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Treatment of hyposialylation in mouse model of DMRV/hIBM with novel synthetic sugar compounds

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Distal myopathy with rimmed vacuoles or hereditary inclusion body myopathy (DMRV/hIBM) is an autosomal recessive disorder characterized by muscle atrophy, weakness that initially involves the distal muscles, and myofiber degeneration. DMRV/hIBM is secondary to mutations in the *GNE* gene, which encodes an essential enzyme in sialic acid biosynthesis. We recently showed that muscle atrophy and weakness were completely prevented in the DMRV/hIBM mouse after treatment with natural sugar compounds (NeuAc, ManNAc). Although this prophylactic treatment was effective, the increase of sialic acid was minimal in serum and modest in the skeletal muscles. To increase the serum and the bound sialic acid of tissues more remarkably, we screened several synthetic sugar compounds using primary human and murine DMRV/hIBM cultured cells and observed that cell sialylation was highest with tetra-*O*-acetylated ManNAc (Ac4ManNAc). To evaluate the efficacy of this compound in vivo, we administered Ac4ManNAc to DMRV/hIBM mice in two doses (40, 400 mg/kg/day) by oral and subcutaneous routes. Treatment of Ac4ManNAc dose-dependently improved survival, led to amelioration of muscle weakness and atrophy in DMRV/hIBM mice, and prevented appearance of RVs and occurrence of amyloid. More importantly, sialylation of serum and various tissues including skeletal muscle were increased by oral Ac4ManNAc to a level higher than those when natural compounds were used. Furthermore, Ac4ManNAc treatment improved sialylation status of some glycoproteins, like podocalyxin, in a dose-dependent manner. Our results support the use of Ac4ManNAc as a potential drug for therapy toward DMRV/hIBM.

縁取り空胞を伴う遠位型ミオパチーモデルマウスを用いた治療研究によって、アセチル化 ManNAc がミオパチーの発症を予防し、シアル酸量を増加させ、治療薬として天然型糖化合物（ManNAc、NeuAc）よりも有効であることを証明した。