NEUROMUSCULAR DISEASE

Potential therapy for hereditary myopathy

Administering sialic acid metabolites to mice with distal myopathy with rimmed vacuoles (DMRV)–hereditary inclusion body myopathy (hIBM) prevents the onset of muscle atrophy, weakness and degeneration. "This demonstrates that hyposialylation is one of the key factors in the pathogenesis of DMRV–hIBM and suggests a therapeutic strategy for this debilitating myopathy," comments lead author May Christine Malicdan.

DMRV–hIBM is an incurable, autosomal-recessive myopathy that affects young adults, progressively rendering them wheelchair-bound within, on average, 12 years after symptom onset. Characteristic pathological findings include muscle fiber atrophy and degeneration, accompanied by rimmed vacuoles and intracellular inclusions.

DMRV–hIBM is caused by a mutated *GNE* gene, which encodes two enzymes that are essential in sialic acid biosynthesis. "This finding was perplexing; sialic acid is involved in a multitude of functions but its role in muscle is unclear. We hypothesized that DMRV–hIBM is caused by hyposialylation in cells, and that sialic acid replacement could be considered a rational strategy for therapy," adds Malicdan.

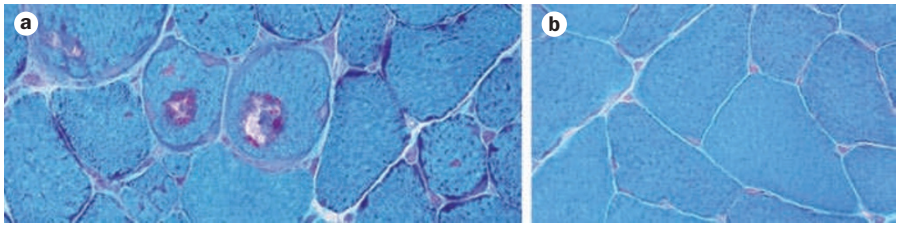

Figure 1 | Muscle sections from DMRV–hIBM mice. **a** | Without sialic acid treatment. **b** | With sialic acid treatment. Image provided by Dr May Christine Malicdan.

The researchers tested this hypothesis by adding sialic acid to the drinking water of DMRV–hIBM mice, a model that closely replicates the human phenotype (Figure 1a). Frequent administration of sialic acid via the preferred intragastric route compensates for its rapid excretion and short half-life, and provides a low, well-tolerated dose. The results also indicated good therapeutic potential—the onset of myopathic symptoms was prevented or delayed in most of the treated mice (Figure 1b).

"Current efforts are ongoing to start clinical trials, but we need to first clarify the role of sialic acid in muscle biology or show how hyposialylation directly contributes to the development of muscle atrophy and weakness," reports Malicdan.

Kathryn Senior

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