Multiple sclerosis: New approach for repairing damaged nerve sheaths

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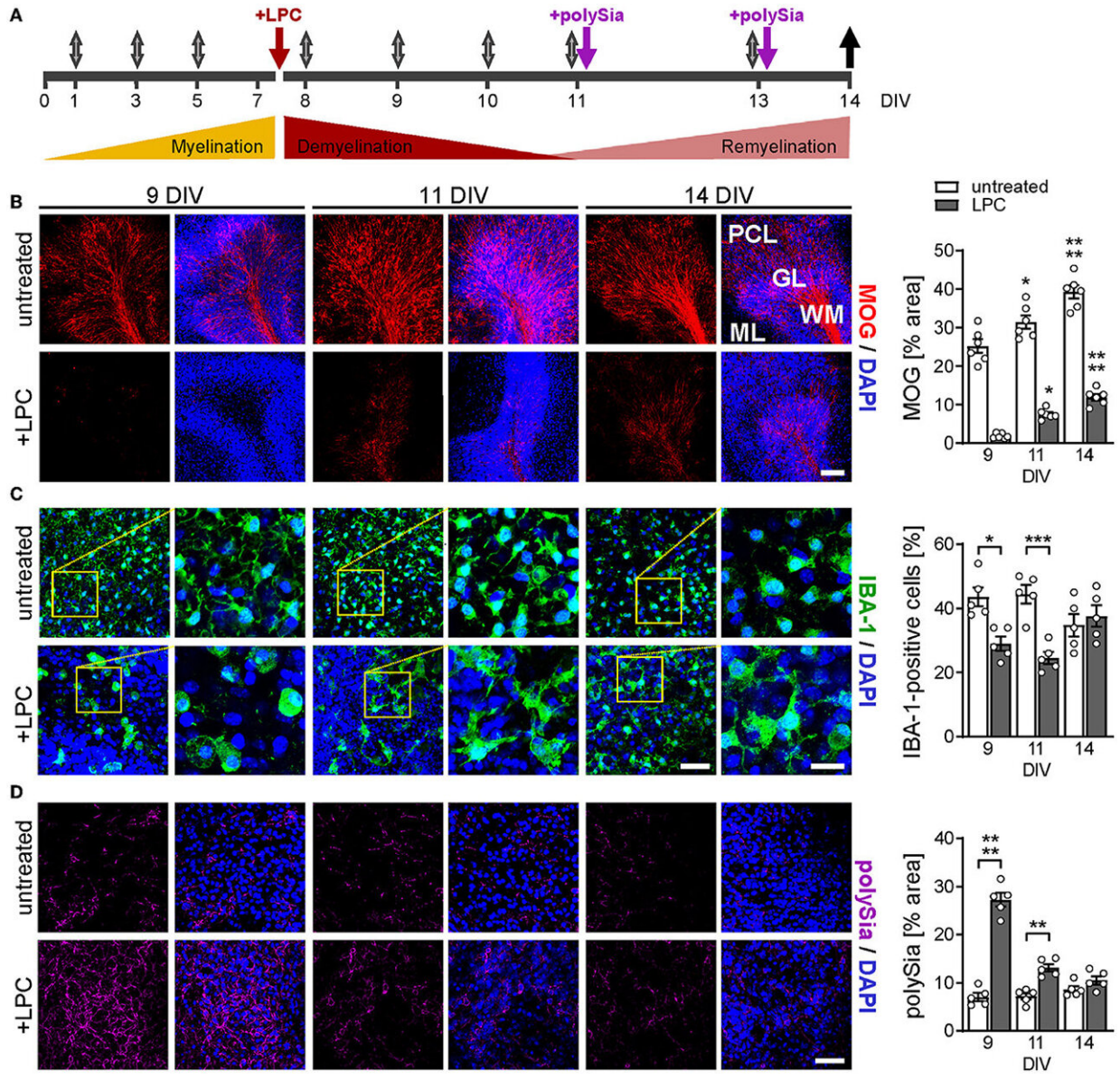

Experimental design and overview of myelin, microglia, and polySia status during de-and remyelination. **(A)** Timeline. Cerebellar slices from P9–P11 mice were cultured for 7 days to complete developmental myelination, and were treated with LPC (7 DIV, red arrow) for white matter demyelination with severe pathology at 9–11 DIV. For polySia treatments (purple arrows), DP8–14 or DP24–30 were added at 11 and 13 DIV to achieve concentrations of 50 and 30μg/ml per slice culture well, respectively. Gray arrows, media exchange, black arrow, sampling of culture media. **(B–D)** Representative micrographs and evaluation of staining for MOG, a marker of terminally differentiated myelinating oligodendrocytes **(B)**, IBA-1 staining for microglia **(C)**, and expression of polySia **(D)** at 9, 11, and 14 DIV, as indicated. Nuclear counterstain with DAPI (blue). Scale bars, 100 μm in **(B)**, 50 μm in **(C)**, overviews, and **(D)**, 20 μm in **(C)**, higher magnification views. Images of MOG display white matter (WM), granular layer (GL), Purkinje cell layer (PCL), and molecular layer (ML). Images of IBA-1 and polySia staining were taken from WM and GL. Morphometric evaluations of MOG **(B)** and polySia **(D)** show individual values and means ± SEM of MOG- or polySia-positive areas in OSCs derived from $n = 6$ or $n = 5$ animals per group, respectively. IBA-1 positive cell numbers **(C)** were evaluated relative to overall cell numbers determined by nuclear DAPI stain, and data represent individual values and means ± SEM of OSCs derived from $n = 5$ animals per group. In **(B–D)**, the two-way ANOVA revealed significant differences, and Tukey's *post-hoc* tests were applied. Significant differences against DIV 9 of the same treatment **(B)** or between untreated and LPC-treated groups of the same DIV **(C, D)** are indicated (*P P P P Frontiers in Cellular Neuroscience (2023). DOI: 10.3389/fncel.2023.1207540

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS). In Germany, more than 280,000 people are affected. In most cases, MS progresses in relapses, which occur completely irregularly as excessive inflammatory reactions in the spinal cord and brain. In the process, misdirected immune cells destroy the protective myelin sheaths of the nerve fibers and thus damage the nerves.

High-dose cortisone is usually used to slow down the inflammation. Preventive immunotherapy is also used to reduce the number and severity of attacks. It is true that the nerve fiber sheaths can be partially restored by the body's own repair processes. But this spontaneous remyelination usually proceeds incompletely in MS patients or fails to occur at all.

And to date, there is no drug that promotes this repair. Researchers from the Department of Neurology with Clinical Neurophysiology and the Institute of Clinical Biochemistry at the Hannover Medical School (MHH) have now discovered a naturally occurring mechanism that can be used to decisively improve the repair of the myelin sheaths.

Sugar compound activates immune cells of the brain

The focus here is on the microglial cells of the brain. In addition to their work as "rubbish collectors" for the removal of damaged cells and foreign bodies, the microglia also take on tasks for the immune response and constantly look for signs of injury or infection. If there is a problem, the microglial cells are activated and release cytokines and other signaling molecules.

This attracts other immune cells such as T and B cells, which normally reside outside the brain. The body's own sugar compound polysialic acid plays a crucial role in the activation of microglia. "The microglia has an immune receptor called Siglec-E that recognizes polysialic acid," explains biochemist Dr. Hauke Thiesler. If the sugar molecule binds to the receptor, the microglia cells switch from the state "pro-inflammatory" to "anti-inflammatory".

This regulatory mechanism can apparently also be controlled from outside. By externally adding polysialic acid to cultures with living tissue sections, the researchers were able to show that previously destroyed

myelin sheaths were almost completely renewed as a result of an anti-inflammatory effect of polysialic acid on the microglia. The results are published in the journal *Frontiers in Cellular Neuroscience*.

Programming key cells for healing

"The microglial cells are the key cells that do the work directly on site and which we want to guide in a certain direction, so to speak, with the help of polysialic acid and thereby program them for healing," says the biochemist.

Because the destruction of the myelin sheaths and nerve cells has serious consequences that can affect all brain and spinal cord functions—but mainly the ability to move and coordinate, the sense of touch and the ability to see. For a large proportion of patients, multiple sclerosis brings severe disabilities.

"Activating the self-healing powers in the brain would be a promising support in MS therapy, which currently focuses exclusively on the immune system outside," says Dr. Lara-Jasmin Schröder from the Department of Neurology with Clinical Neurophysiology. "Those affected are usually 20 to 40 years old when clinical symptoms of MS first appear," says the medical biologist. This leaves plenty of time to intervene in the regeneration between MS attacks and prevent nerve damage.

Admittedly, the studies on the tissue section cultures have only limited significance. But the researchers are optimistic based on the "striking results" that myelin regulation also works in the living organism. "The advantage is that the Siglec-E receptor in the brain actually only sits on the microglia cells and the polysialic acid can therefore intervene there in a very targeted way," explains Dr. Thiesler.

And because the mechanism generally reduces inflammatory activity, the procedure could also be interesting for other neurodegenerative diseases, the biochemist suspects. Next, the research team would like to test the results in the animal model and use the MS expertise available in Lower Saxony for this.

More information: Lara-Jasmin Schröder et al, Polysialic acid promotes remyelination in cerebellar slice cultures by Siglec-E-dependent modulation of microglia polarization, *Frontiers in Cellular Neuroscience* (2023). DOI: 10.3389/fncel.2023.1207540

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