Mesenchymal Stem Cells and Biomaterials for Orthopaedic Applications

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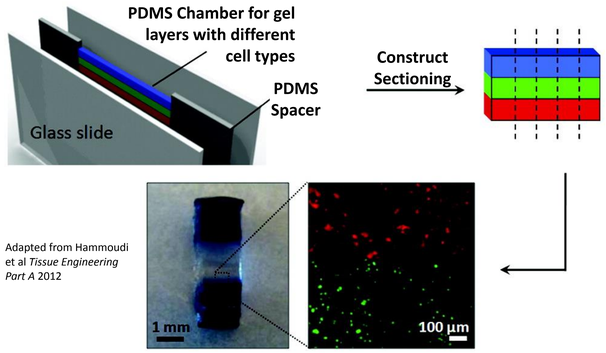
Mesenchymal Stem Cell Co-Culture Model

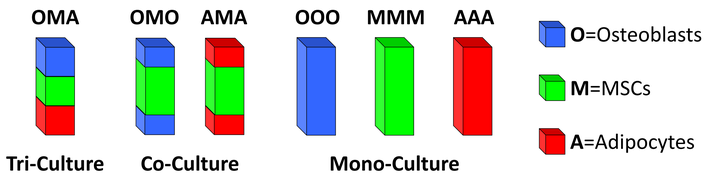
Bulk Hydrogel Culture Platform

- PEG-DA hydrogels can be used to create co-culture systems that mimic stem cell microenvironment



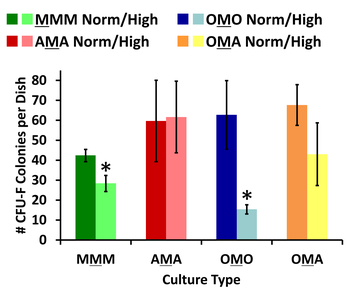
Experimental Design

- Constructs were cultured in normal and high glucose conditions for 7 days



MSC Clonogenicity

- MSC hydrogel blocks were degraded post-culture and MSC colony-forming ability was measured using colony-forming assays



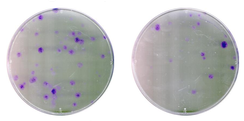
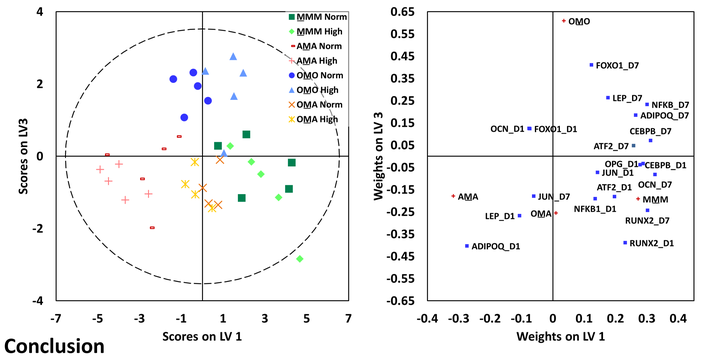


Figure 1. Images of MSC colonies.

Figure 2 (left). Number of MSC colonies at each condition. * = significantly different than the same set of neighboring cells at normal glucose, $p < 0.05$.

MSC Gene Expression

- MSCs gene expression was measured with qPCR and analyzed using multivariate statistical methods



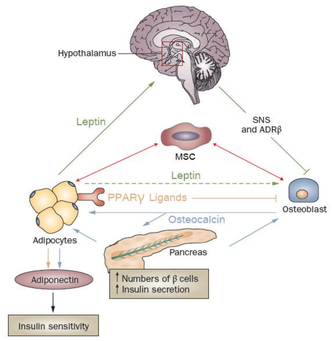
Conclusion

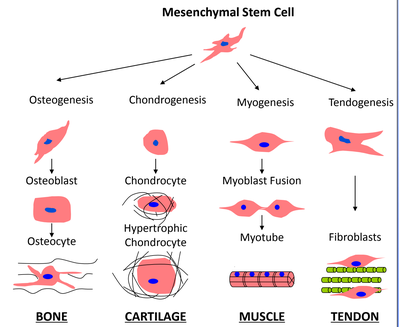
- MSCs were uniquely responsive to neighboring cells and glucose levels, indicating that hydrogels can be used to model the *in vivo* environment

Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs)

- Multipotency allows differentiation into various orthopaedic cell types
- MSC in aggregate form have anti-inflammatory properties





Caplan, A.,Tissue Engineering, 2005.

MSC Microenvironment

- Involves complex interactions between cells, ECM, and soluble factors
- Regulates MSC behavior
- Has been observed to change in disease states

MSCs can be utilized in model systems to study cell interactions in orthopaedic diseases and as a cell therapy to treat injured orthopaedic tissue.

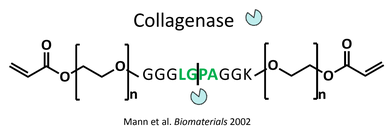
Biomaterials

PEG-DA Hydrogel

Poly(ethylene-glycol)-diacrylate (PEG-DA)

- Cytocompatible
- Can be photopatterned
- Allows integration of adhesive peptides to promote cell viability

MMP-Sensitive PEG-DA Material



Mann et al. *Biomaterials* 2002

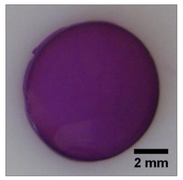
Collagenase-Sensitive PEG-DA

- Integration of collagenase-degradable amino acid sequence into PEG-DA polymer
- Allows viable MSC retrieval after at least 7 days of culture

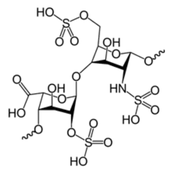
Heparin Glycosaminoglycan

- Used in clinical practice as an anti-coagulant
- Administered to patients with strong inflammatory pathologies:
  - Asthma
  - Ulcerative colitis
  - Burns
- Potential anti-inflammatory effects inhibit of cytokine production and cell migration

Heparin Hydrogel



Heparin Structure



Biomaterials can be utilized to direct stem cell response in a variety of applications for orthopaedic tissue engineering.

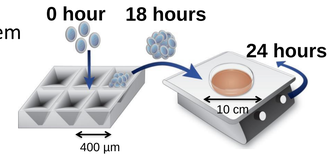
Acknowledgements

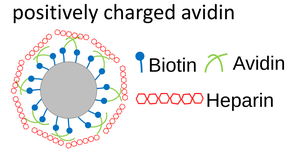
NSF Stem Cell Biomanufacturing IGERT to JL and TER:, NIH CTEng to JL; NSF CAREER award to JST, 21EB009153 to JST, Texas A&M Health Science Center College of Medicine, Institute for Re-generative Medicine at Scott & White Healthcare for human MSCs through a grant from NCRR of the NIH (P40RR017447), and the McDevitt Laboratory at Georgia Tech for suspension rotary culture use.

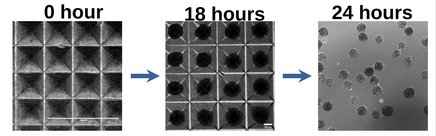
Mesenchymal Stem Cell Therapies

Heparin-Coated MSC Spheroids

- MSCs are aggregated in AggreWell™ system
- Spheroids are coated with heparin using layer-by-layer deposition of biotin and avidin
- Heparin electrostatically interacts with positively charged avidin







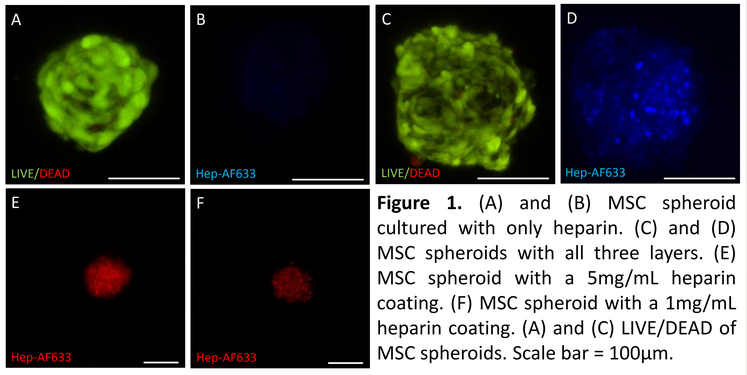


Figure 1. (A) and (B) MSC spheroid cultured with only heparin. (C) and (D) MSC spheroids with all three layers. (E) MSC spheroid with a 5mg/mL heparin coating. (F) MSC spheroid with a 1mg/mL heparin coating. (A) and (C) LIVE/DEAD of MSC spheroids. Scale bar = 100µm.

MSC Spheroid Anti-Inflammatory Response

- Anti-inflammatory response of coated spheroids were assess through PGE2 production and TNF-α reduction

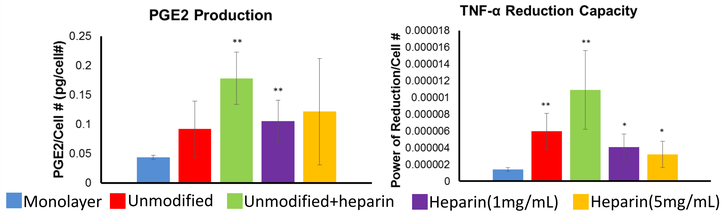


Figure 2. n=6; * indicates significant difference from unmodified spheroid with heparin ($p \leq 0.05$); **indicates significant difference from monolayer ($p \leq 0.05$).

MSC Spheroid Heparin Release

- Heparin coating was released from spheroid surfaces after 1 day, whereas, biotin-heparin surfaces remain localized to cells

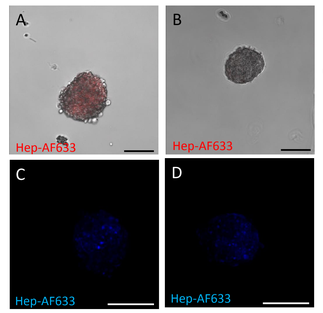
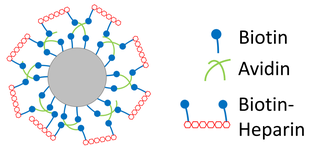


Figure 3: MSC spheroid with heparin coating immediately after modification (A) and after 1 day of culture (B). MSC spheroid coated with biotin-heparin immediately after modification (C) and after 1 day of culture (D). Scale bar = 100µm.



Conclusion

- MSC spheroids can be coated with heparin without compromising viability
- Heparin coating does not decrease anti-inflammatory properties of MSCs
- Heparin can be modified with biotin to retain heparin on cell surface