The FEBS Journal

FEBS PRESS science publishing by scientists

COMMENTARY

A new player in the game: identification of *C1ql1* as a novel factor driving OPC differentiation

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Keywords
complement component 1, q subcomponent-like-1; differentiation; myelination; oligodendrocyte precursor cells

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(Received 21 October 2024, revised 10 November 2024, accepted 30 October 2024)

doi:10.1111/febs.17321

Oligodendrocytes (OLGs) are the myelin-producing cells in the central nervous system (CNS). Following injury, these cells are prone to death, leading to demyelination and, eventually, axonal loss and neurodegeneration. Upon injury, the damaged CNS repopulates the lesion with oligodendrocyte precursor cells (OPCs) that consequently mature into OLGs to repair the myelin damage and prevent further axonal loss. In this issue, Altunay *et al.* identified that complement component 1, q subcomponent-like-1 (*C1ql1*), a factor known to play a role in neuron–neuron synapses, is also expressed by OPCs and drives their differentiation into OLGs. These data suggest that *C1ql1* or other downstream factors could be therapeutic targets in the context of demyelinating disorders in which remyelination fails, such as in multiple sclerosis (MS).

Comment on: https://doi.org/10.1111/febs.17256

Myelination in health and disease

Myelin is a protective sheath surrounding axons that ensures fast and efficient nerve signal transduction [1]. While myelination begins during early development, it continues during adulthood in response to learning and environmental stimuli. In the central nervous system (CNS), robust myelination strongly depends on the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes (OLGs) that enwrap the axons with their membranes. In multiple sclerosis (MS), the immune system mistakenly attacks the myelin sheath. OLGs are among the primary targets that undergo degeneration during MS [2]. While the exact mechanisms underlying OLG death in MS are not completely understood, they likely involve factors such as proinflammatory cytokines, oxidative stress, glutamate-mediated excitotoxicity, autoantibodies, complement deposition, and cytotoxic immune cells. In an attempt to restore the myelin sheath, OPCs proliferate and migrate to the damaged area, where they differentiate into newly formed myelinating OLGs [1].

Abbreviations
AD, Alzheimer's disease; ADGRB3, adhesion G protein-coupled receptor B3; C1ql1, complement component 1, q subcomponent-like-1; CC1, anti-APC antibody; CNS, central nervous system; KO, knockout; MBP, myelin basic protein; MS, multiple sclerosis; OLG, oligodendrocyte; Olig2, oligodendrocyte transcription factor 2; OPC, oligodendrocyte precursor cell; P15, postnatal day 15; PDGFRα, platelet-derived growth factor receptor alpha; SCoRe, spectral confocal reflectance; TEM, transmission electron microscopy; TIMP-1, tissue inhibitor of metalloproteinases-1; VEP, visual evoked potential.

However, as the disease progresses, this endogenous process of remyelination fails, consequently leading to progressive neurological problems [3]. OPC dysfunction and remyelination failure are also prominent in other degenerative diseases such as Alzheimer's disease (AD), and amyotrophic lateral sclerosis, where there is a high unmet clinical need [4,5]. As a result, research has shifted toward mapping all the different molecules and signaling pathways responsible for each phase of the intricate, multistep process of OPC differentiation. Identified factors can provide new stepping stones for developing repair-promoting therapies for demyelinating disorders.

Novel factor to add to the list of OPC differentiation modulators

In addition to the established markers of OPC differentiation, such as oligodendrocyte transcription factor 2 (Olig2), platelet-derived growth factor receptor alpha (PDGFRα), and myelin basic protein (MBP), many regulatory factors involved in this process remain unknown. The study by Altunay *et al.* [6], published in *The FEBS Journal*, introduces a novel factor, *C1ql1*, which has a dual role in regulating OPC differentiation, both promoting and inhibiting the process depending on the context (Fig. 1). *C1ql1* was previously recognized as a key inducer of neuronal synapse formation but is now shown by the authors to also be expressed by Olig2$^+$ OPCs. Notably, all PDGFRα$^+$ OPCs in the gray matter and nearly all in the white matter were found to express *C1ql1* mRNA, whereas only a subset of CC1$^+$ OLGs expressed it. The reason why only a subset of differentiation-committed OLGs retain *C1ql1* mRNA expression remains to be investigated. To investigate C1QL1 protein expression, the authors generated an epitope-tagged knockin mouse model, in which an HA-tag was inserted into the endogenous gene locus. This new mouse line (HA-*C1ql1* mouse line) is already fully characterized [7]. By using the HA-*C1ql1* mouse model, the authors demonstrated that only a subset of PDGFRα$^+$ OPCs actively express the C1QL1 protein, suggesting the involvement of potential posttranslational regulatory mechanisms [6].

To determine the involvement of *C1ql1* in OPC differentiation, loss- and gain-of-function experiments were performed [6]. In the OPC-specific *C1ql1* knockout (KO) model, a significant reduction in both PDGFRα$^+$ OPCs and CC1$^+$ OLGs was observed, along with decreased compact myelin at postnatal day 15 (P15). By 8 weeks of age, these deficits were nullified indicating a developmental delay in myelination rather than a permanent deficiency. Instead of traditional transmission electron microscopy (TEM), the authors used spectral confocal reflectance (SCoRe) microscopy, a novel imaging technique that uses the optical properties of compact myelin [8]. Similarly, in a toxin-induced demyelination model, *C1ql1* KO in OPCs led to a reduced OLG presence and remyelination as confirmed by g-ratio analysis [6,9]. Despite the observed reduction, g-ratio values in KO mice still improved compared to the demyelination phase. Conversely, overexpression of *C1ql1* via viral vectors increased OLG density in the gray matter and enhanced remyelination. Both rat and mouse primary cultures were used to demonstrate a direct effect of C1QL1 on OPCs, revealing increased MBP expression following C1QL1 incubation, while less MBP was present in C1QL1 KO conditions.

These findings suggest that *C1ql1* is a compelling target for further investigation, potentially acting as a dual-function factor, given its ability to target both OPCs and neurons. This duality could confer a synergistic advantage, enhancing both differentiation and providing neuronal support. However, further research is necessary to provide more robust evidence supporting the potential of *C1ql1* as a therapeutic agent. First, the specific mechanisms by which *C1ql1* promotes OPC differentiation need to be elucidated. This could either reveal a previously unknown pathway or confirm an existing one, thereby validating common molecular targets. Second, it is important to investigate whether *C1ql1*-induced myelination also leads to functional improvements, which can be evaluated through behavioral testing or more clinically relevant methods such as visual evoked potential (VEP) measurements [10]. Finally, the authors should present translational data demonstrating dysregulated *C1QL1* signaling in patient samples, such as iPSC-derived OPCs or postmortem brain tissue from important demyelinating diseases.

Differentiation factors: are we there yet?

Several studies have highlighted the role of individual factors in the maturation of OLGs. Similar to the findings of Altunay *et al.*, we and others have underscored the involvement of tissue inhibitor of metalloproteases-1 (TIMP-1) in promoting OPC differentiation and remyelination in toxin-induced demyelination models [6,11,12]. Next to disease, the absence of TIMP-1 also affects developmental myelination, similar to what is reported here for *C1ql1* [6,13]. However, compensatory mechanisms seem to emerge at later stages, mitigating

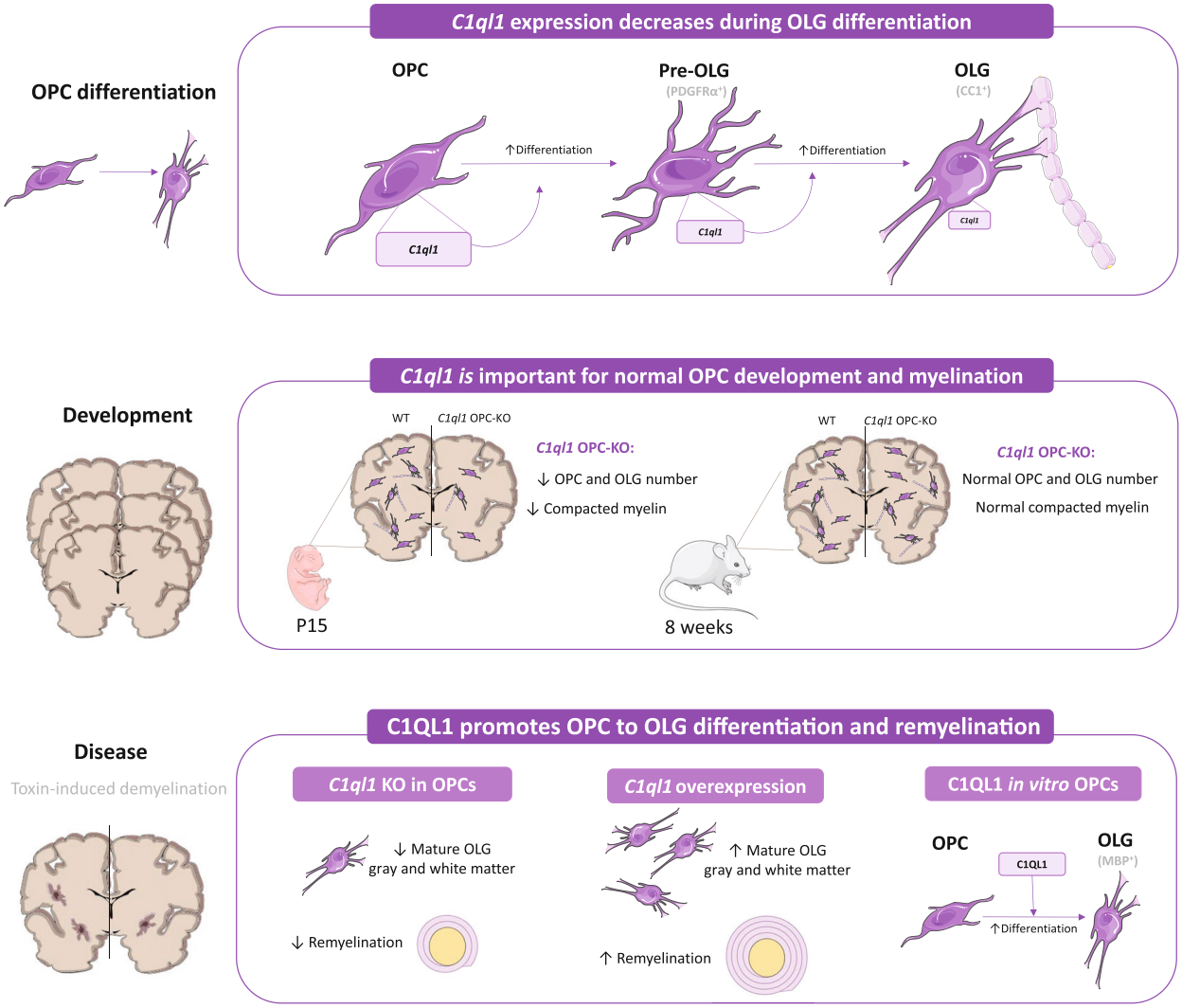

Fig. 1. *C1ql1* is involved in OPC differentiation and (re)myelination. Altunay *et al.* demonstrated that *C1ql1* is involved in OPC differentiation and (re)myelination. *C1ql1* expression decreases during OLG differentiation, with a high expression in PDGFRα^{+} OPCs (pre-OLG) in both gray and white matter. Only a small subset of CC1^{+} OLGs expressed *C1ql1*. Mice at the age of P15 with an OPC-specific KO of *C1ql1* had reduced numbers of OPCs and OLG along with a decrease in compacted myelin, but this effect was nullified at the age of 8 weeks. In a cuprizone-induced de- and remyelination model, C1QL1 was shown to regulate OPC maturation and promote remyelination evidenced by a *C1ql1* OPC-specific KO and *C1ql1* overexpression mouse model. *In vitro* OPC cultures showed a direct differentiation stimulating effect on OPCs upon the addition of C1QL1. C1ql1, complement component 1, q subcomponent-like-1; KO, knockout; MBP, myelin basic protein; OLG, oligodendrocyte; OPC, oligodendrocyte precursor cell; P15, post-natal day 15. Images were modified using Inkscape from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Common Attribution 3.0 Generic License.

deficits in myelin content. While these mechanisms have not been the primary focus of most studies, it would be valuable to explore whether they are consistent across factors or specific to each of them. Additionally, in the demyelination model, *C1ql1* deficiency decreased remyelination but did not prevent it, also pointing toward possible other active pathways in favor of repair. In the case of MS, it remains questionable whether a single factor will be enough to act as a potent remyelination booster, taking into account the presence of a plethora of inhibitory signals [1]. The fact that *C1ql1* impacts gray matter oligodendrogenesis in the Altunay *et al.*'s study might be of particular interest for progressive MS, which remains untreatable, as gray matter pathology is strongly associated with disease progression in MS [6,14]. One aspect that was not considered in this study is the impact on aging [15]. This is important as aged OPCs are reported to

be less prone to differentiation-promoting signals [15]. This is of interest in light of aging diseases such AD that have been more and more associated with myelination abnormalities. Likewise, different brain regions harbor distinct OPC populations, which express different markers, making it essential to explore whether expression varies across regions and whether the C1QL1 receptor is present on these different subsets [16].

Conclusion

Despite extensive efforts to identify key regulators of OPC differentiation, many factors remain elusive. The study of Altunay *et al.* is the first to discover a role for *C1ql1* in OPC differentiation. However, the downstream mediators still remain to be uncovered. Furthermore, the observation that the C1QL1 receptor, ADGRB3, is more highly expressed in remyelinating lesions than chronic active ones suggests that C1QL1 administration could hold therapeutic potential for enhancing OPC differentiation in patients with chronic demyelinating disorders.

Acknowledgements

The authors are supported by grants from MS Liga Vlaanderen, Fondation Charcot Stichting België, Stichting MS Research and Fonds Wetenschappelijk Onderzoek (FWO-Vlaanderen) to TV, MS, JVB, and FM (G042121N, 1272324N, 1209123N, and 1SH2E24N).

Conflict of interest

MS and TV have a proprietary interest in selective PDE4D inhibitors for the treatment of demyelinating disorders and neurodegenerative disorders. All other authors declare no conflict of interest.

Author contributions

JVB and NH were responsible for conceptualization and writing the commentary. JVB and FM generated the figure. All authors have reviewed, edited, and approved the commentary.

References

1 Lubetzki C, Zalc B, Williams A, Stadelmann C & Stankoff B (2020) Remyelination in multiple sclerosis: from basic science to clinical translation. *Lancet Neurol* **19**, 678–688.
2 Spaas J, van Veggel L, Schepers M, Tiane A, van Horssen J, Wilson DM 3rd, Moya PR, Piccart E, Hellings N, Eijnde BO *et al.* (2021) Oxidative stress and impaired oligodendrocyte precursor cell differentiation in neurological disorders. *Cell Mol Life Sci* **78**, 4615–4637.
3 Gruchot J, Weyers V, Gottle P, Forster M, Hartung HP, Kury P & Kremer D (2019) The molecular basis for remyelination failure in multiple sclerosis. *Cells* **8**, 825.
4 Raffaele S, Boccazzi M & Fumagalli M (2021) Oligodendrocyte dysfunction in amyotrophic lateral sclerosis: mechanisms and therapeutic perspectives. *Cells* **10**, 565.
5 Mathys H, Davila-Velderrain J, Peng Z, Gao F, Mohammadi S, Young JZ, Menon M, He L, Abdurrob F, Jiang X *et al.* (2019) Author correction: single-cell transcriptomic analysis of Alzheimer's disease. *Nature* **571**, E1.
6 Altunay ZM, Biswas J, Cheung HW, Pijewski RS, Papile LE, Akinlaja YO, Tang A, Kresic LC, Schouw AD, Ugrak MV *et al.* (2024) C1ql1 expression in oligodendrocyte progenitor cells promotes oligodendrocyte differentiation. *FEBS J* doi: 10.1111/febs.17256
7 Cheung HW, Schouw AD, Altunay ZM, Maddox JW, Kresic LC, McAllister BC, Caro K, Alam S, Huang A, Pijewski RS *et al.* (2024) Creation of a novel CRISPR-generated allele to express HA epitope-tagged C1QL1 and improved methods for its detection at synapses. *FEBS Lett* **598**, 2417–2437.
8 Gonsalvez DG, Yoo S, Fletcher JL, Wood RJ, Craig GA, Murray SS & Xiao J (2019) Imaging and quantification of myelin integrity after injury with spectral confocal reflectance microscopy. *Front Mol Neurosci* **12**, 275.
9 Zirngibl M, Assinck P, Sizov A, Caprariello AV & Plemel JR (2022) Oligodendrocyte death and myelin loss in the cuprizone model: an updated overview of the intrinsic and extrinsic causes of cuprizone demyelination. *Mol Neurodegener* **17**, 34.
10 Castoldi V, Marenna S, d'Isa R, Huang SC, De Battista D, Chirizzi C, Chaabane L, Kumar D, Boschert U, Comi G *et al.* (2020) Non-invasive visual evoked potentials to assess optic nerve involvement in the dark agouti rat model of experimental autoimmune encephalomyelitis induced by myelin oligodendrocyte glycoprotein. *Brain Pathol* **30**, 137–150.
11 Houben E, Janssens K, Hermans D, Vandooren J, Van den Haute C, Schepers M, Vanmierlo T, Lambrichts I, van Horssen J, Baekelandt V *et al.* (2020) Oncostatin M-induced astrocytic tissue inhibitor of metalloproteinases-1 drives remyelination. *Proc Natl Acad Sci U S A* **117**, 5028–5038.
12 Nicaise AM, Johnson KM, Willis CM, Guzzo RM & Crocker SJ (2019) TIMP-1 promotes oligodendrocyte differentiation through receptor-mediated signaling. *Mol Neurobiol* **56**, 3380–3392.

13 Moore CS, Milner R, Nishiyama A, Frausto RF, Serwanski DR, Pagarigan RR, Whitton JL, Miller RH & Crocker SJ (2011) Astrocytic tissue inhibitor of metalloproteinase-1 (TIMP-1) promotes oligodendrocyte differentiation and enhances CNS myelination. *J Neurosci* **31**, 6247–6254.
14 Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkiel KA, Thompson AJ & Miller DH (2008) Gray matter atrophy is related to long-term disability in multiple sclerosis. *Ann Neurol* **64**, 247–254.
15 Leenders F, Koole L, Slaets H, Tiane A, Hove DVD & Vanmierlo T (2024) Navigating oligodendrocyte precursor cell aging in brain health. *Mech Ageing Dev* **220**, 111959.
16 Marques S, Zeisel A, Codeluppi S, van Bruggen D, Mendanha Falcao A, Xiao L, Li H, Haring M, Hochgerner H, Romanov RA *et al*. (2016) Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system. *Science* **352**, 1326–1329.