11th World Congress on Computational Mechanics (WCCM XI)
5th European Conference on Computational Mechanics (ECCM V)
6th European Conference on Computational Fluid Dynamics (ECFD VI)
July 20 - 25, 2014, Barcelona, Spain

MODELING AND SIMULATION OF TRABECULAR BONE REMODELING CONSIDERING INTERCELLULAR SIGNALING BETWEEN BONE CELLS

Yoshitaka Kameo[1]*, Yoshihiro Ootao[2] and Masayuki Ishihara[3]

[1] Department of Mechanical Engineering, Osaka Prefecture University
1-1 Gakuen-cho, Naka-ku, Sakai-shi, Osaka 599-8531, Japan
kameo@me.osakafu-u.ac.jp
[2] Department of Mechanical Engineering, Osaka Prefecture University
1-1 Gakuen-cho, Naka-ku, Sakai-shi, Osaka 599-8531, Japan
ootao@me.osakafu-u.ac.jp
[3] Department of Mechanical Engineering, Osaka Prefecture University
1-1 Gakuen-cho, Naka-ku, Sakai-shi, Osaka 599-8531, Japan
ishihara@me.osakafu-u.ac.jp

Key Words: *Bone remodeling, Trabecula, Bone cell, Intercellular signaling.*

Bone remodeling is a continuous process of adaptation to the changing mechanical environment, which is accomplished by bone-resorbing osteoclasts and bone-forming osteoblasts [1]. Such a coupling activity of effector cells is called a remodeling cycle and believed to be orchestrated by osteocytes embedded in the bone matrix according to the mechanical stimuli. Osteoclasts originate from hematopoietic stem cells, and on the other hand osteoblasts derive from mesenchymal stem cells and undergo terminal differentiation into osteocytes. The differentiation and activation of these bone cells are governed by the complex intercellular signaling between a large number of cells.

One of the most important signaling pathways associated with bone remodeling is RANK-RANKL interaction, which regulates osteoclastogenesis. Osteoclast differentiation is induced by the binding of receptor activator of nuclear factor-κB (RANK) expressed on the membrane of osteoclast precursor cells and RANK ligand (RANKL). Although the major source of RANKL *in vivo* is still unclear because it is found on several cell types, including osteoblasts and osteocytes, recent experimental study shows that osteocytes express a much higher amount of RANKL than osteoblasts [2]. This suggests that osteoclastic bone resorption is initiated by the cell-cell contact between osteoclast precursor cells and mesenchymal cells in bone, and the intercellular signaling depends on the stages of cellular differentiation.

In order to investigate the quantitative relationship among the mechanical and biochemical factors involved in bone remodeling process, computational approaches provide a powerful tool. We previously developed a mathematical model for trabecular bone remodeling incorporating the possible mechanisms of cellular mechanosensing and intercellular communication [3,4]. The remodeling simulation based on our model can represent the functional adaptation of trabecular bone to the mechanical environment. However, this model is insufficient to elucidate the effects of the complex intercellular signaling on the structural changes in bone.

In this study we constructed an extended remodeling model by considering RANK-

RANKL signaling pathway. This model assumes that the differentiation of osteoclast precursor cells into active osteoclasts requires adequate RANK expression on mesenchymal cells as well as RANKL expression on their own surface, while osteoclast precursor cells are induced by the mechanical stimuli that osteocytes receive. We hypothesized that the amount of RANK expression increases with the differentiation from osteoblasts into osteocytes. Combining the remodeling model with the voxel finite element method, we demonstrated the morphological changes in a single trabecula under uniaxial loading. As a result of remodeling simulation, the remodeling cycle, i.e., the autonomous cycle of osteoclastic bone resorption and osteoblastic bone formation was observed. In addition, disruption of RANKL on mesenchymal cells inhibited bone resorption due to a lack of osteoclasts like osteopetrosis, in agreement with the experimental findings [2]. These results indicated that the proposed mathematical model has the potential to express essential features of collaborative activities of bone cells during bone remodeling.

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