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Recapitulating bone development through engineered mesenchymal condensations and mechanical cues for tissue regeneration

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Abstract

Large bone defects cannot form a callus and exhibit high complication rates even with the best treatment strategies available. Tissue engineering approaches often use scaffolds designed to match the properties of mature bone. However, natural fracture healing is most efficient when it recapitulates development, forming bone via a cartilage intermediate (endochondral ossification). Because mechanical forces are critical for proper endochondral bone development and fracture repair, we hypothesized that recapitulating developmental mechanical forces would be essential for large bone defect regeneration in rats. Here, we engineered mesenchymal condensations that mimic the cellular organization and lineage progression of the early limb bud in response to local transforming growth factor–β1 presentation from incorporated gelatin microspheres. We then controlled mechanical loading in vivo by dynamically tuning fixator compliance. Mechanical loading enhanced mesenchymal condensation–induced endochondral bone formation in vivo, restoring functional bone properties when load initiation was delayed to week 4 after defect formation. Live cell transplantation produced zonal human cartilage and primary spongiosa mimetic of the native growth plate, whereas condensation devitalization before transplantation abrogated bone formation. Mechanical loading induced regeneration comparable to high-dose bone morphogenetic protein-2 delivery, but without heterotopic bone formation and with order-of-magnitude greater mechanosensitivity. In vitro, mechanical loading promoted chondrogenesis and up-regulated pericellular matrix deposition and angiogenic gene expression. In vivo, mechanical loading regulated cartilage formation and neovascular invasion, dependent on load timing. This study establishes mechanical cues as key regulators of endochondral bone defect regeneration and provides a paradigm for recapitulating developmental programs for tissue engineering.

Keywords: spongiosa; mechanosensitivity; mechanosensitivity; chondrogenesis; pericellular; angiogenic; neovascular