## Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis

*A.P. Russell,[1] S. Wada,[2] L. Vergani,[3] S. Lamon ,[1] T. Ushida,[2] G.D. Wadley,[1] G. Soraru,[3] C. Angelini[3] and T. Akimoto,[2] [1]Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC 3125, Australia, [2]Division of Regenerative Medical Engineering, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, Bunkyo, 13−0033 Tokyo, Japan and [3]Neurosciences Department, University of Padua, 35129 Padua, Italy.*

**Introduction:** Skeletal muscle mitochondrial dysfunction plays a role in amyotrophic lateral sclerosis (ALS). PGC-1α signalling and miRNAs are involved in mitochondrial biogenesis and muscle function. The regulation of PGC-1α and miRNAs have not been investigated in skeletal muscle of ALS patients. This study measured, in *vastus lateralis* muscle samples from healthy control subjects (n=10), patients with ALS (n=14) and patients with neurogenic disease (ND) (n=10): (1) expression levels of PGC-1α and several downstream targets involved in mitochondrial biogenesis and function; (2) mitochondrial enzyme activity and (3) expression levels of selected miRNAs. A functional protein/miRNA relationship was also investigated *in vitro* using reporter assays and *in vivo* using miR-23a transgenic mice.

**Results:** When compared with healthy control subjects, patients with ALS had reduced levels of PGC-1α mRNA and protein and ERRa and Mfn2 mRNA. NRF-1 and Mfn1 mRNA as well as COXIV mRNA and protein, as well as citrate synthase and COX activities, were also significantly lower in patients with ALS and ND. miRNA 23a, 29b, 206 and 455 were increased in skeletal muscle of ALS patients. miR-23a repressed PGC-1α translation in a 3′UTR dependent manner. Mice over expressing miR-23a also had a reduction in PGC-1α, cytochome-b and COXIV protein levels.

**Discussion/Conclusion:** Skeletal muscle mitochondrial dysfunction in ALS patients is associated with reduced PGC-1α and several of its targets involved in mitochondrial biogenesis and function, as well as increases in miRNAs potentially implicated in muscle and neuromuscular junction regeneration. miR-23a directly targets and reduces muscle PGC-1α protein levels, and impairs muscle mitochondrial function. The increase in miR-23a and associated decrease in PGC-1α protein levels in ALS potentially has a causal effect on muscle mitochondrial dysfunction. miR-23a may be a therapeutic target to ameliorate muscle function and pathogenesis of ALS.