News Release

Title

Young bone marrow transplantation prevents aging-related muscle atrophy in a senescence-accelerated mouse prone 10 model

Key Points

• The SAMP10 mice that underwent young bone marrow transplantation (YBMT) showed an amelioration of aging-associated changes in the skeletal muscle size and dysfunction after 16 wks.

• At the molecular and cellular levels, YBMT elevated not only the plasma GDF-11 and HDL levels but also the levels of proteins or genes of IRS, p-Akt, p-mTOR, myogenin, COX-4, PGC-1α, and Bcl-2 and lowered the NADPH oxidase gp91phox subunit protein expression, superoxide production, and pro-apoptotic caspase-9 protein expression in the soleus and gastrocnemius muscles of SAMP10 mice.

• YBMT mice showed enhanced numbers of $PCNA^+$, $Pax7^+$ and $CD34^+$/integrin-$\alpha7^+$ cells and improved the regeneration of muscle.

• GDF-11 depletion diminished the YBMT-mediated muscle benefits, accompanied by harmful molecular changes (in gp91phox, Bcl-2, and caspase-9); these changes were rectified by rGDF-11 treatment.

Summary

These findings suggest that YBMT can prevent muscle wasting and dysfunction by mitigating apoptosis and proliferation via a modulation of GDF-11 signaling and mitochondrial dysfunction in SAMP10 mice.

Research Background

Young bone-marrow transplantation (YBMT) has been shown to stimulate vascular regeneration in pathological conditions, including aging. Here, we investigated the benefits and mechanisms of the preventive effects of YBMT on loss of muscle mass and function in a senescence-associated mouse prone 10 (SAMP10) model, with a special focus on the role of growth differentiation factor-11 (GDF-11).

Research Results

Nine-week-old male SAMP10mice were randomly assigned to a non-YBMT group and a YBMT group (n=7) that received the bone-marrow of 8-wk-old C57BL/6 mice. Compared to the non-YBMT mice, the YBMT mice showed the following significant increases ($p<0.05$): endurance capacity (>61.3%); grip strength (>37.9%), percentage of slow myosin heavy chain fibers (>14.9%–15.9%). The YBMT also increased the amounts of proteins or mRNAs for insulin receptor substrate-1, p-Akt, p-extracellular signal-regulated protein kinase1/2, p-mammalian target of rapamycin, Bcl-2, peroxisome proliferator-activated receptor-γ coactivator (PGC-1α),

plus cytochrome *c* oxidase-IV and the numbers of proliferating cells ($p<0.05$) and $CD34^+$/integrin-α_7^+ muscle stem cells ($p<0.05$). The YMBT significantly decreased the levels of gp91phox, caspase-9 proteins, and apoptotic cells ($p<0.05$) in both muscles; these beneficial changes were diminished by the blocking of GDF-11 ($p<0.05$). An administration of mouse recombinant GDF-11 improved the YBMT-mediated muscle benefits ($p<0.05$). Cell therapy with young bone marrow from green fluorescent protein (GFP) transgenic mice exhibited GFP^+ myofibers in aged muscle tissues.

Research Summary and Future Perspective

Cell therapy with bone marrow stimulates the muscles' responses in pathological conditions, including sarcopenia. However, the molecular mechanisms by which BM-MSCs improve the loss of muscle mass and function that are associated with aging are poorly understood. It was reported that therapies for patients with ischemic heart disease using stem and progenitor cells from aged patients have been disappointing [43]. Our present results indicate that in SAMP10 mice, sarcopenia can be ameliorated by YBMT via the improvement of protein anabolic responses, the imbalance between muscle apoptosis and proliferation, and mitochondrial biogenesis that are partially mediated by GDF-11 signaling. The transplantation of bone marrow from healthy young animals to animals at advanced ages in an attempt to restore the "young" muscle response should be investigated further as a powerful strategy that may prevent age-associated declines in muscle regeneration and function by recruiting and improving the delivery of BM-MSCs to the damaged muscle tissues.

Publication

Aiko Inoue, Limei Piao, Xueling Yue, Zhe Huang, Wenhu Xu, Chenglin Yu, Lina Hu, Xiangkun Meng, Hongxian Wu, Takeshi Sasaki, Kohji Itakura, Hiroyuki Umegaki, Masafumi Kuzuya, Xian Wu Cheng. Young bone marrow transplantation prevents aging-related muscle atrophy in a senescence-accelerated mouse prone 10 model. The paper on the above result was published online (before print) in an English journal *Journal of Cachexia, Sarcopenia and Muscle* on September 5, 2022.
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