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Mathematical Modeling and Analysis of Force-induced Bone Adaptation

In biological systems, all living organisms are able to react to the biophysical signals arising in their environment. To do that, the constituent cells are provided with mechanisms that allow them to perceive biophysical signals and to react accordingly to accommodate to the demanding environment. Bone as a biological system is not exempted from this mechanoresponsive capacity. In the last decades significant progress has been made from the experimental site as well as the medical insights [1], to understand the effects produced by application of mechanical loading on bone tissue and on bone cells. Experimental studies have shown the key role played by mechanical usage on bone tissue adaptation, and the promotion of cellular behaviors, like proliferation, differentiation, or apoptosis. However, the precise biological mechanisms behind the organization and regulation of the site-specific bone adaptation process remain poorly understood.

The functional adaptation of bone is the process whereby bone adapts its mass and structure to withstand changes in biophysical demands. The process of bone remodeling is the suitable mechanism used by bone to renew, repair and maintain bone surfaces along life. In bone remodeling, two cellular activities are highly coordinated to achieve the renewal process at a particular site, mainly resorption and formation. Resorption is the process by which highly specialized cells, the osteoclasts, destroy bone tissue by creating resorption pits, and afterwards release the bone matrix constituents to the blood. Conversely, in the formation process osteoblast cells synthesize and secrete the osteoid, new unmineralized matrix, and afterwards organize as well the osteoid mineralization.

Following the mechanostat hypothesis [2], bone can adapt its shape and structure by the tissue level mechanisms of modeling and/or remodeling. In bone modeling, resorption and formation happen on different bone sites, a process that arises during growth and development. Conversely, in bone remodeling, both cellular activities occur sequentially at the same bone site, with resorption being followed by formation. In adult skeleton, bone remodeling runs in general as a self-maintenance mechanism used to repair microdamage or fractures, or to strengthen a bone surface supporting increasing mechanical stress. To organize and regulate the sequencing

events in remodeling, the involved cells act as a multicellular team which evolves accordingly and is known as the basic multicellular unit or BMU.

To start bone remodeling a bone surface target is activated, maybe due to microdamage reparation or osteocytes apoptosis. Then, the BMU operation starts by recruiting osteoclast and osteoblast progenitors to the site to be resorbed. Osteoclast progenitors differentiate and get fused into multinucleated osteoclasts who are attracted to the site and start resorption. In osteonal remodeling [3], a fully developed BMU contains teams of osteoclasts actively resorbing at the cutting cone, followed by teams of osteoblasts producing and depositing layers of osteoid at the closing cone. The coupling among resorption and formation may happen during the reversal stage coming after resorption, where the site may be prepared for the coming formation phase. During bone remodeling tight organization and regulation of the cellular interactions are required because sustained imbalances in the quantity or quality of the renewed bone can derive in bone disorders compromising the biomechanical integrity and performance of the skeleton.

The bone cells involved in the remodeling process are osteoclasts, osteoblasts, lining cells, and osteocytes. Osteoclasts are cells of hematopoietic origin responsible for bone resorption, whereas osteoblasts are cells of mesenchymal origin that produce and deposit the new matrix. Osteoclasts and osteoblasts are cells found, however, only temporary on bone surfaces. Osteoclasts are found actively resorbing a surface, while osteoblasts are found actively producing new matrix. Instead, osteocytes and lining cells are the osteoblastic lineage cells residing in the bone matrix. Lining cells derive from osteoblasts who have stopped synthesizing osteoid during bone formation and differentiate to a very flat cell covering the bone surfaces. Osteocytes are terminally differentiated osteoblasts, which are embedded into the matrix during the mineralization process. They live in lacunae that are small cavities inside the matrix, and extend their cytoplasmic extensions through the canaliculi. Due to these fingerlike extensions osteocytes keep in contact with other osteocytes within the matrix and other cells on the bone surface, thus forming a highly interconnected network that makes them the suitable cells for sensing and transducing the mechanochemical signals [4].

The understanding of the bone remodeling dynamics and the adaptation of bone to mechanical loading is of relevant scientific interest due to the potential use of physical exercise to counteract aging-induced bone loss and to avoid the decline of bone mass and strength in conditions of bone loss, such as osteoporosis or immobilization. Osteoporosis is a worldwide spread bone disorder where bone strength and mass are highly compromise thus increasing the risk of fractures. For instance, postmenopausal osteoporosis has been associated to a failure of the capacity of bone to maintain bone strength when estrogen levels are diminished [5]. In addition, the fact that astronauts lose bone mass during prolonged spaceflights, or patients in bed rest condition present osteopenia, show the key role play by earth gravity, locomotion and physical activity on the body, specially on the skeleton maintenance [1].

In this work, we employ a systems biology approach to get a better understanding of the process of force induced bone adaptation. To achieve this, firstly a mathematical model describing the adaption of bone due to mechanical and chemical stimuli was developed [6,7], and secondly, system theoretical methods are applied

for the analysis of the complex interactions and the design of treatment therapies for bone disorders [8,9].

The mathematical description focuses on the remodeling process as an essential tissue level mechanism used by adult skeleton to maintaining bone strength throughout life. The main operational stages of the bone multicellular unit during bone remodeling covered are activation, resorption, and formation. In the model, osteocytes are introduced as the main mechanotransducers, sensing the mechanical loading changes and releasing local factors, e.g. nitric oxide and prostaglandins, that influence the interactions among osteoclast and osteoblast cell populations, mainly regulated through the RANKL/RANK/OPG signaling pathway.

For a better understanding of the bone adaptation process, and the identification/discrimination of possible therapeutic targets for remodeling-related bone disorders, a theoretical method for global sensitivity analysis is applied to the mathematical model to explore the effects of parameters/inputs variation on the stationary behavior of bone cells and tissue adaptation. In addition, the use of theoretical methods allows to explore for beneficial effects of combining mechanical and non-mechanical agents in the treatment of particular bone disorders, such as postmenopausal osteoporosis, or bed rest/immobilization.

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