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COMMENTARY

Multiple targets for multiple sclerosis

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Multiple sclerosis (MS), a leading cause of non-traumatic disability in young adults, is a chronic inflammatory demyelinating disease of the central nervous system (CNS) associated with aberrant autoimmune responses. It has long been thought that therapeutic development should be centered on immunomodulatory agents. However, none of the agents tested could prevent chronic progressive disease and disability. On the other hand, direct repair of injured myelin might represent an alternative strategy for treating MS. This may be achieved by either promoting the inherent repair mechanism of neurons or by recruiting cells derived from oligodendrocyte progenitor cells (OPCs), which are unfortunately silent in MS. The latter approach was recently demonstrated by Najm et al at Case Western Reserve University and Northwestern University.[1] They demonstrated that miconazole and clobetasol, screened from a library of bioactive small molecules on mouse pluripotent epiblast stem cell-derived OPCs,[2–4] promoted precocious myelination, significantly increased the number of new oligodendrocytes and enhanced remyelination. Strikingly, both small molecules reversed the disease severity in mouse models of MS.

The subsequent genome-wide RNA sequencing and phosphoproteomic analyses on mouse OPCs showed that the activity of clobetasol is mediated by the glucocorticoid receptor signaling axis, whereas miconazole functions through the mitogen-activated protein (MAP) kinase pathway, with potential cell-type specificity. To interpret the potential impact of these treatments on immune cell survival and function, subsequent immune response assays were performed, which showed that only clobetasol alters the naïve T-cell differentiation and secretion of cytokines. These findings indicate that clobetasol plays a role in both immunomodulation and the promotion of myelination, whereas miconazole acts as a direct remyelinating agent, with no effect on the immune system. Most importantly, both drugs enhanced the generation of human oligodendrocytes from human OPCs *in vitro*, with miconazole exhibiting the most reproducible and potent effects. Although miconazole and clobetasol are currently only approved for topical administration in humans, meaning that significant optimization of the dosing, delivery and potentially the chemical constitution will be required to enhance the on-target pharmacology in OPCs, this study provides new hope for the currently untreatable chronic progressive phase of MS.

It remains unknown how the remyelinating and immune system effects interact, and the precise mechanisms underlying the resultant recovery after the administration of these two drugs remain unclear. However, the study by Najm et al suggests that OPCs can be selectively modified and differentiated into oligodendrocytes by two different drugs identified using a high-throughput screening method, both of which resulted in amelioration of the MS phenotype *in vivo*. Compared with genetically engineered stem cells, which may exhibit alterations of their structure and function that might interfere with the microenvironment and glia-neuron interactions, a major advantage of using drug-modified cells is that the treatment can be stopped at any time depending on the clinical outcome of the MS and the side effects. In addition, the manipulation of isolated target cells provides a new method for dealing not only with MS, but also with a variety of other diseases, such as cancer and neurodegenerative diseases. For instance, the drug-based high-throughput screening strategy used in this study could be

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useful to identify small molecules targeting cancer stem cells, which would ultimately lead to the optimized treatment of patients with cancer. Therefore, we think that the drug-based modulation of target cells represents a breakthrough in research related to physiology and disease.

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