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A review of bioregulatory and coupled mechanobioregulatory mathematical models for secondary fracture healing

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ABSTRACT

Fracture healing is a complex biological process involving many cellular and molecular events. During fracture healing, biochemical signals play a regulatory role in promoting the healing process. Although many experiments have been conducted to study fracture healing, not all of the mechanisms are clearly understood. Over the past years, a lot of mathematical models and computational simulations have been established to investigate the fracture healing process. These models offer a powerful tool to study the interplay between cell behaviour, mechanical stimuli and biochemical signals and help design new treatment strategies. However, most of the mathematical models focus on the effect of mechanical stimuli and few models consider the important role of biochemical signals during fracture healing. In this review, we first emphasize the importance of biochemical signals during fracture healing. Then, existing bioregulatory and coupled mechanobioregulatory models are presented. Finally, some limitations and possible solutions are discussed.

1. Introduction

Bone is a unique tissue that can renew itself and maintain skeletal integrity through resorption [1]. Unlike other tissues, bone tissue is a unique and the only tissue that can heal without scaring [2]. Despite bone's unique self-regeneration capacity and continuing research efforts, delayed healing and non-unions resulting from bone fractures often occur. Fractures not only bring pains to patients, but also cost societies large amounts of money. It is reported that the cost of treating non-unions is between £7 000 and £79 000 per person [3–6]. In the US, the cost of osteoporosis related fractures reached 17 billion dollars in 2005 and it is estimated that by 2025, the annual costs will rise by 50% [7]. In addition, once delayed healing or non-unions occurs, the secondary intervention or additional treatments will make additional pains and economical burden to fracture patients. As such, in order to offer effective treatments, a better understanding of complex biological process of bone healing is necessary.

The emergence of computational simulation of bone fracture healing offers help in two different ways. On one side, after validated by experimental observation, a good and strong mathematical healing model describing biological healing events can be developed. These healing models can be used to investigate the influence of different factors such as interfragmentary movement, type of fixator and fixator configuration related to fracture healing and obtain optimal healing environment. With the help of these healing models, doctors can design the optimal treatment strategies. On the other side, due to the complexity of bone fracture healing process and its multiple time and length scale span, there are still some mechanisms underlying fracture healing remaining unknown. Although experimental data can be obtain from different length and time scale, the links between these levels such as the transduction of mechanical stimuli from bone tissue level to cellular even intracellular level are not fully understood. With the assistance of mathematical healing models, these missing links can be established. Once validated, these models can provide valuable insights.

A variety of fracture healing mathematical models regulated by mechanical stimuli (mechanoregulatory mathematical models) have been developed. However, few mathematical models simulate the regulatory role of biochemical signals (bioregulatory mathematical models) and their coupling mechanisms (coupled mechanobioregulatory mathematical models) during fracture healing in vivo. The clinical application of these models are still in their infancy. This review aims to make a proper evaluation on the current bioregulatory models and coupled mechanobioregulatory models and address the important role of bioregulatory and coupled mechanobioregulatory models in simulating bone fracture healing. In order to better understand bioregulatory and coupled mechanobioregulatory healing models, we first reviewed the

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bone healing biology and biochemical signals (growth factors and oxygen) that has been established in the previous mathematical models (Section 2). Then, we reviewed the current bioregulatory and coupled mechanobioregulatory healing models. Their modelling process, actual mathematical models and their advantages and disadvantages are outlined (Section 3). Finally, we summarised limitations of these current healing models and focused on the future trend of mathematical healing models and their potential contributions to real world clinical applications (Section 4).

2. The role of biochemical signals in fracture healing

2.1. Fracture healing process

Primary healing and secondary healing are known as two healing types according to their difference in gap size [8]. When the fracture gap is small, bone tissue forms directly during the healing process and there is no intermediate tissue formation [9]. The healing process can last from months to years. Different from the strict healing conditions in primary healing, secondary healing often involves interfragmentary movement between the fracture ends. The gap is surrounded by an external callus and the tissue differentiation process occurs in it sequentially [10,11]. When compared with primary healing, secondary healing has features of higher occurrence probability in daily life and more complex healing processes. Therefore, in this review, we mainly focus on the secondary fracture healing process.

Secondary fracture healing is a complicated biological process in which tissue regeneration occurs inside and around the fracture site [12]. It includes cell activities, growth factor production, angiogenesis and transmission of oxygen and nutrients. From a temporal point of view, the healing process is generally divided into the following four phases: the inflammatory phase, the soft callus phase, the hard callus phase and the remodelling phase [13,14]. A detailed description of these four phases is provided here.

2.1.1. Inflammatory phase

The inflammatory phase (Fig. 1a) begins immediately after bone ruptures. The haemorrhage causes a haematoma to form in the fracture region and brings many related biological factors [15]. The connective tissue consists of fibrin and is produced by platelets and thrombotic factors. In addition, there are many related growth factors, including interleukin-1 (IL-1), interleukin-6 (IL-6), insulin-like growth factors (IGFs), transforming growth factors-betas (TGF-s), platelet-derived growth factors (PDGFs) and bone morphogenetic proteins (BMPs) [12,16]. Through circulation, mesenchymal stem cells springing from the broken periosteum and soft tissues around the fracture region also arrive at the periosteum and the initial callus forms [14,17].

2.1.2. Soft callus phase

During the soft callus phase (Fig. 1b), the mesenchymal stem cells start differentiating into specific cells at different regions in the callus according to conditions such as the related growth factors, restoration condition of vascular network, and oxygen conditions [18,19]. Due to the complete vascular network and sufficient oxygen and nutrients supply far away from the gap and near the cortex, osteoblasts are directly formed by the differentiation of mesenchymal cells and finally synthesize intramembranous woven bone. This process is known as intramembranous ossification. In the central area near the fracture gap where the vascular network is damaged and the oxygen content is very low, mesenchymal cells differentiate into chondrocytes and cartilage is formed to stabilize the fracture zone mechanically. This process is known as chondrogenesis.

2.1.3. Hard callus phase

In the hard callus phase (Fig. 1c), endochondral ossification occurs until bone forms [18,19]. Endochondral ossification involves complex biological processes that include cartilage maturation, cartilage calcification and cartilage degradation. In addition, vascularity and osteogenesis also occur in this phase. Before endochondral ossification begins, mature chondrocytes no longer proliferate and start to calcify. Then, apoptosis of chondrocytes occurs and blood vessels invade in the place of the chondrocytes. This also brings along osteoblasts. Then, woven bone is produced by osteoblasts which compromises the hard callus. When the fracture gap is filled with bony callus, a clinical union is reached [20] and then the remodelling phase begins.

2.1.4. Remodelling phase

Remodelling phase (Fig. 1d) is the last phase during fracture healing. At the beginning of this phase, woven bone is replaced by lamellar bone and the excess external callus are resorbed [21,22]. Then the poorly placed bone is resorbed with the activity of osteoclasts and new bone forms along lines of stress with the activity of the osteoblasts [23]. As woven bone is gradually replaced by lamellar bone, bone is finally restored to its original function [24,25].

2.2. Biochemical signals in the fracture healing process

During fracture healing, there are many growth factors that participate in the healing process. The place and corresponding time of release and diffusion of these proteins have a huge effect on the initiation and regulation of the healing response and tissue formation [26]. These factors are released by different cells and regulate the cell behaviour including cell migration, proliferation and differentiation. The following sections of this review will focus on the common factors involved in bone repair and their respective roles.

2.2.1. Transforming growth factor-β (TGF-β)

TGF-β is an important osteogenic growth factor during fracture healing. It exists in the fracture site and the periosteum and is produced by platelets, inflammatory cells, osteoblasts, osteoclasts and chondrocytes [27]. Under acidic conditions or the action of proteases, TGF-β is activated to become the most potent chemoattractant for macrophages [28–31]. TGF-β also has an important effect on cell proliferation, differentiation and matrix synthesis [32]. During the process of intramembranous ossification, mRNA of TGF-β is strongly expressed in the proliferating osteoblasts, and during the process of chondrogenesis and endochondral ossification, mRNA of TGF-β is strongly expressed in the proliferating chondrocytes [33]. The production of TGF-β stimulates the formation of bone by inducing mesenchymal stem cells to differentiate into chondrocytes or osteoblasts [34–36], regulating calcification of cartilage matrix and stimulating osteoblast activity [22,37,38]. In addition, TGF-β also has other functions. It inhibits the differentiation and mineralization of osteoblasts [39,40], inhibits production and activity of osteoclasts [41] and increases production of bone and cartilage components such as types I, II, III, IV, VI and X collagen, fibronectin, osteopontin, osteonectin, thrombospondin, proteoglycans and alkaline phosphatase [36,42,43].

2.2.2. Platelet-derived growth factors (PDGFs)

PDGFs are produced by monocytes, platelets, macrophages and endothelial cells [28]. In the inflammatory phase, the expression of PDGFs is weak [28]. In the later phases, their expression rises and remains constant [27]. PDGFs can initiate fracture repair and callus formation, stimulate proliferation of mesenchymal stem cells and help promote the processes of chondrogenesis and intramembranous ossification [27]. As a potent mitogen, it helps promote proliferation of connective tissue cells [44]. In addition, PDGFs can stim-

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