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Aggregation of human Mesenchymal Stem/Stromal cells (hMSCS) into spheroids enhances their anti-inflammatory potential

Joni H. Ylostalo
Texas A&M Health Science Center, USA

Mesenchymal stem/stromal cells (MSCs) have drawn great interest recently as a possible therapeutic cell for multiple diseases because of their ability to home to sites of injury, modulate inflammation, inhibit apoptosis, and activate exogenous stem cells. Previous reports suggested that culture as aggregates/spheroids can increase the therapeutic potential of MSCs. To study the effects of aggregation on MSCs in detail and how aggregation relates to the anti-inflammatory effects observed *in vivo*, MSCs were grown in hanging drops to promote spheroid formation. MSCs aggregated rapidly and compacted into a spheroid, causing dramatic changes in their transcriptome. MSC spheroids and spheroid conditioned medium (CM) strongly inhibited stimulated macrophages from secreting pro-inflammatory cytokines while increasing the secretion of anti-inflammatory cytokines, and increased the number of macrophages expressing CD206. The anti-inflammatory activity of CM from spheroid MSCs was abolished by an inhibitor of COX2, a siRNA for COX2 and an antibody to PGE2. Furthermore, the anti-inflammatory action of MSC-derived PGE2 on stimulated macrophages was mediated by the EP4 receptor. Gene expression assays of MSC spheroids demonstrated an increased expression in Notch and IL1 signaling molecules. Inhibition of IL1 signaling with neutralizing antibodies, or IL1 receptor antagonist abolished the production of PGE2 and the anti-inflammatory effects of MSC aggregates on stimulated macrophages. Similar results were obtained when Notch signaling was inhibited. The novel finding of coordination of Notch and IL1 signaling in MSCs in relation to the potent PGE2-mediated anti-inflammatory effects highlights the stemness nature of these cells with promises of great therapeutic interventions.

Biography

Joni H. Ylostalo received his PhD from Tulane University in Biomedical Sciences in 2008 under the supervision of Dr. Darwin J. Prockop studying human mesenchymal stem/stromal cells (hMSCs) at the Center for Gene Therapy. Since 2008 Joni has served as a Senior Research Associate at the Institute for Regenerative Medicine at Texas A&M Health Science Center performing translational and basic research with hMSCs. Joni is also the Director of the Microarray Core Facility at the institute. He has over 30 peer-reviewed publications in various national and international journals concerning MSCs, gene expression analysis, and protein biochemistry.

Ylostalo@medicine.tamhsc.edu