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**Synovial Fluid Proteomics and Bioinformatics Highlights Potential Mechanisms of Umbilical Cord-MSC Induced Radiographic Improvement in an Ovine Model of Osteoarthritis**

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**Objectives**

A promising therapy for early osteoarthritis (OA) is the transplantation of human umbilical cord-derived mesenchymal stromal cells (hUC-MSCs).The synovial fluid (SF) from a pre-clinical ovine model treated with hUC-MSCs has been profiled using proteomics and bioinformatics to elucidate potential mechanisms of therapeutic effect.

**Methods**

Four weeks after a medial meniscus transection surgery, sheep were injected with 107 hUC-MSCs in Phosphate Buffered Saline (PBS) or PBS only (n=7) and sacrificed at 12 weeks. SF was normalised for protein abundance (ProteoMinerTM) and analysed using label-free quantitation proteomics. Bioinformatic analyses (Ingenuity Pathway Analysis (IPA) and STRING) were used to assess differentially regulated functions from the proteomic data. Human orthologues were identified for the ovine proteins using UniProt and DAVID resources and proteins that were ≥±1.3 fold differentially abundant between treatment groups, were included in the bioinformatics analyses.

**Results**

hUC-MSC treated animals demonstrated significantly less joint space narrowing. Nineteen SF proteins were differentially abundant in treated compared to control sheep (FC±2.0; p<0.05). Biglycan (a small leucine-rich proteoglycan of the cartilage extracellular matrix) abundance was increased by 2.1 fold in treated compared to untreated sheep (p=0.024). IPA indicated that lipid synthesis (z-score=1.772; p=0.00267) and immune cell migration pathways (cell movement of mononuclear leukocytes: z-score=1.761; p=0.00259), amongst others, were likely to be activated in the treated sheep. Conversely, tissue damage (z-score=-2; p=0.00019), senescence (z-score=-1.981; p=0.00007) and necrosis (z-score=-1.728; p=0.00829) associated pathways as well as inflammation (z-score=-1.718; p=0.00057) and vascular permeability (z-score=-1.698; p=0.00002) were likely to be inhibited in treated cf. untreated sheep.

**Conclusions**

hUC-MSC treatment prevented/delayed OA progression, demonstrated via a reduction in joint space narrowing. SF proteome bioinformatics revealed potential mechanisms of therapeutic action related to immunomodulation and the inhibition of multiple cell death, and tissue damage associated pathways. Further, a potential predicted upregulation in lipid synthesis in treated sheep represents a novel mechanism warranting further investigation.

Additional work is required to validate our discovery phase proteomic findings in studies which specifically target and manipulate the proposed mechanisms highlighted in this study.