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Engineering hydrogels for dynamic modulation of stem cell activity

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Introduction. Patient derived mesenchymal stem cells (MSCs) are a promising cell-based autologous therapy for numerous diseases due to the propensity to differentiate to numerous lineages without risk of rejection. Another interesting aspect of the therapeutic potential of these cells is their proven ability to secrete molecules that are immunomodulatory and pro-angiogenic, e.g. living cytokine factories, which may be implanted at a site of injury to promote healing. However, clinical efficacy has proven to be variable, which we postulate is due in part to insufficient control over the injectable biomaterials employed. In our laboratory we have noted a gradual loss of the multipotent phenotype during expansion on tissue culture plastic, and we recently showed how controlling extracellular matrix properties can attenuate this loss of "stemness"(1) and direct the MSC secretome and its pro-angiogenic properties(2).

In this paper I present our strategy designing materials to engineer MSC secretion. First I will demonstrate a combinatorial approach to identify optimal materials properties for promoting secretion of pro-angiogenic molecules from MSCs. Next I will show how micropatterning single cells can be used to activate a pro-angiogenic phenotype that may prove useful for in vitro "priming" of MSCs prior to therapy. Finally, I will demonstrate a magnetically-tunable hydrogel that can stiffen in response to permanent magnets for dynamic control of both MSC differentiation and secretion of pro-angiogenic molecules.

Results. Polyacrylamide hydrogels were fabricated across a range of physiologically relevant mechanical properties and chemically functionalized to enable covalent conjugation of oxidized glycoproteins using a polydimethylsiloxane stamp. By changing subcellular curvature at the perimeter of single cells we were able to modulate the MSC secretome and enhance tubulogenesis in human microvascular endothelial cells (hMVECs; **Figure 1A**). Chemically functionalized magnetic iron particles were embedded in a polyacrylamide matrix followed by matrix protein conjugation and MSC culture. Using permanent magnets we 'switched' the gel properties between soft and stiff and demonstrate a change in MSC spread area. Conditioned media from the MSC cultures were used in a functional angiogenesis assay that employs human microvascular endothelial cells (hMVECs) within 3D matrigel. Treating hMVECs with conditioned media from MSCs cultured under a magnetic field showed higher angiogenic potential than those cultured without a magnetic field (**Figure 1B**).

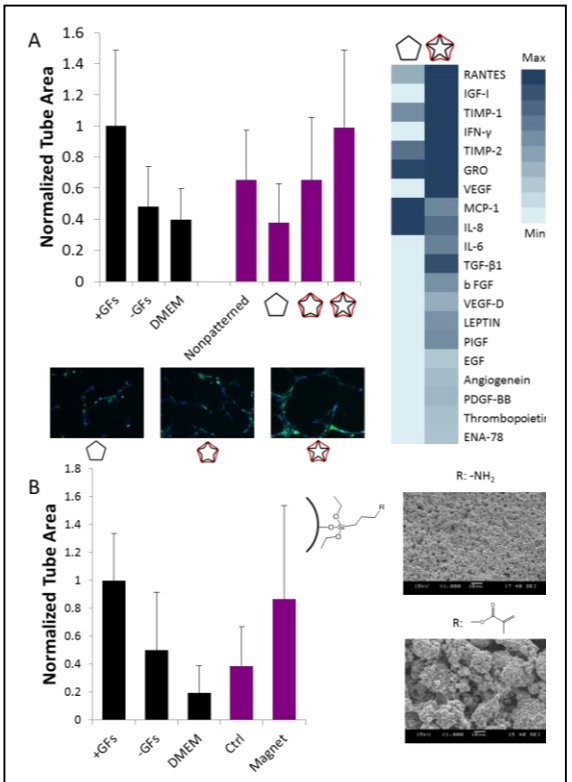

Figure 1. Tubulogenesis in microvascular endothelial cells when treated with conditioned media from (A) mesenchymal stem cells cultured in different geometries; (B) mesenchymal stem cells cultured on magnetoactive hydrogels. Right: scanning electron micrograph of functionalized carbonyl iron particles within polyacrylamide.

Conclusions. Controlling the materials properties and the geometry of single cells during *in vitro* stem cell culture can be used to engineer a desired, therapeutically relevant, phenotype. Incorporating functionalized iron particles into hydrogel matrices enabled magnetoactive hydrogels, that reversible respond to fields for guidance of pro-angiogenic signaling. These combinations of tools will prove useful for defining the optimal materials properties for stem cell-based therapies, and may further serve as a mechanism to activate a patients cells *ex vivo* prior to implantation.

(1) Lee et al., ACS Biomaterials Science and Engineering, 2015, 1, 218-226
(2) Abdeen et al., Tissue Engineering Part A., 2014, 20 (19-20), 2737-2745