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Id 36

Systemic but not intra-articular infusion of human adipose-derived mesenchymal stromal cells (hAD-MSCs) attenuates acute arthritis flare in a rabbit model.

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BACKGROUND

Scarce data exist on the effect of mesenchymal stromal cell (MSC) as a therapy in acute joint inflammation. Dosing and rout of administration are essential factors to achieve a positive therapeutic outcome. Therefore, we aimed to compare different local intra-articular (IA) doses with a systemic infusion of MSCs to evaluate their anti-inflammatory effect in a model of acute gouty arthritis.

METHODS

- Gouty arthritis was induced in New Zealand white rabbits by IA injection of MSU crystals (50mg) in each knee. Controls received PBS instead.
- Systemically-treated rabbits (MSU+MSC AUR) received a single clinical-adjusted dose of $2x10^6$ hAD-MSCs/kg through the auricular artery.
- Two different IA doses of MSC were tested: Same dose as the systemic approach 10^6 MSC/kg (MSU+MSC IA-HIGH). Another group received a lower dose of $2.5x10^5$ MSC/kg (MSU+MSC IA-LOW) in each knee.
- Inflammation was followed up measuring knee swelling and serum C-Reactive Protein. Animals were sacrificed 72h after injury for histological studies in the synovium.

1 *Effect of systemic and local administration of hAD-MSCs in MSU crystal-induced arthritis model.*

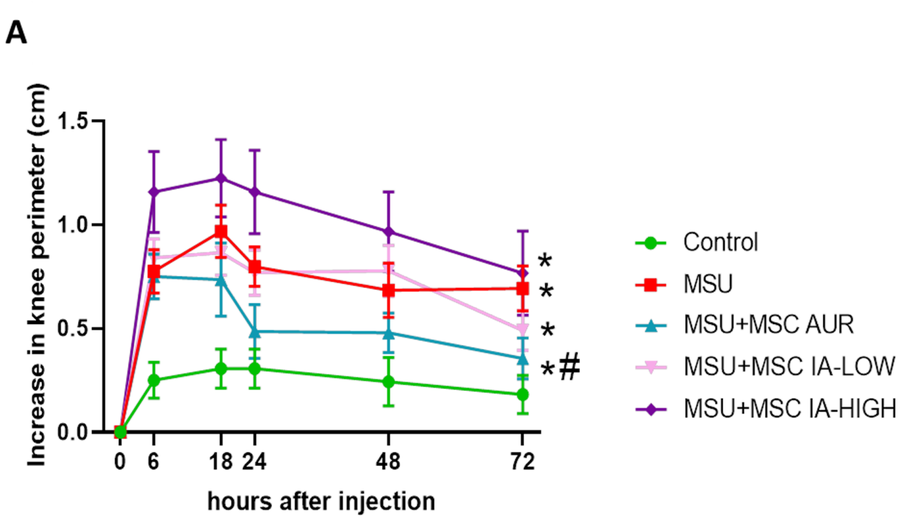

Figure 1. Systemic administration of hAD-MSC through the right auricular artery, but not local injection into the arthritic knee attenuates knee synovitis. A, joint swelling evolution of each limb during 72 h after MSU crystal injection, comparing different administration routes and doses. Bars show the mean and SEM (n = 10 for control, n = 22 for MSU, n = 18 for MSU+MSC AUR group, n = 6 for MSU+MSC IA-HIGH group, n = 16 for MSU+MSC IA-LOW group). Two-way ANOVA for the comparison between groups, *p<0.05 vs. Control, #p<0.05 vs. MSU. B, serum CRP concentration levels of each rabbit at 24 h and 72 h of study. Bars show the mean and SEM (n = 5 for control, n = 10 for MSU, n = 9 for MSU+MSC AUR group, n = 3 for MSU+MSC IA-HIGH group, n = 8 for MSU+MSC IA-LOW group). Mann-Whitney test, *p<0.05 vs. Control, #p<0.05 vs. MSU.

2 Immunohistochemical analysis of macrophage population within synovial membranes

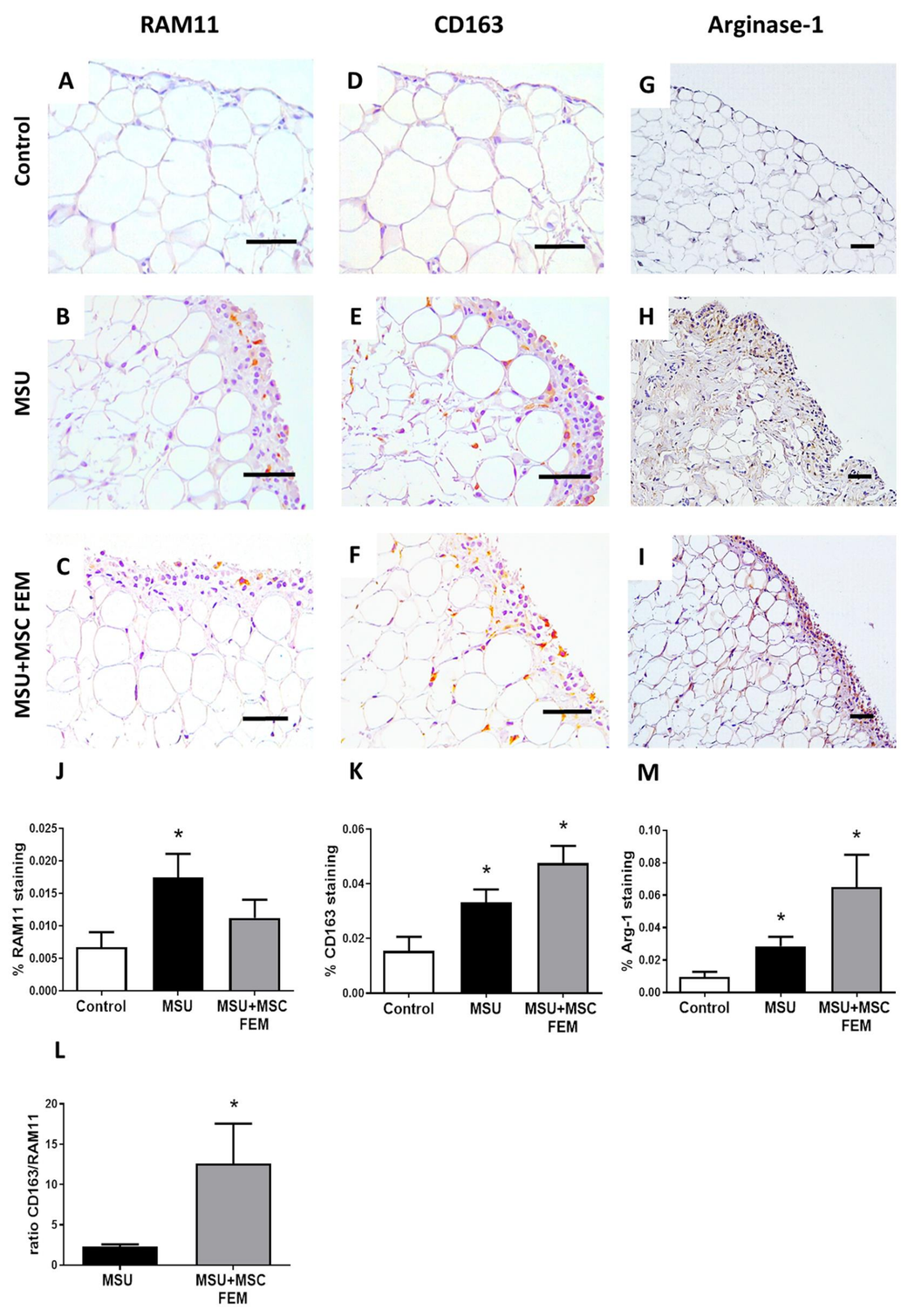

Figure 2. Systemic administration of hAD-MSCs promotes M" macrophage polarization in synovial membranes 72 hours after insult. Representative sections of RAM11 antigen staining (A-C) in the synovium of control (A), MSU and (B) and MSU+MSC FEM (C) groups; CD163 staining (D-F) in control (D), MSU and (E) and MSU+MSC FEM (F) groups; and arginase-1 staining (G-I) in control (G), MSU and (H) and MSU+MSC FEM (I) groups, scale bars = 50 µm. Densitometric analysis of RAM11 (J), CD163 (K), Arginase-1 (M) staining percentage in the synovium of each group. L, ratio of CD163 to RAM11 positive staining. Bars show the mean and SEM (n = 7 – 8 for controls, n = 14 for MSU and n = 9 – 12 for MSU+MSC FEM group). Mann-Whitney test, *p<0.05 vs. Control, #p<0.05 vs. MSU.

CONCLUSIONS

A single systemic dose of hAD-MSCs, but not IA administration, was able to attenuate the intensity and duration of the inflammatory response, favoring polarization of synovial macrophages to an anti-inflammatory phenotype.

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