Multifunctional hydrogels that promote osteogenic hMSC differentiation through stimulation and sequestering of BMP2

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The extracellular environment is known to control many cell functions including differentiation. In tissue engineering research, synthetic extracellular environments have often been tailored to provide cells with a physical or chemical cue, essentially enabling the transmission of outside-in signals. In addition, more complex systems have been designed that present cells with growth factors that can be released upon demand, enabling bidirectional (i.e., from the scaffold to the cells and from the cells to the scaffold). Here, we functionalized poly(ethylene glycol) hydrogels with fluvastatin delivery molecules and heparin to enable bidirectional signaling. First, by incorporating a fluvastatin releasing monomer and carefully controlling the dose and release profile of this therapeutic to provide encapsulated cells with a constant dose over about one week, BMP2 and ALP production by human mesenchymal stem cells (hMSCs) was increased 2.2-fold and 1.7-fold at day 28 over hMSCs cultured in the absence of fluvastatin. By introducing a heparin functionality to sequester and localize hMSC-produced BMP2, the osteogenic differentiation of hMSCs was augmented over fluvastatin delivery alone. Osteopontin and CBFA1 gene expression was 6-fold and 4-fold greater by hMSCs in heparin-functionalized, fluvastatin delivering hydrogels versus no heparin controls at day 28. Therefore, by introducing a means for bidirectional signaling, intelligent biomaterials can be designed to very quickly result in the osteogenic differentiation of hMSCs.