Mitochondria as a therapeutic target to improve muscle strength in Duchenne muscular dystrophy

MC Hughes¹, SV Ramos¹, C Bellissimo¹ and CGR Perry¹.

¹Muscle Health Research Center, School of Kinesiology, York University

Duchenne muscular dystrophy (DMD) is a severe muscle wasting disease affecting 1 in 3500 boys. A progressive decline in skeletal muscle function begins in early childhood eventually leading to complete immobility by early teenage years. While skeletal muscle atrophy manifests first within this disease, cardiac and/or respiratory failure is the ultimate cause of premature death amongst individuals with DMD. Presently, there is no cure for this debilitating disease. Current therapies are corticosteroid based and have successfully increased years of mobility as well as life-span in DMD patients, but unfortunately also result in many negative side effects. As such, the identification of new therapies that can not only extend lifespan but improve quality of life for individuals with DMD are of the utmost importance. In order to establish such therapies, it is necessary to elucidate the underlying cellular defects that contribute to muscle degeneration in DMD. Recent work from our laboratory identified impairments in mitochondrial bioenergetics (decreased oxygen consumption, elevated oxidative stress) in quadriceps and diaphragm muscle from 4-week old mice with DMD. These impairments were associated with decreased body weight, lean muscle volume and overall muscle function as well as increased levels of muscle damage. Beginning at 4 days of age, DMD mice were then treated with a mitochondrial-targeted peptide (SBT-20, Stealth Biotherapeutics, USA) that has been shown to improve mitochondrial respiration and lower mitochondrial reactive oxygen species. Following 4 weeks of treatment, while body weight of the drug treated animals was unchanged relative to untreated DMD animals and significantly lower than healthy wildtype (WT) controls, both lean muscle volume as well as muscle function (grip strength) were significantly improved in relation to DMD controls. These improvements were associated with increased mitochondrial respiration and lower mitochondrial reactive oxygen species emission in quadriceps and diaphragm muscle. Despite these improvements, specific force and mass of isolated quadriceps muscle and specific force of isolated diaphragm muscle remained unchanged relative to DMD and significantly lower than WT animals following drug treatment. Ongoing experiments will determine whether there were differences in muscle damage following drug treatment. Preliminary results from this study suggests SBT-20 lowers DMD disease severity through regional specific responses affecting muscle force or muscle mass and further highlights the mitochondria as a therapeutic target for this disease.