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Review Article

# Inflammation, fracture and bone repair

Florence Loi [a], Luis A. Córdova [a,b], Jukka Pajarinen [a], Tzu-hua Lin [a], Zhenyu Yao [a], Stuart B. Goodman [a,c,*]

[a] 300 Pasteur Drive, Edwards Building, Room R116, Department of Orthopaedic Surgery, Stanford University, Stanford, CA 94305, USA
[b] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Chile, Sergio Livingstone Polhammer 943, Independencia, 8380000 Santiago, Chile
[c] 300 Pasteur Drive, Edwards Building, Room R114, Department of Bioengineering, Stanford University, Stanford, CA 94305, USA

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ABSTRACT

The reconstitution of lost bone is a subject that is germane to many orthopedic conditions including fractures and non-unions, infection, inflammatory arthritis, osteoporosis, osteonecrosis, metabolic bone disease, tumors, and periprosthetic particle-associated osteolysis. In this regard, the processes of acute and chronic inflammation play an integral role. Acute inflammation is initiated by endogenous or exogenous adverse stimuli, and can become chronic in nature if not resolved by normal homeostatic mechanisms. Dysregulated inflammation leads to increased bone resorption and suppressed bone formation. Crosstalk among inflammatory cells (polymorphonuclear leukocytes and cells of the monocyte–macrophage–osteoclast lineage) and cells related to bone healing (cells of the mesenchymal stem cell-osteoblast lineage and vascular lineage) is essential to the formation, repair and remodeling of bone. In this review, the authors provide a comprehensive summary of the literature related to inflammation and bone repair. Special emphasis is placed on the underlying cellular and molecular mechanisms, and potential interventions that can favorably modulate the outcome of clinical conditions that involve bone repair.



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* Corresponding author at: Department of Orthopaedic Surgery, Stanford University School of Medicine, 450 Broadway Street, Redwood City, CA 94063, USA.
*E-mail addresses:* floi@stanford.edu (F. Loi), lcordova@stanford.edu (L.A. Córdova), jpajari@stanford.edu (J. Pajarinen), tzuhua@stanford.edu (T. Lin), zhenyuy@stanford.edu (Z. Yao), goodbone@stanford.edu (S.B. Goodman).

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## 1. Introduction and scope of the problem

Bone loss and subsequent repair are important issues in orthopedics and related specialties. A clear understanding of the principles underlying bone loss and repair is essential for the treatment of traumatic injuries (fractures and non-unions), patients with bone infection, osteonecrosis, arthritis, osteoporosis, spinal fusion, wear particle associated osteolysis, metabolic bone disease, tumors and other diseases affecting bone. The subject of bone loss and repair has great clinical and economic importance. Approximately 100,000 fractures develop a non-union each year in the USA [1]. The average cost for treatment of an established non-union is approximately US$11,333 [2]. Fragility fractures secondary to senile osteoporosis are a major source of pain and disability, and affect 50% of women and 25% of men over age 50 [3]. Medical care for these fractures will cost over US$25 billion by 2025. The number of surgical cases that use auto- or allograft bone to repair bone defects or obtain a robust fusion totals approximately 1.5 million cases in the USA, with an additional 2.2 million cases worldwide per year [4]. In 2011 alone, there were about 465,070 spinal fusion procedures performed in the USA, the majority of which use bone grafts or byproducts [5]. These are but a few examples of the social and financial burden that bone loss and repair places on our society, and the urgent need for a deeper understanding of the etiology, biological mechanisms, and methods for prevention of fracture non-unions and healing of bone.

Although bone loss and repair were once simply thought to involve only osteoblasts and osteoclasts, currently there has been great emphasis on more complex interactions among cells of the mesenchymal stem cell-osteoblast lineage, and the monocyte–macrophage–osteoclast lineage. Indeed it is now generally appreciated that crosstalk among inflammatory cells and cells related to bone healing is essential to the formation repair and remodeling of bone [6]. This fact is not surprising, given that acute inflammation has been recognized as the first stage of fracture healing [7].

The processes of bone healing are biologically intertwined with those of acute inflammation and the innate immune system. When humans or lower organisms experience a perturbing stimulus that may potentially jeopardize their existence or function, the innate immune system is activated in order to re-establish the normal homeostatic state [8–11]. Local and circulating cells of the monocyte/macrophage lineage function as tissue sentinels that become activated and respond immediately to serious adverse stimuli via a pre-programmed non-antigen specific series of events. Monocyte/macrophages sense and regulate subsequent biological events to mitigate the adverse stimulus and re-establish pre-morbid local anatomy and physiology. If this does not occur, permanent tissue alterations may result due to ongoing active inflammation, fibrosis, or chronic inflammation, in which active inflammation, fibrosis and attempts at repair all occur simultaneously [12].

Bone is a complex organ with numerous functions including hematopoiesis, regulation and storage of key minerals, the protection of vital life-sustaining organs, facilitation of locomotion etc. When bone is subjected to injurious, pro-inflammatory stimuli (trauma, infection and so forth), the same biological processes regulated by the innate immune system ensue, as with other tissues and organ systems, to effect local repair and bone healing. These events necessitate ongoing communication between cells of the monocyte–macrophage–osteoclast lineage, which directly confronts the offending stimulus (such as with infection), but then initiates repair through the process of macrophage transformation (polarization) into a pro-healing phenotype, and through the liberation of cytokines, chemokines and other factors that promote angiogenesis and the homing of cells of the mesenchymal stem cell-osteoblast lineage [6,8,10,13–15]. In addition, mesenchymal-derived cells modulate inflammatory cells to promote resolution of pro-inflammatory activities, and reconstitution of normal tissue.

This review will summarize the fundamental principles of bone healing and repair after exposure to adverse physical and biological trauma, elucidate the mechanisms by which this occurs, emphasize the important interactions and cross-talk among cells of the monocyte–macrophage–osteoclast and mesenchymal stem cell-osteoblast lineages, and provide discussion on new opportunities for enhancing bone repair by modulating the processes of inflammation.

## 2. Bone healing and repair

### 2.1. Types of fracture healing

Bone is a highly dynamic tissue that undergoes a constant process of remodeling to accommodate changing mechanical stresses, and to repair developing fatigue fractures. In addition to this process of remodeling, bone has a remarkable potential for regeneration. Indeed, under optimal conditions bone can heal completely without fibrous scar formation into a form and function that is indistinguishable from the state prior to the injury. The process of fracture healing is highly complex, and in many respects poorly understood. Several fundamental principles governing bone regeneration have, however, been well established as have several key factors that critically influence the outcome of healing. Indeed, optimizing the conditions for healing is the basis and the goal of all fracture treatment.

One of the best recognized factors that influence outcome and also the type of bone repair is the degree of displacement between the fractured bone ends as well as the mechanical stability of the fracture environment [16–18]. While optimal fracture healing requires proximity of the fracture ends as well as a degree of mechanical stability achieved e.g. with splinting, instability and major displacement at the fracture site interfere with healing. This is presumably caused by repeated mechanical trauma exceeding the durability of the provisional tissues, resulting in repeated cell and tissue damage, chronic inflammation, and ultimately in a non-union. Perfectly rigid fixation with no micromotion can also lead to suboptimal bone regeneration; the reasons for this phenomenon are poorly understood. Thus some amount of motion is required for bone regeneration but what is the optimal amount of motion is still unclear.

Rigidly fixed fractures with good reduction and inter-fragmentary compression typically achieved with plates and screws are characterized by a minimal fracture gap and inter-fragmentary movement. Under these conditions bone can heal directly, via a process known as primary fracture healing. In a case of exact reduction, bone heals via direct contact healing which resembles the process of normal bone remodeling: osteoclast mediated bone resorption advances directly through the fracture line, followed by new bone deposition by osteoblasts thus leading directly to re-establishment of the Haversian system [19,20]. Gap healing refers to a similar mechanically stable situation but with a slightly larger gap existing between the bone fragments; this void is filled with direct deposition of intramembranous woven bone and the mature bone Haversian system is re-established via the osteoclast-mediated remodeling process [21,22].

In most fractures, including the ones treated with external splinting, intramedullary nails or external fixator devices, complete rigidity is typically not achieved resulting in more motion at the fracture site and a degree of intermittent displacement between the bone ends [18,23]. In these cases, the healing progresses via a multi-staged process