Journal of Biomechanics 44 (2011) 1765–1770

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

The turnover of mineralized growth plate cartilage into bone may be regulated by osteocytes

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ARTICLE INFO

Article history:
Accepted 6 April 2011

Keywords:
Endochondral ossification
Mechanoregulation
Osteocytes
Remodeling algorithm

ABSTRACT

During endochondral ossification, growth plate cartilage is replaced with bone. Mineralized cartilage matrix is resorbed by osteoclasts, and new bone tissue is formed by osteoblasts. As mineralized cartilage does not contain any cells, it is unclear how this process is regulated. We hypothesize that, in analogy with bone remodeling, osteoclast and osteoblast activity are regulated by osteocytes, in response to mechanical loading. Since the cartilage does not contain osteocytes, this means that cartilage turnover during endochondral ossification would be regulated by the adjacent bone tissue. We investigated this hypothesis with an established computational bone adaptation model. In this model, osteocytes stimulate osteoblastic bone formation in response to the mechanical bone tissue loading. Osteoclasts resorb bone near randomly occurring microcracks that are assumed to block osteocyte signals. We used finite element modeling to evaluate our hypothesis in a 2D-domain representing part of the growth plate and adjacent bone. Cartilage was added at a constant physiological rate to simulate growth. Simulations showed that osteocyte signals from neighboring bone were sufficient for successful cartilage turnover, since equilibrium between cartilage remodeling and growth was obtained. Furthermore, there was good agreement between simulated bone structures and rat tibia histology, and the development of the trabecular architecture resembled that of infant long bones. Additionally, prohibiting osteoclast invasion resulted in thickened mineralized cartilage, similar to observations in a knock-out mouse model. We therefore conclude that it is well possible that osteocytes regulate the turnover of mineralized growth plate cartilage.

1. Introduction

During growth, bone is formed through endochondral ossification, which involves highly organized cartilaginous growth plates. In these growth plates, chondrocytes proliferate, hypertrophy, and synthesize extracellular matrix, which becomes mineralized. Mineralization combined with low oxygen tension attracts blood vessels, and chondrocytes in mineralized areas undergo apoptosis (van der Eerden et al., 2003; Gerber et al., 1999). The newly formed blood vessels bring in osteoclast-like cells, which resorb the mineralized cartilage (Vu et al., 1998; Nordahl et al., 1998), and osteoblasts, which form new bone (Mackie et al., 2008). However, it is unclear how these processes of cartilage resorption and bone formation are regulated during endochondral ossification.

Conversely, in bone remodeling, the regulation of osteoclastic bone resorption and osteoblastic bone formation has been investigated extensively. It is generally believed that bone remodeling is controlled by osteocytes, which act as mechanosensors and regulate osteoblast and osteoclast activity (Cowin et al., 1991; Lanyon, 1993; Klein-Nulend et al., 2003). Osteocytes are suitable for this function since they form an extensive network by gap junction connections to each other, lining cells, and osteoblasts (Klein-Nulend et al., 2003; Bonewald, 2006). Furthermore, cell culture studies have demonstrated that osteocytes are sensitive to mechanical loading and fluid flow (Klein-Nulend et al., 1995; Mullender et al., 2004).

The replacement of mineralized cartilage with bone during endochondral ossification seems quite similar to bone remodeling. However, unlike bone, mineralized cartilage does not contain cells that can regulate osteoclast and osteoblast action. Therefore, we hypothesize that signals from osteocytes within the bone adjacent to the mineralized cartilage extend into the latter tissue, thereby regulating its turnover. We investigated this hypothesis using a widely accepted computational model of osteocyte-regulated bone adaptation (Ruimerman et al., 2001, 2005a).

The computational model is based on the theory of Huiskes et al. (2000), that describes the metabolic processes in bone as a result of bone tissue loading sensed by osteocytes. Osteocytes are assumed to react to the strain energy density (SED) rate by

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doi:10.1016/j.jbiomech.2011.04.011