OXIDISED MICRORNAS AS NOVEL REGULATORS OF MUSCLE LOSS DURING AGEING

Raul Gonzalez-Ojeda, Gibran Pedraza-Vazquez, Karen Guerrero-Vazquez, Ana Soriano, Rachel McCormick, Anthony Sannicandro, Brian McDonagh, Katarzyna Goljanek-Whysall *. Department of Physiology, School of Medicine, NUI Galway, Galway, Ireland; University of Liverpool, UK

*Presenting author

There is currently a disproportionate increase in age-related health issues, with one of the major problems being the age-related loss of muscle mass and function sarcopenia. Redox and epigenetic factors are key regulatory pathways associated with ageing. MicroRNAs, stable RNAs with half-life >24h, regulate muscle homeostasis post-transcriptionally. Oxidative modification of microRNAs could result in the regulation of non-native targets. Redox balance is disrupted during ageing and the accumulation of oxidised, most likely pathogenic, microRNAs in muscle leads to their disrupted specificity for regulating protein content.

We have established microRNAs which are susceptible to oxidation in musclewasting conditions using RNA-Seq and oxi-RNA-Seq in different conditions, using muscle samples from mice and humans. The analyses of oxidised miR sequences revealed features associated with miR oxidation. We next validated miRs which were oxidised in muscle and profiled their target genes using RNA-Seq and global mass spectrometry in vitro and in vivo. Integrating omics and functional approaches, we have shown that miR-378 is oxidised in muscle of mice and humans during ageing and disease. Oxidised miR-378 regulates different genes to miR-378 and leads to myotube atrophy in vitro. Moreover, our data show that inhibiting oxidised miR-378 in old mice positively affects myofibre size and muscle strength. Together, these data demonstrate miR oxidation as a novel pathological mechanism of muscle wasting which may be amenable to therapeutic development.

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