The Biology of Bone and Ligament Healing

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KEYWORDS

- Bone fracture healing • Tendon and ligament healing • Arthrodesis
- Tissue regeneration • Wound healing • Charcot neuropathy
- Fifth metatarsal fractures

KEY POINTS

- Bone healing occurs through primary or secondary ossification to restore the functional integrity of the affected bone.
- Charcot neuropathy and certain fifth metatarsal fractures have poor healing success rates that are exacerbated by specific risk factors and comorbidities.
- Ligament and tendon healing is not a regenerative process but occurs through a distinct wound healing process that requires short-term fibrocartilage formation and long-term tissue remodeling to restore function.

INTRODUCTION

Foot and ankle function relies on bones, ligaments, and tendons (BLT) for strength, support, and movement. Injuries to these lower extremities occur frequently at work or during sport-related activities and still account for more than 20% of all emergency department visits annually.[1] Foot and ankle injuries are common in patients between 20 and 60 years old and frequently include ligament and bone. Trauma care has made

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advances over the past 3 decades, which has contributed to a steady decline in the rate of ligament injury. Despite these improvements, the rate of serious bone injury has continued to grow over this same time.[1] BLT tissue injuries trigger an inflammatory response, which stimulates synthesis of cytokines, growth factors, and other mediators to coordinate the normal tissue healing response. When BLT injuries are complex or associated with other comorbidities and risk factors, mechanical or biochemical intervention is required to help return the injured tissue back to its original strength and function. The normal mechanisms that guide BLT healing as well as current treatment challenges for these injuries are the focus of this article.

THE BIOLOGY OF BONE HEALING

Fractured bone is capable of undergoing repair and regeneration. Approximately 10% of fractures, however, result in delayed fracture healing (delayed union), malunion, or nonunion.[2] In these cases, the patients experience persistent pain and ultimately require medical intervention to promote healing of the fracture.[3,4] Fracture healing can be classified into primary and secondary healing. Primary healing requires rigid fixation because it can only occur in the complete absence of motion at the fracture site whereas secondary healing requires minimization of motion (eg, cast or splint) at the fracture site. Secondary healing benefits from limited motion at the fracture site to promote callus formation that ultimately leads to internal immobilization of the fracture. The sequence of events that takes place during fracture healing and bone development has been extensively studied at the cellular and molecular levels.[5–9] These findings have increased the level of understanding of bone healing and may further advance surgical and therapeutic strategies for promoting the repair of damaged bone. This section discusses the biology of different forms of fracture healing, with secondary healing discussed first because it is the most common form of healing, followed by an overview of bone-to-bone fusions.

Secondary Healing

Secondary healing involves endochondral (EC) ossification, which mediates the stabilization of the injury and restoration of damaged vasculature prior to regeneration of the tissue during the fracture healing process. This fracture healing process can be divided into 3 overlapping phases: (1) inflammatory, (2) reparative, and (3) remodeling, where intramembranous (IM) and EC ossification occur during the reparative phase (**Fig. 1**).[10] Various cellular components are recruited at different stages in response to growth factors and cytokines. The inflammatory phase occurs immediately after injury. In humans, the inflammatory phase lasts approximately 1 week whereas in mice, the inflammatory phase lasts less than 4 days.[11] The damaged vasculature and bone marrow facilitate the influx of primitive mesenchymal stem cells (MSCs) into the fracture site.[10] During hemostasis, platelets release transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) for the stimulation and chemotaxis of undifferentiated MSCs and macrophages. Macrophages are initially recruited to remove debris, necrotic tissue, and pathogens at the site of injury. A recent study demonstrated that fracture healing is impaired in macrophage-depleted mice wherein EC ossification is altered.[12] Macrophages express fibroblast growth factor 1 (FGF-1) and fibroblast growth factor 2 (FGF-2), interleukin-1 (IL-1), and TGF-β during the inflammatory phase which may help promote angiogenesis within the fracture.[12] MSCs recruited from the exposed bone marrow, periosteum (outer lining), or endosteum (inner lining) differentiate into fibroblasts, chondrocytes, and osteoblasts during the reparative phase.[13]

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