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Connective Tissue Growth Factor (CTGF) Promotes Osteoblast Differentiation and Stimulates Bone Formation

S. N. Popoff*¹, F. F. Safadi*¹, M. D'Angelo*¹, A. H. Selim¹, V. Zakhaleva¹, S. L. Smock², T. A. Castleberry*², B. Lu², S. C. Marks*³, T. A. Owen*². ¹Anatomy and Cell Biology, Temple Univ. School of Medicine, Philadelphia, PA, USA,

²Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Groton, CT, USA, ³Cell Biology, Univ. of Massachusetts Medical School, Worcester, MA, USA.

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Connective tissue growth factor (CTGF) is a secreted, extracellular matrix-associated protein that regulates diverse cellular functions. CTGF mRNA expression and protein production has been demonstrated in various cell types including fibroblasts, endothelial cells, chondrocytes, and most recently by our lab, in osteoblasts. In primary cultures of osteoblasts, CTGF mRNA levels exhibit a bimodal pattern of expression being relatively high during proliferation and increasing again to peak levels as the cells terminally differentiate. Furthermore, the protein is synthesized by osteoblasts and secreted into the medium. For this study, we generated recombinant rat CTGF (rCTGF) and examined its effects in primary rat osteoblast cultures. Since the mitogenic effect of CTGF has been universally demonstrated in various cell types, we first examined its effect on cell proliferation and, as expected, rCTGF showed a dose-dependent increase in cell proliferation. We also examined the effects of rCTGF on various functional parameters associated with osteoblast differentiation; rCTGF significantly increased alkaline phosphatase activity, osteocalcin gene expression and calcium deposition/matrix mineralization. Based on the results from osteoblast cultures, we tested its capacity to induce bone formation *in vivo* using a local delivery system that has been used to test the anabolic effect of other known osteoinductive agents. Adult male rats (12-16 weeks of age) were anesthetized, the distal femur was surgically exposed and 1 microgram of rCTGF in 20 microliters saline was injected into the marrow cavity; control femurs were injected with the same volume of saline or 1% BSA. One week later, the animals were euthanized and femurs removed for radiographic or histological analyses. Recombinant CTGF-injected femurs showed increased radiodensity within the marrow cavity compared with control-injected femurs. Histologically, the rCTGF-injected femurs had islands of newly formed woven bone within the marrow cavity; the bony trabeculae were lined with rows of active, cuboidal osteoblasts and labeled intensely with calcein. There was no evidence of an osteogenic response in any of the control-injected femurs. Collectively, data from these experiments establish that CTGF plays an important role in regulating osteoblast differentiation and bone formation.

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