

Healthy Tendon Stem Cell-derived Exosomes Promote Tendon-to-bone Healing of the Aged-chronic Rotator Cuff Tear by Breaking the Positive-feedback Loop between Senescent Tendon Stem Cells and Macrophages

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INTRODUCTION: Senescent tendon stem cells (s-TSCs) generally exist in aged and chronically-torn rotator cuff tendons with greatly compromised multi-differentiation potencies, and they are closely associated with impaired tendon-to-bone healing results after surgical repair. Macrophages play a crucial role in the process of inflammatory infiltration after tissue damage or repair. It is reported that senescent cells secrete senescence-associated secretory phenotype that triggers a pro-inflammatory response. Thus, we inferred that there might be a positive-feedback loop between s-TSCs and macrophages, while additional healthy tendon stem cell-derived exosomes (h-TSC-Exos) treatment might break such a positive-feedback loop through modulation of macrophage polarization, alleviating senescent profiles of s-TSCs and improving tendon-to-bone healing results of aged-chronic rotator cuff tears (RCTs) after repair.

METHODS: First, in in-vitro studies, the cross-talk between s-TSCs and macrophages with regard to their biological profiles was studied. Second, the effect of additional h-TSC-Exos treatment on the cross-talk between s-TSCs and macrophages was then investigated. After that, h-TSC-Exos were loaded on a hyaluronic-acid based hydrogel, and the effect of h-TSC-Exos-loaded hydrogel (h-TSC-Exos-H) on tendon-to-bone healing results after repair was further investigated using an aged-chronic RCTs rat model through in-vivo studies. An unpaired, two-tailed Student's t-test was used to determine statistical significance between every two groups. One-way ANOVA with Tukey's post-hoc test was used for comparison of multiple groups.

RESULTS SECTION: S-TSCs with prominent senescent profiles (significant SA-β-gal and nuclear p16 and p21 staining, and compromised multi-potencies in tenogenic, chondrogenic, and osteogenic differentiation) accumulated in aged rats (18 months) with chronically torn rotator cuff tendons, and their conditioned medium (CM) was able to promote macrophage polarization mainly towards the M1 phenotype, whose CM reciprocally accelerated s-TSCs further senescence (increased SA-β-gal and nuclear p16 and p21 staining, and further compromised multi-potencies in tenogenic, chondrogenic, and osteogenic differentiation). Additional h-TSC-Exos (extracted from healthy TSCs-CM isolated from intact rotator cuff tendons in 6-month-old rats) treatment skewed macrophage polarization from the M1 phenotype to M2 phenotype, whose CM reciprocally alleviated senescent profiles of s-TSCs (reduced SA-β-gal and nuclear p16 and p21 staining, and improved multi-potencies in tenogenic, chondrogenic, and osteogenic differentiation). By use of the same aged-chronic RCTs rat model, h-TSC-Exos-H was found to be able to promote tendon-to-bone healing results with regard to both histological and biomechanical properties at 4 and 8 weeks postoperatively, which was achieved by skewing the micro-environment in the tendon-to-bone interface from a pro-inflammatory state to an anti-inflammatory state at acute postoperative stage (2 weeks postoperatively) and alleviating s-TSCs senescence.

DISCUSSION: H-TSC-Exos promote tendon-to-bone healing results of the aged-chronic RCTs by breaking the positive-feedback loop between s-TSCs and macrophages through modulation of macrophage polarization and alleviation of s-TSCs senescence.

CLINICAL RELEVANCE: The present study proposed a potential strategy to improve healing results of aged-chronic RCTs after surgical repair.

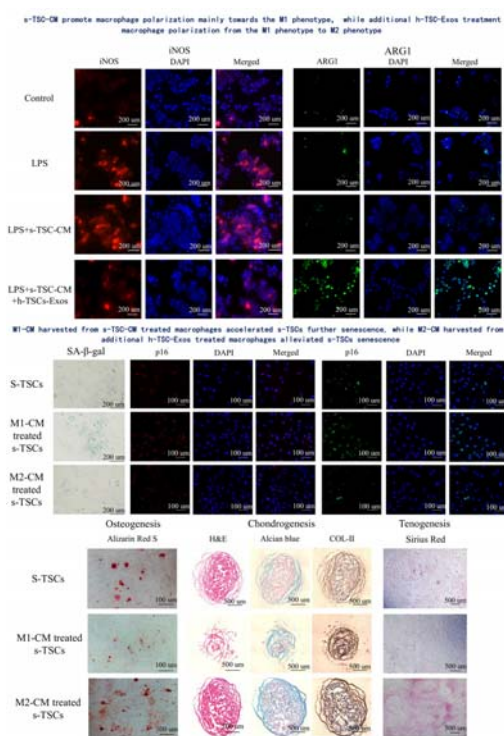


Figure 1

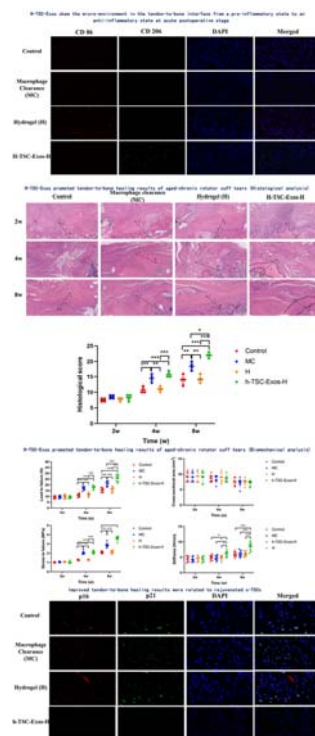


Figure 2