Commonly Used Orthopaedic Clinical Therapeutics Affect the Cytokine Activity of Culture-Expanded Mesenchymal Stem Cells

Jacob G Calcei, Tracey L. Bonfield, Ryan Furdock[1], Laurie D Harrison, David Richard Fletcher[2], Evan Marshall Rudo, James Everett Voos[3]
[1]University Hospitals Cleveland Medical Center, [2]CWRU, [3]UNIVERSITY HOSPITALS CASE MEDICAL CENTER

INTRODUCTION: Hyaluronic acid (HA), platelet-rich plasma (PRP), and methylprednisolone are widely used to manage osteoarthritis (OA). More recently, human bone marrow derived mesenchymal stem cells (BM-MSCs) have garnered interest as a non-operative means for OA symptom modification. Anti-inflammatory cytokine secretion is a major component of BM-MSC action. We sought to describe the effect of HA, PRP, and methylprednisolone on the cytokine profile of BM-MSCs at multiple stages of culture expansion.

METHODS: Nine BM-MSC cell lines from 4 human donors underwent three stages of culture expansion: passage 2 (P2), passage 3 (P3), and passage 4 (P4). Levels of OA-related cytokines (IL-1β, IL-6, IL-8, IL-10, Stem cell Factor [SCF], Stem Cell Derived Factor-alpha [SDF-α]) were measured using Luminex multiplexing technology. The BM-MSC preparations were evaluated at each passage, 24 hours following exposure to HA, PRP, or methylprednisolone.

RESULTS: Culture expansion altered cytokine production, however treatment with OA therapeutics further altered these responses implicating the potential of combined treatment of culture expanded hMSCs and OA therapeutics. Figure 1 demonstrates the behavior of cytokines after exposure to HA, PRP or methylprednisolone. Further, we tested different concentrations of the therapeutics to determine optimal dosing.

Exposure to increasing doses of HA reduced BM-MSC expression of SCF, SDF-α, VEGF, CCL20, and adiponectin ($p<0.05$ for all). PRP increased IL-1 levels in P2 and P3 ($p<0.05$ for both), IL-6 in P2 (100 pg/mL vs 5500 pg/mL, $p<0.001$), and IL-8 in P3 (900 pg/mL vs 3900 pg/mL, $p<0.001$). PRP did not affect IL-10 expression ($p>0.05$). Aside from an increase in IL-6 production for P2 (200 pg/mL vs 1500 pg/mL, $p<0.05$), methylprednisolone did not affect cytokine expression.

DISCUSSION AND CONCLUSION: Orthopaedic therapeutic adjuvants influence the inflammatory cytokine profile of BM-MSCs at multiple stages of culture expansion. These therapeutics have potential to be used with BM-MSCs to create an optimal cytokine environment for treatment of degenerative joint disease.

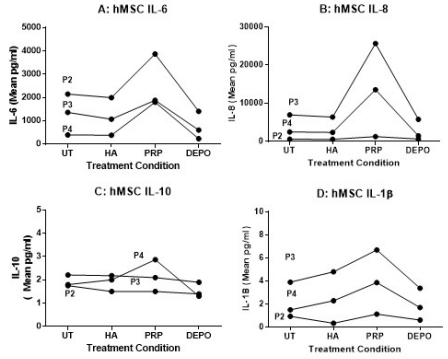

Figure 1: hMSCs and Osteoarthritis Adjuvants. Human bone marrow derived hMSCs were culture expanded over 4 passages and treated with hyaluronan (HA), platelet rich plasma (PRP) and methylprednisolone (DEPO). Culture expansion significantly altered cytokine production, however treatment with current OA therapeutics further altered these responses implicating the potential of combined treatment of culture expanded hMSCs with OA therapeutics.