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Losartan Improve the Muscle Regeneration Potential of Muscle Derived Stem Cell in Contusion Injury Mouse Model

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Summary:
Losartan could effectively enhance the beneficial effect of transplanted MDSC and reduce the scar formation and increase muscle regeneration in the injured skeletal muscle. These findings could contribute to the development of biological treatments to accelerate muscle healing after muscle contusion injury.

Abstract:
INTRODUCTION
Muscle contusions are one of the most common muscle injuries. Although these injuries are capable of healing, incomplete functional recovery often occurs. We have previously reported that losartan, one of the FDA approved Angiotensin II Receptor Blockers, can promote muscle healing and reduce the formation of fibrosis in injured skeletal muscle. It is also known that rapid revascularization after muscle injury is very important for early muscle healing, and we have previously reported that better functional recovery of injured skeletal muscle can be achieved by transplanting muscle with muscle derived stem cells (MDSCs). However, the MDSCs can differentiate toward a fibrotic lineage and in an attempt to limit this potential, and due to the fact that the transplantation of the MDSCs could not completely inhibit the formation of fibrosis. In this study, we combined the transplantation of MDSCs with the administration of losartan to see if we could further reduce the scar formation and increase muscle regeneration.

METHODS
The contusion injury model was created in the tibialis anterior (TA) muscle of mice. MDSCs were isolated from mice. 10mg/kg/day losartan were administered beginning 3 days post-injury and continued until the endpoint. At 4 days post-injury, MDSCs were transplanted into the injured TA muscle. Mice were divided into 3 groups, 1) MDSC/losartan group, 2) MDSC group, and 3) injured control group with PBS injection. At 1, 2, and 4 weeks post-injury, a muscle physiological testing was performed. After that, animals were euthanized and the TA muscles were evaluated histologically.

RESULTS
MDSC Transplantation Enhanced Muscle Regeneration in Injured Muscle: At 2 weeks post-injury. The MDSC treated groups showed a significantly higher number of regenerating myofibers when compared with the control group. Moreover, the diameters of the regenerating myofibers in the MDSC/losartan group were significantly larger when compared with the other groups.

Administration of Losartan Decreased Fibrosis Formation in Injured Muscle: At 4 weeks post-injury. The MDSC/losartan group had significantly less fibrotic area when compared with the control and MDSC groups.
MDSC Transplanted Muscle Showed Rapid Improvement of Muscle Torque: At 2 weeks post-injury, the MDSC treated groups showed significantly greater specific peak twitch and tetanic torques when compared with the control group.

At 4 weeks post-injury, the MDSC/losartan group showed a significantly greater specific peak tetanic torque when compared with the other groups.

MDSC Transplantation after Losartan Treatment Enhanced Follistatin, Smad7 and MyoD Expressions in Injured Muscle: At 1 week post-injury, the MDSC/losartan group showed significantly greater Follistaatin expression when compared with the other groups. At 2 weeks post-injury, the MDSC/losartan group showed significantly greater Smad7 and MyoD expression when compared with the other groups.

DISCUSSION

Losartan enhanced MDSC differentiation towards myogenic cells and inhibited fibrosis formation via an increase in Smad7 and MyoD expression. Furthermore, losartan enhanced the recovery of muscle torque. These results suggest a possible mechanism for the beneficial effects imparted by losartan when administered to MDSC transplanted skeletal muscle following injury. These findings could contribute to the development of biological treatments to accelerate muscle healing after muscle injury.