

Angiogenesis Is Required for Successful Bone Induction During Distraction Osteogenesis

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ABSTRACT: The role of angiogenesis during mechanically induced bone formation is incompletely understood. The relationship between the mechanical environment, angiogenesis, and bone formation was determined in a rat distraction osteogenesis model. Disruption of either the mechanical environment or endothelial cell proliferation blocked angiogenesis and bone formation. This study further defines the role of the mechanical environment and angiogenesis during distraction osteogenesis.

Introduction: Whereas successful fracture repair requires a coordinated and complex transcriptional program that integrates mechanotransductive signaling, angiogenesis, and osteogenesis, the interdependence of these processes is not fully understood. In this study, we use a system of bony regeneration known as mandibular distraction osteogenesis (DO) in which a controlled mechanical stimulus promotes bone induction after an osteotomy and gradual separation of the osteotomy edges to examine the relationship between the mechanical environment, angiogenesis, and osteogenesis.

Materials and Methods: Adult Sprague-Dawley rats were treated with gradual distraction, gradual distraction plus the angiogenic inhibitor TNP-470, or acute distraction (a model of failed bony regeneration). Animals were killed at the end of distraction (day 13) or at the end of consolidation (day 41) and examined with μ CT, histology, and immunohistochemistry for angiogenesis and bone formation ($n = 4$ per time-point per group). An additional group of animals ($n = 6$ per time-point per group) was processed for microarray analysis at days 5, 9, 13, 21, and 41.

Results and Conclusions: Either TNP-470 administration or disruption of the mechanical environment prevented normal osteogenesis and resulted in a fibrous nonunion. Subsequent analysis of the regenerate showed an absence of angiogenesis by gross histology and immunohistochemical localization of platelet endothelial cell adhesion molecule in the groups that failed to heal. Microarray analysis revealed distinct patterns of expression of genes associated with osteogenesis, angiogenesis, and hypoxia in each of the three groups. Our findings confirm the interdependence of the mechanical environment, angiogenesis, and osteogenesis during DO, and suggest that induction of proangiogenic genes and the proper mechanical environment are both necessary to support new vasculature for bone induction in DO.

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Key words: biomechanics, distraction osteogenesis, angiogenesis, TNP-470, microarray analysis