Regulation of skeletal muscle microRNAs in young and old adults following acute resistance exercise

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Sarcopenia is the age-related loss of muscle mass and function. The onset and progression of sarcopenia is associated with attenuated activation of Akt/mTOR signalling, a key signalling pathway increasing muscle protein synthesis (MPS), in response to anabolic stimuli such as resistance exercise. MicroRNAs (miRNAs) are small regulatory molecules that selectively target and inhibit the expression of specific genes. MiRNA expression levels are sensitive to resistance exercise and they can also regulate muscle growth and regeneration. The regulation of miRNAs following resistance exercise, that may potentially influence the Akt/mTOR pathway, are poorly understood. This study investigated changes in miRNA expression following an acute bout of resistance exercise in young and old subjects, with a focus on miRNA species predicted to target Akt/mTOR signalling and MPS.

Ten young (18-30 years) and 10 older (60-75 years) males completed knee extensor exercise (3×14 repetitions) at 60% of maximal voluntary contraction. Muscle biopsies were collected before and 2 hours after exercise. Protein members of the Akt/mTOR signalling pathway were measured by western blot. MiRNA expression was measured using TaqMan® microRNA arrays and analysed bioinformatically (Ingenuity Systems IPA) for their association with the Akt/mTOR pathway and MPS.

Following resistance exercise phospho-Akt and phospho-p70 S6 kinase, a downstream target of mTOR, were elevated in all the subjects. Myostatin, a negative regulator of muscle mass was elevated in old subjects when compared to young subjects. Eight microRNAs were differentially expressed between young and old subjects at rest. Expression levels of another 20 miRNAs were modulated with exercise in young and/or old subjects. The miR-99a/b/100 family of miRNAs were reduced with exercise in young subjects and elevated with exercise in old subjects. This family of miRNAs is known to target the mTOR protein and indirectly regulates p70 S6 kinase phosphorylation. Bioinformatics analysis identified a further 6 miRNAs predicted to target members of the Akt/mTOR signalling pathway.

This study has identified 28 microRNAs that are differentially regulated with age and exercise in young and old subjects. Nine of these miRNAs are potentially important for the regulation of MPS *via* the Akt/mTOR signalling pathway. Modulating their expression levels in human primary muscle cells will provide further insight into their causal role in regulating Akt/mTOR signalling and MPS.