



Commentary

p57kip2 nuclear export as a marker of oligodendrocytes differentiation: Towards an innovative phenotyping screening for the identification of myelin repair drugs

Barbara Monti

Department of Pharmacy and Biotechnology, University of Bologna, 40126 Bologna, Italy



ARTICLE INFO

Article History:

Received 10 March 2021

Accepted 10 March 2021

The article from Küry and collaborators, published in *EBioMedicine*, demonstrates for the first time the worth of an innovative phenotyping screening for the identification of myelin repair drugs [1]. This original approach is based on the previous identification from the same research group that the cyclin dependent kinase inhibitor p57kip2 is a main intrinsic, negative regulator of both Schwann cell [2] and oligodendrocytes differentiation [3], glial cells involved in peripheral and central nervous system (CNS) myelination, respectively [4]. In particular, the subcellular translocation of p57kip2 leads to oligodendrocytes precursor cells (OPCs) differentiation and myelin formation. Therefore, the phenotypic screening here proposed is particularly suitable to identify molecules able to induce myelination, with the aim to counteract demyelination [1]. Demyelinating diseases, affecting the nervous system with a variety of etiologies, can be classified into primary disorders, such as multiple sclerosis (MS) and other idiopathic inflammatory-demyelinating diseases, and secondary disorders that can be originated by infectious, ischemic, metabolic or toxic causes. The most common demyelinating disease, MS, is a progressive inflammatory, autoimmune disorder characterised by inflammatory cells infiltration, demyelination, gliosis and axonal loss, affecting the optic nerves, brainstem, spinal cord, cerebellar and subcortical white matter, thus resulting in chronic progressive motor disabilities, as well as cognitive and psychiatric disturbances [5]. MS affects more than 2 million people worldwide, twice as many women as men, primarily younger adults (average onset age is 30 years). At 25 years after diagnosis, about half of patients will require permanent wheelchair use, so MS represents a crucial medical, social and economic problem that absolutely requires to be addressed. In fact, no cure is now available and pharmacological treatments can only relieve symptoms [6]. Thus, there is urgent need for a specific drug

development to treat MS and the other demyelinating disorders. Actually, there are two principal rational approaches for MS drug development: counteracting demyelination or promoting remyelination. These approaches are not mutually exclusive and can be directed either towards immune cells, to reduce inflammation and to modulate their activation, or towards oligodendrocytes, to induce myelination/remyelination [7,8]. Oligodendrocytes are glial cells derived from neural stem cells (NSCs) and/or OPCs, which differentiate to produce myelin sheet that wrap neurons, allowing fast axonal conduction and supporting neuronal survival and function. Myelination is a physiological process that massively takes place during post-natal development; in differentiated CNS, remyelination continuously occurs during all the life, but especially after injuries due to many different pathological causes. In MS, inflammatory events determine demyelination, thereby remyelination is necessary to repair the damage and to protect neurons, but, first, remyelination requires oligodendrocytes differentiation. Therefore, the new frontier in therapeutic approaches to counteract MS is the identification of drug candidates able to induce oligodendrocytes differentiation [9]. In this framework, the screening procedure proposed by Küry and collaborators is useful not only to identify new compounds, but also for drug repurposing, which is particularly interesting for a fast development of new therapeutic approaches. In fact, these authors clearly demonstrated that the subcellular localization of p57kip2 easily allows identifying pro-differentiation and pro-myelinating molecules in rodent OPCs, further tested in *ex vivo* and *in vivo* models, *i.e.* organotypic cerebellar slices and the cuprizone-mouse model of demyelination respectively [1]. The role of this cell cycle inhibitor depends on its subcellular localisation: nuclear accumulation of p57kip2 blocks differentiation of OPCs and therefore myelination, while its nuclear export leads to oligodendrocytes differentiation and therefore, myelination [10]. Thus, the subcellular localisation of p57kip2 might be used as a marker of myelination's induction, as well as a readout to screen molecules for myelin repair, as successfully shown in this issue. In fact, with this approach, a library of more than 1000 FDA-approved compounds was rapidly tested leading to the identification of 21 molecules able to enhance p57kip2 nuclear export in primary rodent OPCs; among them, compounds already identified as involved in OPCs differentiation pathways have been selected, further demonstrating the validity of this phenotypic screening. These molecules were also tested for OPCs differentiation

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2021.103276>.E-mail address: b.monti@unibo.it<https://doi.org/10.1016/j.ebiom.2021.103298>2352-3964/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

through the analysis of myelin protein expression, thus selecting 4 compounds, which were further analysed for their promyelinating effect in the *in vitro* model of primary human OPCs, in the *ex vivo* model of organotypic slices and *in vivo*, in the rat cuprizone model of de- and re-myelination. This approach allowed unequivocally identifying 2 compounds able to enhance remyelination in all these different models, *i.e.* parbendazole and danazol, which are respectively FDA-approved drugs as anthelmintic and for the treatment of endometriosis [1]. Thus, Küry and collaborators clearly demonstrated that this phenotypic screening based on p57kip2 nuclear export is a powerful approach, which can be extended to larger libraries, to identify compounds able to induce OPCs differentiation and therefore myelination to counteract MS and other devastating demyelinating disorders, which is an urgent, unmet medical need.

Declaration of Competing Interest

The author declares no conflict of interest.

Acknowledgements

The author's research activity on demyelinating disease is supported by Telethon GGP19067, without any active role in writing this commentary.

Contributors

BM wrote this commentary.

References

- [1] Manousi A, Göttle P, Reiche L, Cui Q-L, Healy L, Akkermann R, Gruchot J, Schira-Heinen J, Antel JP, Hartung H-P, Küry P. Identification of novel myelin repair drugs by modulation of oligodendroglial differentiation competence. EBioMedicine 2021. doi: [10.1016/j.ebiom.2021.103276](https://doi.org/10.1016/j.ebiom.2021.103276).
- [2] Heinen A, Kremer D, Göttle P, Kruse F, Hasse B, Lehmann H, Hartung HP, Küry P. The cyclin-dependent kinase inhibitor p57kip2 is a negative regulator of Schwann cell differentiation and in vitro myelination. Proc Natl Acad Sci USA 2008;105 (June 24(25)):8748–53. doi: [10.1073/pnas.0802659105](https://doi.org/10.1073/pnas.0802659105).
- [3] Kremer D, Heinen A, Jadasz J, Göttle P, Zimmermann K, Zickler P, Jander S, Hartung HP, Küry P. p57kip2 is dynamically regulated in experimental autoimmune encephalomyelitis and interferes with oligodendroglial maturation. Proc Natl Acad Sci USA 2009;106(June 2(22)):9087–92. doi: [10.1073/pnas.0900204106](https://doi.org/10.1073/pnas.0900204106).
- [4] Kuhn S, Gritti L, Crooks D, Dombrowski Y. Oligodendrocytes in development, myelin generation and beyond. Cells 2019;8(November 12(11)):1424. doi: [10.3390/cells8111424](https://doi.org/10.3390/cells8111424).
- [5] Barkhof F, Koeller KK. Demyelinating diseases of the CNS (brain and spine). In: Hodler J, Kubik-Huch R, von Schulthess G, editors. Diseases of the brain, head and neck, spine 2020–2023. IDKD Springer Series. Cham: Springer; 2020. doi: [10.1007/978-3-030-38490-6_13](https://doi.org/10.1007/978-3-030-38490-6_13).
- [6] Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med 2018;378 (2):169–80. doi: [10.1056/NEJMra1401483](https://doi.org/10.1056/NEJMra1401483).
- [7] Villoslada P, Steinman L. New targets and therapeutics for neuroprotection, remyelination and repair in multiple sclerosis. Expert Opin Investig Drugs 2020;29(5):443–59. doi: [10.1080/13543784.2020.1757647](https://doi.org/10.1080/13543784.2020.1757647).
- [8] Faissner S, Plemel JR, Gold R, Yong VW. Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. Nat Rev Drug Discov 2019;18(12):905–22. doi: [10.1038/s41573-019-0035-2](https://doi.org/10.1038/s41573-019-0035-2).
- [9] Skaper SD. Oligodendrocyte precursor cells as a therapeutic target for demyelinating diseases. Prog Brain Res 2019;245:119–44. doi: [10.1016/bs.pbr.2019.03.013](https://doi.org/10.1016/bs.pbr.2019.03.013).
- [10] Göttle P, Sabo JK, Heinen A, Venables G, Torres K, Tzekova N, Parras CM, Kremer D, Hartung HP, Cate HS, Küry P. Oligodendroglial maturation is dependent on intracellular protein shuttling. J Neurosci 2015;35(January 21(3)):906–19. doi: [10.1523/JNEUROSCI.1423-14.2015](https://doi.org/10.1523/JNEUROSCI.1423-14.2015).