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ELSEVIER SYMPOSIUM ON BIOLOGY OF AGING UNPACKED: IMPLICATIONS FOR GEROSCIENCE AND HEALTHSPAN

OXIDISED MICRORNAS – NOVEL MECHANISM OF MUSCLE AGEING?

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MicroRNAs (miRs) control two thirds of the protein-coding transcriptome, and act as key regulators of development and disease. miR expression changes in multiple tissues during ageing and disease. We have previously shown that microRNAs are important regulators of gene expression during muscle ageing. There is growing evidence for a new gene expression paradigm, in which miR oxidation can lead to dysregulated interactions with target mRNAs. We hypothesised that miR oxidation represents a novel mechanism of epitranscriptomic reprogramming in tissue homeostasis, and oxi-miR accumulation during ageing or disease disrupts gene regulation, leading to tissue degeneration. Given the extent of miR-mediated gene expression regulation, it is key to understand the potential and pitfalls of this phenomenon. We demonstrated that miRs are oxidised (oxi-miRs) during acute and chronic redox imbalance in muscle, using muscle samples from older people and cancer or COVID-19 patients, as well as mouse models of ageing, cachexia and critical illness. Using machine learning, we demonstrated microRNA features associated with increased likelihood of oxidation. We also identified several microRNAs consistently oxidised in muscle during pathological conditions. Next, we investigated the function of six oxidised miRs in vitro and in vivo. We demonstrated that oxidised miRs regulated different sets of genes than non-oxidised miRs and this results in phenotypic consequences. Moreover, miR oxidation appears to result in activation of cellular stress pathways. Finally, inhibition of oxi-miRs in vivo resulted in ameliorating loss of muscle size and strength in models of ageing. Together, these data demonstrate fundamentals of miR oxidation, oxi-miR-mediated gene targeting and signalling during redox imbalance and further deciphers fundamental biological mechanisms of miR-mediated gene regulation, a phenomenon with enormous biological and biomedical impact and potential therapeutic implications for muscle loss and beyond.

Keywords: *muscle ageing, sarcopenia, microRNAs, oxidised microRNAs.*