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ROLE OF MICRORNA-146a DEFICIENCY ON MUSCLE ATROPHY AND REGROWTH IN MICE

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Abstract:

Background: Aging is characterized by episodes of disuse atrophy followed by poor recovery. MicroRNA 146a (miR146a) regulates innate immunity, inflammatory responses and antiviral pathways by specifically blocking the translation of specific molecules within a common pro-inflammatory pathway (MyD88/NFKB). Research has found the miR146a expression regulates nuclear factor-kB (NF-kB) transcriptional activity, by inhibiting the molecules TRAF6, IRAK1, IRAK2 and possibly FADD which are all components of the MyD88 signaling cascade. As a consequence of targeting these regulatory components, expression and release of many pro-inflammatory cytokines are prevented. Dr. Drummond and colleagues have previously found that mice lacking miR146a were more susceptible to diet-induced obesity and heightened inflammatory pathways in several tissues. Moreover, Dr. Drummond's lab has shown that mice lacking MyD88 are protected from disuse-induced muscle atrophy and have reduced inflammation in the muscle. Since miR146a has an anti-inflammatory role, we hypothesized that mice deficient in miRNA-146a would have a worsened muscle inflammatory response following disuse translating into insulin resistance and further loss in muscle and poor recovery, thus mimicking an aged phenotype.

Objective: To better understand how miR146a effects muscle atrophy and regrowth we have conducted experiments and analysis on muscle tissue in mice that are deficient in miR146a, that have been exposed to hindlimb unloading (muscle disuse) and following 7d ambulatory recovery after hindlimb unloading. We hypothesize that in the absence of miR146a the mice will be insulin resistant and have excessive muscles loss during disuse and impaired muscle regrowth and following disuse when re-ambulating.

Methods: Age matched wild type (WT) and whole body miR146a knockout mice were randomly divided into 2 groups: 1) Ambulatory controls and 2) mice that undergo 14 days of hindlimb unloading followed by 7 days of ambulatory recovery (7dRec). All mice were monitored for water and food intake. For the mice that underwent recovery from hindlimb unloading (7dRec), the mice were removed from the hindlimb suspension apparatus, housed in individual cages, then allowed to freely ambulate for 7 days. Following the respective time points (i.e., 14d HU + 7d recovery), the mice were euthanized and then individual muscles from their hindlimbs (soleus, gastrocnemius, and plantaris) were dissected, frozen and prepared for histological examination. Muscle weights were calculated. Prior to termination, we conducted grip strength tests.

Results: When comparing the grip strength of the mice between the groups, miR146a KO mice had a weaker grip strength than the wildtype mice. Soleus, plantaris and gastrocnemius muscle weights and overall body weight responded similarly to hindlimb unloading and recovery in both groups.

Conclusion: We conclude that muscle from miR-146a KO mice responded similarly to WT age-matched animals during hindlimb unloading and recovery and is opposite what we hypothesized. Thus, although miR-146a KO mice were weaker to begin with, absence of miR146 does not further worsen muscle atrophy and recovery. Thus, we speculate that there might be a maximum disuse atrophy response that these mice undergo and lack of miR146 does not further contribute to muscle atrophy and poor recovery. Alternately, it is possible that miR-146a does not participate in muscle atrophy and rate of muscle recovery following disuse.

Due to COVID-19 I was unable to complete the study. The next steps would have been comparing macrophage subsets in muscle of miR146a and WT mice. I hope to continue this research in the future.

Figure 1. Grip strengths of miR 146a mice. Shows miR 146a mice that underwent the 14 day hindlimb unloading and 7 day recovery have a weaker grip strength than the miR 146a ambulatory control mice.

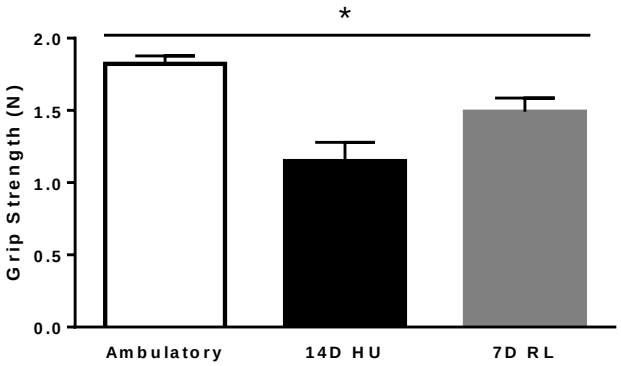

Figure 2. Soleus measurements miR 146a compared to control. Shows miR 146a are weaker than control mice that are the same age.

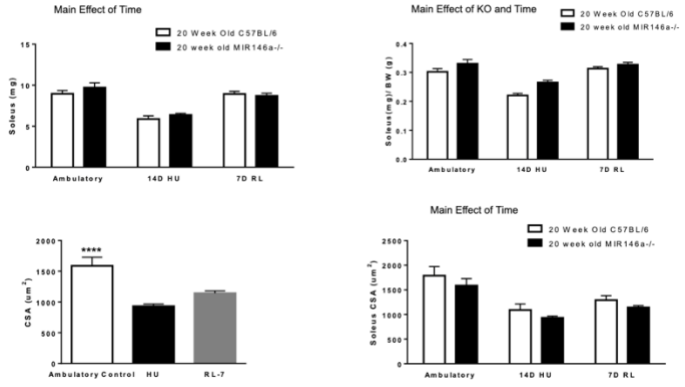

Figure 3. Plantaris and Gastrocnemius graphs. Shows Mir146a are weaker than control mice that are the same age.