A review: Bone remodeling biological computing model

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Keywords: agent based model; bone reconstruction; biomaterial

Abstract. In order to explore a suitable bone graft substitute to improve the success rate of bone graft, the bone reconstruction modeling has become a hot research topic. Over the past several decades, there have been a lot of models developed for the bone reformation. This study mainly discusses the current research progress of the bone reconstruction, several cutting edge key techniques and the challenges of bone reconstruction in the distant future.

1 Introduction

Bone regeneration is comprised of a well-orchestrated series of biological events of bone induction and conduction, involving a number of cell types and intracellular and extracellular molecular signaling pathways, with a definable temporal and spatial sequence, in an effort to optimize skeletal repair and restore skeletal function[1]. The mutual adjustment between osteoblasts (bone formation) and osteoclasts(bone resorption)[2] play the key role in bone remodeling. Because the balance of internal skeletal system is achieved by bone remodeling, thus bone remodeling is important for the reconstruction of the skeletal system. The recent study[3] found that Hematopoietic stem cells (HSC) will firstly differentiate into the pro-osteoclasts which is related to the bone resorption. However, Bone marrow mesenchymal stem cells (MSC) will firstly differentiated into pro-osteoblasts which is related to the bone formation.

From the view of cell mechanics, the differentiation pathway of cells is formed by the expression of corresponding genes.Especially, BMP, TGFb and Wnt are the most important growth factors which can not only stimulate the expression of Runx2 and Osx through a variety of pathways[4], but also promote the differentiation of MSC into osteoblasts. However, Runx2 [5]can inhibit the differentiation of pro-osteoblasts into active osteoclasts. To demonstrate how biological molecules such as genes or proteins impact on the process of bone formation, biologists have to do a number of experiments due to the uncertainty and complexity of biological systems. To reduce the cost of the experiments, biologists are looking such the mathematical model that can study the bone regeneration by in silico method.

Since the beginning of the 21st century, many biomaterial scientists did a lot of studies for the bone reconstruction in the investigation on the relationship between osteoclasts and osteoblasts[6], osteogenic differentiation[7], bone mechanical stimulus[8], cell mechanics[9], bone cells signaling pathway[10] and bone growth factors[11]. For example, Lemaire et al., [10] proposed a mathematical model to investigate the interactions between osteoblasts and osteoclasts, which is the bone turnover modeling platform. Based on this research, Lemaire et al.,[12] proposed another mathematical model to simulate the tight coupling relation between osteoblasts and osteoclasts. However, it did not take the mechanical stimulus into consideration. Geris et al.,[13] developed a mathematical model to simulate fracture healing, which considers the cell density and growth factor concentration as the continuum variables. Although this model took account of endothelial cell distribution, it is unable to provide more detailed information regarding to the structure and morphology of the capillary network. Lacroix et al.,[14] developed a biomechanical model to simulate tissue differentiation and bone regeneration, but it didn’t use intelligent algorithm to train the key parameters and validate the predictive power of the model, respectively.

In the next section, we are going to review several popular research areas of bone reformation.

2 Research Methods In Bone Regeneration Model

2.1 Signaling transduction pathway simulation

Cell signaling is part of a complex system of communication that governs basic cellular activities and coordinates cell actions[15].The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis [16]. The cellular pathway is a series of enzymatic reaction pathways, and the molecular signals in the process of the cell membrane are introduced into the cell by cell membrane. Usually, it consists of the following steps[17].: specific cell release information material→ information material reach the target cells by diffusion or blood circulation to→binding with the target cell receptors→ conversion the signal and start the intracellular messenger system→ target cells produce biological effects. Through this process organism response to the external stimuli. Therefore, how to look for a suitable method simulate signaling pathway is our future research direction.

Since the mid 1990s, Lemaire et al.,[12]proposed a cell population model to describe the interactions between osteoblasts and osteoclasts by studying the intercellular signaling pathway RANK-RANKL-OPG[18](Fig.1). After that, two major kinds of modeling methods were developed to simulate signaling transduction pathway to regulate bone reformation [19]. One is a continuous stochastic method, which is using differential equations to describe multiple scale bone reformation. For example, Geris et al.,[11] proposed a continuum-type model by employing a set of partial differential equations to describe the spatio-temporal evolution of the densities of cells and the concentrations of growth factors. The other is a continuous-discrete hybrid method, which uses the differential equations to describe the signal pathway for each cell and use discrete agent to simulate each cell’s activity a set of pre-set rules. For example, Sun et al., [19] employed the partial differential equation to model the diffusion of the growth factor, the ordinary differential equations to describe the signaling pathway and the agent to simulate several type of cells.

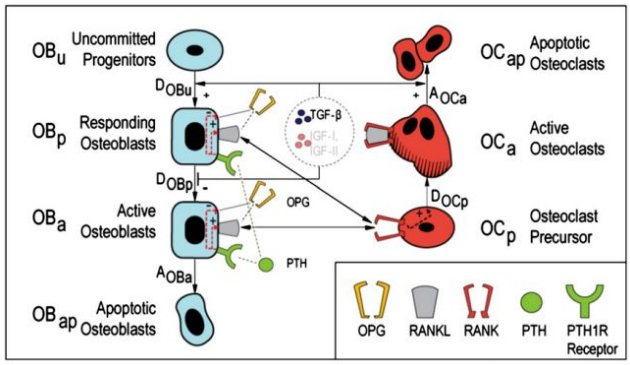

Fig.1. Schematic illustration of bone cell population model: (a) osteoblastic cell lineage and (b) osteoclastic cell lineage taken into account together with RANK–RANKL–OPG pathway[19].

2.2 Mechanical properties for bone remodeling

Stress and strain play the very important role on the growth of bone tissue and bone remodeling which can dating back to the mid-19th century[20]. Since 1967, the first meeting of the International Biomechanics Research conference in Switzerland marked the birth of biomechanics disciplines[21]. In recent years, the research on biomechanics of bone tissue growth has become a popular research area. Bone remodeling[22] is a physiological behavior of tissue morphology and density of phalangeal changes with the mechanical environment. In 1870s, Wolff et al.,[23] proposed the famous Wolff’s law, which indicates the relationship between bones and stress. The high load promotes bone growth, whereas the low load promote bone absorption. This research laid an important foundation for the study of modern mechanics about bone remodeling.

Since 1970s, there have been many theoretical and practical studies [25] on the mechanical properties of the bone, such as the combination of rod hypothesis, the second phase hypothesis, the finite element method, fracture mechanics, and the first test of elastic method and so on. Because the finite element method has the unique ability to compute the complex shape, complex load and the structure of the complex material properties, it has been applied in the past 10 years. At present, finite element analysis is being used to study the process of bone structure and bone remodeling, which is used to test and optimize the design of artificial joints as well as study the mechanical properties of cartilage and intervertebral disc.

In 1972, after the finite element method was introduced into the revolution about 15 years, this new method for skeletal mechanics traits analysis was firstly introduced into the orthopedic literature[24]. In the following decades, along with the interdisciplinary research of mathematics, computer and biology, scientists gradually developed a variety of bone remodeling mechanics model by finite element method. For example, Checa et al.,[8] established a mechano-biological model for tissue differentiation by using a lattice-based modeling approach. Recently, Sanz-Herrera et al., [25] built up such a mathematical model for bone tissue regeneration that can investigate a set of physiological process associated with bone cells, such as porosity, mechanical property and permeability and so on.

The previous research[26] on the biomechanical mathematical model of bone remodeling is usually used to investigate the changes of bone mass by using the finite element analysis technique. Since the size of mechanical stimulation is related to the phenotype of bone tissue, the finite element modeling procedure is descried as Fig. 2: (1) the model is developed by ABAQUS[27], which can compute the mechanical stimulation for the model.; (2) Then, numerical methods will be employed to compute the new bone density, elastic modulus and Poisson's ratio; (3) By iteration, we can locate cell ’ s phenotype, cell ’ s differentiation process and the oxygen concentration of bone tissue.

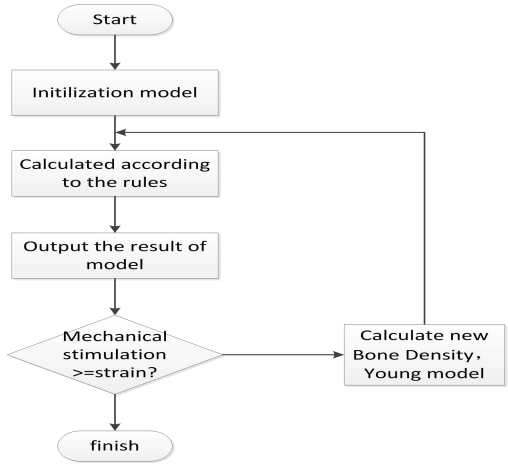

Fig.2. Schematic illustration of the computational algorithm

2.3. Research on the growth factors

Angiogenesis is a complex process, bone regeneration and revascularization are interacted each other. Since the vascular system provides essential nutrients and the transportation of the metabolic material, the blood supply system is important in the bone repair and regeneration process. Previous reports[28] already turned out many kinds of cytokines in the process of angiogenesis, such as: BMP2, TGF-β, Wnt, VEGF, TGFb, PDGF,GH, etc.To simulate real process of bone growth, Sun et al., [29]have developed a cytokine combination therapy predictive model based on the related signaling pathway. And Sun et al.,[11]continued this research to investigate the bone regeneration under the 3d porous calcium phosphate scaffolds, which demonstrated that the combined growth factors may better promote the bone formation than single growth factor.

At present, many bone regeneration and growth factors have been used in bone tissue engineering, but there are still many problems need to be further studied. For example: what is the optimal dose of the growth factor for bone regeneration?

3 Conclusions

Until now, scientists already did a lot of research on bone remodeling model. Because the microenvironment of the bone reformation is extremely so complicated that the classical macroscopic experimental technique can not be used to do further research. Thus, we need to develop such a comprehensive method that can systematically investigate the whole process of bone formation.

Acknowledgement

This work supported by the Natural Science Foundation of China under Grant No. 61372138, Chongqing excellent youth award and the Chinese Recruitment Program of Global Youth Experts, as well as by Fundamental Research Funds for the Central Universities No. XDJK2014B012 and NO. XDJK2016A003.

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