Mixed glial cultures were kept for 11 DIV in medium with DMEM (Gibco) and 10% fetal bovine serum (Biosera). OCPs were isolated as described previously (McCarthy and de Vellis, 1983).

**Organotypic Cerebellar Slices**

Remyelination of rat cerebellar slices was prepared as described previously (Birgubauer et al., 2004). After 7 DIV, the medium was replaced with organotypic slice medium containing 0.5 mg/mL lyssolecithin for 16 hr. After 16 hr, the medium was replaced with PC-conditioned organotypic slice medium and non-conditioned control medium.

**Statistical Analyses**

Graphs show mean values ± SEM, and statistical analysis were performed using GraphPad Prism 5.0 (GraphPad) and SPSS 20 (IBM). Parametric one-way ANOVA, Tukey post hoc analyses, Student’s t test, or Mann-Whitney U tests (when not normally distributed) were used when comparing one parameter. For statistical analysis with two parameters, such as time course experiments with different treatments, two-way ANOVA with Bonferroni post hoc was used. For distance frequency distribution analysis, chi-square test was used.
was used (Figure 1M; Figures S1G and S1H). All experiments were performed as indicated by n in the figure legends. Significance was as follows: *p* < 0.05, **p** < 0.01, and ***p*** < 0.001.

For further details, see the Supplemental Experimental Procedures.

**SUPPLEMENTAL INFORMATION**

Supplemental Information includes Supplemental Experimental Procedures and four figures and can be found with this article online at http://dx.doi.org/10.1016/j.celrep.2017.08.007.

**AUTHOR CONTRIBUTIONS**

S.L. and F.J.R. conceived the project. A.G.D.L.F., S.L., L.A., R.J.M.F., and F.J.R. designed the study. S.L., A.G.D.L.F., L.F.B., C.B., L.A., R.J.M.F., and F.J.R. wrote and edited the manuscript. S.L. and A.G.D.L.F. designed the figures. A.G.D.L.F., S.L., H.T., C.Z., A.K., G.A.G., L.D.C., M.A.M., J.A., C.B., R.J.M.F., L.A., and F.J.R. planned the experiments. A.G.D.L.F., S.L., M.E.S., P.v.W., P.R., O.E., C.Z., G.A.G., A.K., M.A.M., J.A., and L.D.C. conducted the experiments. A.G.D.L.F., S.L., H.T., C.Z., A.K., P.R., A.O., L.B., A.K., M.A.M., J.A., and F.J.R. collected data. A.G.D.L.F., S.L., M.E.S., G.A.G., L.D.C., C.Z., P.R., A.T., L.H., A.K., M.A.M., J.A., and L.D.C. analyzed data. A.G.D.L.F., S.L., P.R., G.A.G., A.K., M.A.M., J.A., C.B., R.J.M.F., L.A., and F.J.R. interpreted data. H.T., A.T., P.R., A.O., P.Z., S.C.D., and L.B. assisted technically. R.J.M.F., L.A., and F.J.R. supervised the project. C.B., L.A., R.J.M.F., and F.J.R. supported this study financially.

**ACKNOWLEDGMENTS**

We thank Hannelore Bauer, Peter Hammerl, and Andreas Traweger for technical advice and support. This work was supported by research funds from Chilean FONDECYT Program CONICYT Grants 1161787 (to F.J.R.) and 1141015 (to L.F.B.) and Stand-Alone Grant E-12/15/077-RIV (to F.J.R. and A.T.); the European Union Seventh Framework Program (FP7/2007-2013) under Grant Agreements HEALTH-F2-2011-278580 (INMIND), HEALTH-F2-2011-279288 (IDEA), and F7-REPQOT-316120 (GlowBrain); Austrian Science Fund FWF Special Research Program (SFB) F44 (F4143-B23) “Cell Signaling in Chronic CNS Disorders”; and State Programs d’avenir” IHU-A-ICM and Obra Social La Caixa, the Swedish Science Foundation (2015-00550), the Swedish Cancer Foundation (15 0735), the Knut and Alice Wallenberg Foundation (2015.0030), the European Research Council (AdG 294556 BBBARRIER), and the Leducq Foundation (14CVD02). P.v.W. was supported by National Health & Medical Research Council of Australia Early Career Fellowship 628928. Work in A.K.’s group was funded by the Swiss National Science Foundation (31003A_159514/1; http://www.snf.ch/en/) and TheSynopsis Foundation (http://www.alzheimer-synapsis.ch).

Received: May 9, 2016
Revised: May 6, 2017
Accepted: July 28, 2017
Published: August 22, 2017

**REFERENCES**

Allamand, V., and Guicheney, P. (2002). Merosin-deficient congenital muscular dystrophy, autosomal recessive (MDC1A, MIM#156225, LAMA2 gene coding for alpha2 chain of laminin). Eur. J. Hum. Genet. 10, 91–94.

Armulk, A., Genové, G., Mäe, M., Nisancioglu, M.H., Wallgard, E., Niaudet, C., He, L., Norlin, J., Lindblom, P., Strittmatter, K., et al. (2010). Pericytes regulate the blood-brain barrier. Nature 468, 557–561.

Birgbaue, E., Rao, T.S., and Webb, M. (2004). Lysosome-CB induces demyelination in vitro in a cerebellar slice culture system. J. Neurosci. Res. 78, 157–166.

Chen, C.W., Montelatici, E., Crisan, M., Corselli, M., Huard, J., Lazzari, L., and Pèaunt, B. (2009). Pervascular multi-lineage progenitor cells in human organs: regenerative units, cytokine sources or both? Cytokine Growth Factor Rev. 20, 429–434.

Choe, Y., Huyhn, T., and Pleasure, S.J. (2014). Migration of oligodendrocyte progenitor cells is controlled by transforming growth factor (i) family proteins during corticogenesis. J. Neurosci. 34, 14973–14983.

Chun, S.J., Rasband, M.N., Sidman, R.L., Habi, A.A., and Vartanian, T. (2003). Integrin-linked kinase is required for laminin-2-induced oligodendrocyte cell spreading and CNS myelination. J. Cell Biol. 163, 397–408.

Crisan, M., Yap, S., Castella, L., Chen, C.W., Corselli, M., Park, T.S., Andriolo, G., Sun, B., Zheng, B., Zhang, L., et al. (2008). A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell 3, 301–313.

Dore-Duffy, P., Katsychev, A., Wang, X., and Van Buren, E. (2006). CNS microvascular pericytes exhibit multipotential stem cell activity. J. Cereb. Blood Flow Metab. 26, 613–624.

Franklin, R.J., and Ffrench-Constant, C. (2008). Remyelination in the CNS: from biology to therapy. Nat. Rev. Neurosci. 9, 839–855.

Franklin, R.J., Ffrench-Constant, C., Edgar, J.M., and Smith, K.J. (2012). Neuroprotection and repair in multiple sclerosis. Nat. Rev. Neurol. 8, 624–634.

Goldschmidt, T., Antel, J., König, F.B., Bruck, W., and Kuhlmann, T. (2009). Remyelination capacity of the MS brain decreases with disease chronicity. Neurology 72, 1914–1921.

Görtür, C., Dias, D.O., Tomilin, N., Barbacid, M., Shupliakov, O., and Frisén, J. (2011). A pericyte origin of spinal cord scar tissue. Science 333, 238–242.

He, L., Vanlandewijck, M., Rascperger, E., Andouloussi Mäe, M., Jung, B., Lebouvier, T., Ando, K., Hofmann, J., Keller, A., and Betsholtz, C. (2016). Analysis of the brain mural cell transcriptome. Sci. Rep. 6, 35108.

Jadass, J.J., Kremer, D., Göttle, P., Tzekova, N., Domke, J., Rivera, F.J., Ad- jaye, J., Hruby, H.P., Aigner, L., and Küpp, P. (2013). Mesenchymal stem cell conditioning promotes rat oligodendroglial cell maturation. PLoS ONE 8, e71814.

Lange, S., Trost, A., Tempfer, H., Bauer, H.C., Bauer, H., Rohde, E., Rettsamer, H.A., Franklin, R.J., Aigner, L., and Rivera, F.J. (2013). Brain pericyte plasticity as a potential drug target in CNS repair. Drug Discov. Today 17, 456–463.

Leiton, C.V., Aramolate, A., Eyermann, C., Menezes, M.J., Escobar-Hoyos, L.F., Husain, S., Winder, S.J., and Colognato, H. (2015). Laminin promotes metalloproteinase-mediated dystroglycan processing to regulate oligodendrocyte progenitor cell proliferation. J. Neurochem. 135, 522–538.

Lindblom, P., Gerhardt, H., Liebner, S., Abramsson, A., Enge, M., Hellstrom, M., Backstrom, G., Fredriksson, S., Landegren, U., Nystrom, H.C., et al. (2003). Endothelial PDGF-BB retention is required for proper investment of pericytes and oligodendrocyte precursor cells in perivascular regions of cerebral white matter. Neurosci. Lett. 357, 1835–1840.

Maki, T., Maeda, M., Uemura, M., Lo, E.K., Terasaki, Y., Liang, A.C., Shindo, A., Choi, Y.K., Taguchi, A., Matsuyama, T., et al. (2015). Potential interactions between pericytes and oligodendrocyte precursor cells in perivascular regions of cerebral white matter. Neurosci. Lett. 597, 164–169.

Manavski, Y., Boon, R.A., and Dimmeler, S. (2014). Vascular niche controls vascular pericytes in the microvessel wall. Genes Dev. 1835–1840.

Menezu, M.J., McClennan, F.K., Leiton, C.V., Aramolate, A., Shan, X., and Colognato, H. (2014). The extracellular matrix protein laminin α2 regulates the maturation and function of the blood-brain barrier. J. Neurosci. 34, 15260–15280.
Özen, I., Deierborg, T., Miharada, K., Padel, T., Englund, E., Genové, G., and Paul, G. (2014). Brain pericytes acquire a microglial phenotype after stroke. Acta Neuropathol. 128, 381–396.

Relucio, J., Menezes, M.J., Miyagoe-Suzuki, Y., Takeda, S., and Colognato, H. (2012). Laminin regulates postnatal oligodendrocyte production by promoting oligodendrocyte progenitor survival in the subventricular zone. Glia 60, 1451–1467.

Rivera, F.J., Couillard-Despres, S., Pedre, X., Ploetz, S., Caioni, M., Lois, C., Bogdahn, U., and Aigner, L. (2006). Mesenchymal stem cells instruct oligodendrocytic fate decision on adult neural stem cells. Stem Cells 24, 2209–2219.

Tsai, H.H., Niu, J., Munji, R., Davalos, D., Chang, J., Zhang, H., Tien, A.C., Kuo, C.J., Chan, J.R., Daneman, R., and Fancy, S.P. (2016). Oligodendrocyte precursors migrate along vasculature in the developing nervous system. Science 351, 379–384.

Winkler, E.A., Bell, R.D., and Zlokovic, B.V. (2011). Central nervous system pericytes in health and disease. Nat. Neurosci. 14, 1389–1405.

Yuen, T.J., Johnson, K.R., Miron, V.E., Zhao, C., Quandt, J., Harris Singh, M.C., Swire, M., Williams, A., McFarland, H.F., Franklin, R.J., and Ffrench-Constant, C. (2013). Identification of endothelin 2 as an inflammatory factor that promotes central nervous system remyelination. Brain 136, 1035–1047.

Yuen, T.J., Silbereis, J.C., Griveau, A., Chang, S.M., Daneman, R., Fancy, S.P., Zahed, H., Maltepe, E., and Rowitch, D.H. (2014). Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis. Cell 158, 383–396.

Zawadzka, M., Rivers, L.E., Fancy, S.P., Zhao, C., Tripathi, R., Jansen, F., Young, K., Goncharevich, A., Pohl, H., Rizzi, M., et al. (2010). CNS-resident glial progenitor/stem cells produce Schwann cells as well as oligodendrocytes during repair of CNS demyelination. Cell Stem Cell 6, 578–590.

Zhang, H., Jarjour, A.A., Boyd, A., and Williams, A. (2011). Central nervous system remyelination in culture—a tool for multiple sclerosis research. Exp. Neurol. 230, 138–148.

Zhao, C., Fancy, S.P., Franklin, R.J., and Ffrench-Constant, C. (2009). Up-regulation of oligodendrocyte precursor cell alphaV integrin and its extracellular ligands during central nervous system remyelination. J. Neurosci. Res. 87, 3447–3455.
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
De La Fuente, AG; Lange, S; Silva, ME; Gonzalez, GA; Tempfer, H; van Wijngaarden, P; Zhao, C; Di Canio, L; Trost, A; Bieler, L; Zaunmair, P; Rotheneichner, P; O'Sullivan, A; Couillard-Despres, S; Errea, O; Mae, MA; Andrae, J; He, L; Keller, A; Batiz, LF; Betsholtz, C; Aigner, L; Franklin, RJM; Rivera, FJ

Title:
Pericytes Stimulate Oligodendrocyte Progenitor Cell Differentiation during CNS Remyelination

Date:
2017-08-22

Citation:
De La Fuente, A. G., Lange, S., Silva, M. E., Gonzalez, G. A., Tempfer, H., van Wijngaarden, P., Zhao, C., Di Canio, L., Trost, A., Bieler, L., Zaunmair, P., Rotheneichner, P., O'Sullivan, A., Couillard-Despres, S., Errea, O., Mae, M. A., Andrae, J., He, L., Keller, A., ... Rivera, F. J. (2017). Pericytes Stimulate Oligodendrocyte Progenitor Cell Differentiation during CNS Remyelination. CELL REPORTS, 20 (8), pp.1755-1764. https://doi.org/10.1016/j.celrep.2017.08.007.

Persistent Link:
http://hdl.handle.net/11343/254935

File Description:
Published version

License:
CC BY