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Hypoxia regulates osteoblast gene expression.

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Vascular disruption secondary to fracture creates a hypoxic gradient of injury wherein the oxygen tension at the center of the wound is very low. In vivo this hypoxic microenvironment stimulates the expression of a variety of cytokines from inflammatory cells, fibroblasts, endothelial cells, and osteoblasts. In order to begin to dissect this complex system, we have examined the effects of hypoxia on isolated osteoblast gene expression in vitro. Understanding gene expression in this system may facilitate the development of targeted therapeutic modalities designed to accelerate fracture repair and reduce complications. Using an established model of in vitro hypoxia, we have analyzed the expression of genes involved in bone matrix production and turnover. Subconfluent neonatal rat calvarial osteoblasts were exposed to hypoxia (pO(2) = 35-40 mm Hg) and total cellular RNA was collected at 0, 3, 6, 24, and 48 h. Northern analysis was used to analyze the expression patterns of (1) transforming growth factors (TGFs)-beta1, -beta2, and -beta3 and their type I receptor; (2) collagens I and III; and (3) tissue inhibitor of metalloproteinase-1. We have demonstrated a marked elevation of TGF-beta1 gene expression within 3 h of hypoxia. Although neither TGF-beta2 nor TGF-beta3 expression was affected by hypoxia, the TGF-beta type I receptor was substantially upregulated within 6 h. In addition, extracellular matrix scaffolding molecules (collagens I and III) were markedly, but differentially, upregulated. Finally, we have demonstrated that the expression of an inhibitor of extracellular matrix turnover, the tissue inhibitor of metalloproteinase-1, was strikingly decreased in response to hypoxia. These results imply that hypoxia can affect osseous healing by altering the expression of cytokines, bone-specific extracellular matrix molecules, and their regulators.

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