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Novel approach to sialic acid therapy in DMRV/hIBM mouse model

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Distal myopathy with rimmed vacuoles (DMRV), or hereditary inclusion body myopathy (hIBM), is an autosomal recessive myopathy characterized clinically by progressive weakness and atrophy involving the distal muscles, and pathologically by the presence of myofiber vacuolation and degeneration. DMRV/hIBM is secondary to mutations in the *GNE,* a gene which is crucial in sialic acid biosynthesis. We have recently demonstrated that exogenous oral sialic acid metabolites can prevent the onset of myopathy in the DMRV/hIBM mouse, underscoring the role of hyposialylation in the pathogenesis of disease and highlighted a possibility for potential cure. Nonetheless, our previous report is not without limitation, as several issues remain to be clarified, including the nature of study design which was prophylactic, and the obvious short half life of oral sialic acids that require frequent or continuous intake.

In this study, we established allogenic bone marrow transplantation as justified choice for therapy on the principle of providing a continuous source of sialic acid-producing cells from the hematopoietic circulation, thus maintaining an acceptable level in the circulation. Bone marrow cells were isolated from CAG-GFP expressing mice and depleted of mature T cells, and administered to DMRV mice 30 weeks old after a single dose of sublethal irradiation. Chimerism using peripheral leukocytes after RBC lysis was assessed by FACS analysis four weeks after cell transplantation and monthly thereafter. Measurement of　sialic acid level in serum showed a steady increase in levels. Donor cells were seen to engraft into skeletal muscles and other organs of DMRV/hIBM mice. Analysis of muscle physiologic contractile properties and pathology revealed an improvement in muscle phenotype. Evaluation of specific glycoproteins in the muscle demonstrated a remarkable recovery of cellular sialylation. Our results provide a proof of concept for the utility of cell based therapies in DMRV/hIBM.

縁取り空胞を伴う遠位型ミオパチーの治療研究として、モデルマウスに、正常マウスの骨髄細胞を移植した。モデルマウスの表現型が回復した。