

Mechanically induced osteocyte signals explain osteoclast resorption direction and coupling of formation to resorption in cortical bone

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MECHANICALLY INDUCED OSTEOCYTE SIGNALS EXPLAIN OSTEOCLAST RESORPTION DIRECTION AND COUPLING OF FORMATION TO RESORPTION IN CORTICAL BONE

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Introduction

In cortical bone basic multi-cellular units (BMU's) form cylindrical canals for remodeling purposes. These BMUs are up to 2 mm long and 150-250 μm wide. They gradually burrow through the bone, forming (secondary) osteons of renewed bone. In the tip, osteoclasts dig a circular tunnel (cutting cone). They are closely followed by osteoblasts, filling the tunnel (closing cone) [1]. This indicates a coupling mechanism between resorption and formation [2]. Its precise nature, however, is currently uncertain. Another unresolved issue is what guides osteoclast resorption in its directionality. The alignment of osteons along the dominant bone-loading direction suggests that mechanical forces are involved [3]. It was suggested that BMU activity is controlled by osteocytes in the bone matrix, serving as mechanosensors, sending signals through the osteocytic canalicular network to the BMU cells [4,5].

In our current work we investigated whether the above hypotheses about cell-signaling mechanisms, and their potential relationships with mechanical loads, could explain coupling of formation to resorption. We also tried to explain the obvious alignment of the BMU with the predominant loading direction. For that purpose we developed a mathematical theory that can be tested in computer simulation. It assumes that (1) osteocytes within the bone tissue are mechanosensors, and that relative to the mechanical signals they experience, biochemical messengers are transferred through the canaliculi to the internal bone surface. That (2) osteoblasts form bone relative to the total amount of osteocyte signal. That (3) osteoclastic resorption activity is inhibited by the osteocyte signals. That they retract from surfaces receiving high osteocyte signals, but (4) resorb bone where low osteocyte signals are received.

Methods

We tested our theory in a 2-D FEA model. A small piece of compact bone ($2 \times 2 \text{ mm}^2$) with an initial cutting cone was modeled with a resolution of 25 μm . Osteocytes were positioned in the tissue at a density of 1600 mm^{-2} . Relative to the intensity of the load experienced they send signals to their local environments. The intensity was assumed to decrease exponentially with increasing distance. The maximal influence distance of the osteocytes was set to 100 μm . At the inner BMU surface osteoblasts form bone if the total osteocyte signal received is higher than a certain threshold. Three osteoclasts were placed in the tip of the initial cutting cone. Their behavior was mimicked using the Glazier & Graner theory of differential cell adhesion [6]. The structure was loaded with a 6 MPa, 1Hz, cyclic compressive load (Fig. 1). Several additional simulations were performed to investigate the robustness of the proposed theory.

Results

When the simulation was started, the osteoclasts resorbed bone in the principal loading direction, producing a tunnel of 225 μm wide. Osteoblasts closely followed the cutting cone, forming an osteon of renewed bone (Fig. 1). Osteoclast and osteoblast activity was explained by the load-induced osteocyte signals in the tissue surrounding the BMU. These signals were low under the tip of the cutting cone, where osteoclasts are active, and high at the side of the tunnel wall where osteoclasts retract and osteoblasts become active.

Reorientation of the external load, during the simulation process, caused the course of the cutting cone to bend and reorient accordingly. Reduced external mechanical loads on the bone increased the number of osteoclasts active in the cutting cone, and the diameter of the osteon formed. Increased loads had the opposite effect. Complete unloading resulted in undirected, spatially random resorption, not followed by formation.

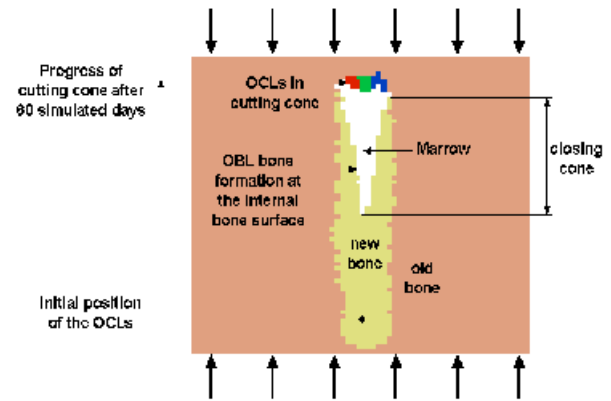


Figure 1: Depiction of the computed morphology after 60 simulated days. Mechanically induced osteocyte signals are capable of directing osteoclast resorption in the external loading direction. They also explain subsequent coupling of osteoblast bone formation to resorption.

Discussion

We tested a mechanobiological theory that relates external forces to local osteoclast and osteoblast expressions in cortical bone remodeling. The theory is largely based on unproven paradigms, but these are not really controversial [4,5,7]. The thought that osteocytes are mechanosensitive signaling cells is widely accepted. The assumed relationships with osteoclast and osteoblast activities seem reasonable as well [8,9].

The cortical-bone remodeling theory we present here is basically similar to the theory that earlier could explain the effects of mechanical loading on modeling and remodeling of trabecular bone structures [10,11]. This makes sense as both cortical and trabecular bone are subject to the same remodeling cycle of activation, resorption and formation and it is reasonable to assume that the underlying mechanisms are largely similar as well [1]. This study showed that it is possible to explain effects of forces on the self-organizational remodeling processes in both cortical and trabecular-bone remodeling with one theory. The theory does not include the initiation of the BMU, however; just its progress. We assume that this event is triggered by the presence of microcracks. The cascade of biochemical processes that are involved in the modeling and remodeling processes are only implicitly assumed, but not explicitly accounted for.

In conclusion, our theory describes a cellular-level, regulatory mechanism, capable of translating mechanical signals to orient osteoclast resorption in the main loading direction. It also shows that coupling of osteoblast formation to osteoclast resorption through mechano-biologically triggered mechanisms is a viable proposal.

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