

## Commentary: "Promoting Myelin Repair through *In vivo* Neuroblast Reprogramming"

Bilal El Waly<sup>1</sup>, Myriam Cayre<sup>1</sup>, Pascale Durbec<sup>1\*</sup>

Aix Marseille University, CNRS, IBDM-UMR 7288, Case 907, Parc Scientifique de Luminy, campus de Luminy, 13288 Marseille, Cedex 09, France

### Article Info

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#### \*Correspondence:

Dr. Pascale Durbec, Aix Marseille University, CNRS, IBDM-UMR 7288, Case 907, Parc Scientifique de Luminy, campus de Luminy, 13288 Marseille, Cedex 09, France; E-mail: pascale.durbec@univ-amu.fr.

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Hundreds of millions of people worldwide are affected by neurological disorders, making them one of the greatest threats to public health. In the last few decades, a more comprehensive view of the complexity of brain physiology has revealed the multiple and key roles of glial cells for proper brain functioning. Thus, our classical neuron-centered view is obsolete, and regenerative approaches to treat neurological disorders need to consider glial cells as possible new targets. An obvious example is shown by oligodendrocytes, the myelin forming cells of the central nervous system. Myelin is necessary to speed up conduction velocity, drives network synchrony and provides metabolic support to axons, preventing neurodegeneration. Unfortunately myelin integrity is often affected in many neurological diseases due to the high sensitivity of oligodendrocytes to metabolic stress and inflammation. This is the case in Multiple Sclerosis (MS), an inflammatory auto-immune disease affecting around 2.5 million people worldwide. In Europe and North America, MS is the second leading cause of invalidity in young adults, second only to invalidities resulting from car accidents. Lesions may form in any location thus producing diverse clinical forms, but with time the disease often becomes progressive leading to physical disability and cognitive decline. Available treatments ( $\beta$ -interferon, glatiramer acetate and others) only target inflammation, reducing the frequency and severity of the relapses. Unfortunately, they are inefficient to prevent neuronal degeneration (that follows long-term demyelination) and thus do not stop evolution of the disease. Therefore, many efforts to develop remyelinating and neuroprotective treatments have been developed these last years. A straightforward approach is the transplantation of cells able to form new myelin sheaths. Different types of myelin-forming cells (oligodendrocyte precursor cells (OPC), Schwann cells, olfactory unsheathing cells) or cells that can differentiate into myelin-forming cells (mesenchymal cells, embryonic stem cells, adult neural stem cells) have been transplanted in rodent models of demyelination. However, limited *In vitro* expansion for some of these cells and/or restricted remyelination around the injection site highlights some limitations of the approach (for review, see<sup>1</sup>). The route of cell administration is thus an important issue in multifocal diseases such as MS. The first clinical trial using autologous Schwann cells in MS patients was not a success and dulled the enthusiasm of these approaches. Neural stem cells present advantages since they are more easily amplified in culture and are equipped with integrins and cytokine receptors conferring upon them a homing behavior to inflamed parenchyma when injected in the blood stream or the cerebrospinal fluid<sup>2,3</sup>. However, the production and integration of new oligodendrocytes remains unfortunately low.

Interestingly, spontaneous remyelination can occur in the brain; this process is very efficient in rodents, yet highly variable in humans; some MS patients present up to 96% of remyelinated lesions, while others do not reach 25%<sup>4</sup>. Thus, an alternative strategy could be to promote such a spontaneous repair process to increase its effectiveness in all patients.

Based on rodent studies, it is known that two sources of cells contribute to this endogenous remyelination: parenchymal OPC disseminated throughout the brain<sup>5,6</sup> and adult neural stem cells located within the subventricular zone (SVZ)<sup>7,8</sup>. Although pOPC were long believed to be the only endogenous source of cells for myelin repair, in mice, SVZ-derived progenitors contribute to corpus callosum remyelination to similar levels as pOPC, but with distinct preferential rostro-caudal / latero-medial localizations<sup>7, 8</sup>. In the adult brain, SVZ neural stem cells mainly produce neuroblasts that migrate toward the olfactory bulb to generate new interneurons. However, they can also produce a small proportion of OPC that migrate to periventricular structures and either remain undifferentiated or mature into oligodendrocytes. This pool of SVZ-derived OPC is largely enhanced after demyelination<sup>9</sup>, and in addition, many neuroblasts are derouted from the rostral migratory stream and reach the demyelinated corpus callosum<sup>10-12</sup>.

SVZ-derived neuroblasts exhibit striking plasticity since they are able to convert into myelinating oligodendrocytes when grafted into dysmyelinated mice<sup>13</sup> or after spontaneous emigration from SVZ to the demyelinated corpus callosum<sup>14</sup>. Since neuroblasts represent the vast majority of cells produced by the adult SVZ and they have a high migration capacity, targeting these cells to promote spontaneous remyelination appears as an attractive strategy. Both developmental studies<sup>15,16</sup> and forced transdifferentiation experiments<sup>17,18</sup> have highlighted Olig2 and Sox10 as key transcription factors for oligodendrocytic fate determination and differentiation respectively. Forced expression of Olig2 and Sox10 in fibroblasts is sufficient to convert them into myelinating oligodendrocytes *In vitro*<sup>17,18</sup>. Viral induction of Olig2 in SVZ progenitors *In vivo* favors gliogenesis at the expense of neurogenesis<sup>19</sup>. Similarly, viral transduction of Ascl1, Olig2 or Sox10 in dentate gyrus neural stem cells enhances the production of oligodendrocytes and favors myelin repair in a demyelinating mouse model<sup>20</sup>. Based on these observations, we decided to target SVZ-derived neuroblasts and trigger the expression of Olig2 and Sox10 in these cells to redirect them into the oligodendrocytic lineage and evaluate this strategy for myelin regeneration<sup>21</sup>.

*In vitro* experiments first validated the specificity and efficiency of our approach. It confirmed that following plasmid transfection of neuroblasts with Olig2 and Sox10, the endogenous program took over the transitory exogenous

expression of these 2 transcription factors, and allowed the efficient conversion of neuroblasts into oligodendrocytes. We then designed plasmids and methodological procedures that allow the targeting of SVZ neuroblasts in neonate mice yet only triggering transcription factor expression at the adult stage. In healthy mice, triggering Olig2 and Sox10 expression in neuroblasts was sufficient to induce ectopic migration to periventricular structures (corpus callosum, striatum and cortex), and to convert neuroblasts to oligodendrocytes. In contrast, control mice neuroblasts transfected with GFP only remained within the rostral migratory stream and reached the olfactory bulb where they differentiated into interneurons. To evaluate the benefit of this strategy in a pathological context, we applied the same approach in mice exposed to the demyelinating drug cuprizone. In these demyelinated mice, we observed that even in control condition (GFP transfection alone), some neuroblasts spontaneously migrated from the SVZ to periventricular white matter and transdifferentiated to oligodendrocytes. However, the forced expression of Olig2 and Sox10 in SVZ-derived neuroblasts accelerated the spontaneous remyelination of the corpus callosum. We furthermore demonstrated that converted neuroblasts significantly contributed to myelin repair<sup>21</sup>.

This study emphasizes an unexpected level of cell fate plasticity in the injured brain, and demonstrates that SVZ-derived neuroblasts may be considered as a complementary source of cells for myelin repair. Parenchymal OPC present the advantage of being disseminated throughout the brain but in case of repeated demyelination they can be depleted while neural stem cells present higher self-renewal potential. Interestingly, myelin formed by oligodendrocytes derived from neural stem cells was reported to be thicker than myelin derived from parenchymal OPC<sup>7</sup>. Neuroblasts represent the main population of cells produced by neural stem cells in SVZ, and they can spontaneously convert into myelinating oligodendrocyte; besides, such conversion can be pushed via the activation of specific transcriptional pathways. Whether such plasticity is preserved during aging has not been investigated in this study because of technical constraints linked to brain electroporation approach.

How these findings may be translated to human therapy is still an open question. The old debate about the presence and persistence of neural stem cells and neurogenesis in the adult human brain has recently been reactivated following the publication of two studies reaching opposite conclusions<sup>22,23</sup>. However, since the discovery of adult neurogenesis in birds and mammals in the 1980s, a large body of evidence supports the hypothesis that the human brain should be no exception and should also benefit from this additional level of plasticity<sup>24</sup>. Interestingly, in MS patients cell proliferation in the SVZ is increased, together

with enhanced numbers of PSA-NCAM+ progenitors in periventricular areas, a marker usually expressed by neuroblasts. Some of these PSA-NCAM+ progenitors co-expressed oligodendrocytic markers such as Olig2 and Sox10<sup>25</sup>. These observations suggest that, as in rodents, SVZ-derived progenitors can be mobilized for myelin repair.

Targeting neuronal progenitors rather than stem cells presents the advantage to limit stem cell exhaustion, which may lead in the long term to deleterious loss of plasticity. The production of oligodendrocytes at the expense of neuroblasts may also present some side effects, however the overall impact on olfactory neurogenesis seemed minor in mice since no reduction in the olfactory bulb size was observed. Although, the methodology we developed in mice is unlikely suited for human applications, recent progress in the search for small molecules targeting lineage-specific pathways confirmed the clinical potential of such approach<sup>26</sup> and could lead to the identification of active compounds promoting myelin repair through cell reprogramming.

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