Immunomodulation using Macrophage Colony Stimulating Factor or Voluntary Wheel Running Rescues Aged Skeletal Muscle Function following Disuse Atrophy

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ABSTRACT

INTRODUCTION

Aging impairs muscle regeneration and function following a period of disuse. Poor recovery of muscle size and strength with aging coincides with a suppressed macrophage response and increased fibrosis. Immunomodulation in the form of exercise and cytokine injections has been demonstrated to improve skeletal muscle regeneration. However, it is unclear if these macrophage-promoting approaches would improve skeletal muscle recovery following disuse in aged animals. Therefore, the purpose of this study was to examine the effectiveness of macrophage colony stimulating factors (MCSF) or voluntary wheel running (VWR) on the recovery of muscle and strength following disuse atrophy in aged mice. Methods: Aged (20-22 mm) male C57BL/6 mice were assigned to an ambulatory control, or underwent 14 days of hindlimb unloading or 14 days of hindlimb unloading followed 14 days of reloading. Mice in the recovery group received a single injection of MCSF or PBS in both triceps surae while a second group of recovery mice underwent 14 days of VWR. Results: We found that MCSF and VWR at the initiation of reloading enhanced soleus muscle regeneration and rescued grip strength above ambulatory control and PBS injection. Moreover, following MCSF and VWR, soleus muscle cross sectional area and the ratio of BHF/BPV (indicative of decreased fibrosis) was also elevated above control and PBS. Conclusions: Overall, these results suggest that immunomodulating approaches such as MCSF and VWR during the recovery phase for disuse atrophy restore aged skeletal muscle mass, myofiber size, and grip strength while also reducing muscle fibrosis.

RESULTS

Figure 1: MCSF Increases Macrophage Content in Aged Soleus Muscle During Initial Reloading Phase A) Experimental Design Figure depicting mice undergoing 14 days of hindlimb unloading followed by an MCSF injection and 4 days of reloading. B) Representative images of Luminex. C) MCSF (100ng) / MB2 (H2O), and an overlayed image with quantification of macrophages per mm2. Values are means ± SEM. Significance was set at p<0.05. *Significant different from each respective PBS population.

Figure 2: MCSF and Voluntary Wheel Running Improve Aged Muscle Recovery Following Disuse Atrophy A) Experimental design depicting treatment groups for PBS, MCSF, and VWR. B) Soleus Muscle mass to bodyweight ratio in HU, PBS, MCSF, and VWR mice. C) Laminin staining and quantification of cross sectional area for HU, PBS, MCSF and VWR mice. D) Grip strength normalized to bodyweight for HU, PBS, MCSF and VWR mice. E) BHF and COLIV staining for HU, PBS, MCSF, and VWR mice. Values are means ± SEM. Significance was set at p<0.05. *Significant different from PBS injection.

Figure 3: MCSF Improves Soleus Muscle Specific Following 14 Days of Recovery A) Specific force frequency curve of PBS control and MCSF mice following 14 day reload. B) Peak specific force in PBS and MCSF mice following 14 day reload. Values are means ± SEM. Significance was set at p<0.05. *Significant different from PBS.

CONCLUSIONS

- A single MCSF injection increases early macrophage recruitment in the soleus muscle of old mice (4 dayreload).
- MCSF and VWR improve soleus muscle to bodyweight following 14 days of reloading after disuse atrophy. MCSF and VWR also restored soleus muscle cross sectional area and grip strength following 14 days of reloading after disuse atrophy.
- MCSF and VWR improve the ratio of BHF/COLIV demonstrating improved fibrosis and improved peak specific force when compared to PBS treated mice during a 14 day reloading period.
- Overall, a single injection of MCSF as well as wheel access during recovery improve aged skeletal muscle recovery following a 14-day period of disuse atrophy.

REFERENCES


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