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Oligodendrocyte transporters feed axons

When we think of oligodendrocytes, we think myelination. But there is increasing evidence that there is much more to oligodendrocyte function than the myelin sheath, and new work shows that oligodendrocytes use a lactate transporter to provide metabolic support to axons and neurons.

Neurons and axons have very high energy demands but are isolated from extracellular metabolites by their myelin sheaths, except at the nodes of Ranvier. It is possible, therefore, that axons depend on energy substrates provided by oligodendrocytes. Rothstein and colleagues set out to test this idea by looking at monocarboxylate transporter 1 (MCT1), the most highly expressed lactate transporter in the CNS.

The authors began by using mice carrying fluorescence reporter genes to show that *Mct1* was almost exclusively expressed in oligodendrocytes. Next, they investigated whether MCT1 was required for neuronal survival in organotypic spinal cord cultures by reducing MCT1 function either genetically or pharmacologically. This reduction increased the death of motor neurons. Removing glucose from the cultures or increasing the metabolic demands of neurons by stimulating depolarization further increased neuronal death; however, when lactate was added to the culture medium, the motor neurons survived despite the reduction in MCT1 function. This provides strong evidence that motor neurons use lactate transported through MCT1 to support their high metabolic needs.

Downregulation of *Mct1* — through injection of a lentivirus that expressed a *Mct1* short hairpin RNA into the spinal cords of mice — also caused death of motor neurons *in vivo*. In a further experiment, the authors generated heterozygous *Mct1*$^{+/-}$ mice and found that although the mice had normal myelination, they gradually developed axonal pathology similar to that seen in patients with amyotrophic lateral sclerosis (ALS) and in animal models of ALS.

Could the loss of motor neurons in patients with ALS be mediated by a similar mechanism? The authors found that the expression of MCT1 was markedly reduced in the motor cortex of patients with ALS and in a mouse model of ALS. These results suggest that lack of access to lactate could contribute to the death of motor neurons in ALS.

These results broaden our understanding of oligodendrocyte function and axonal energy supply. They also support the emerging evidence that oligodendrocytes are involved in the pathogenesis of ALS and could point towards new therapeutic avenues.

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ORIGINAL RESEARCH PAPER Lee, Y. *et al.* Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature* 11 Jul 2012 (doi:10.1038/nature11314)