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Review

Multiple roles of tumor necrosis factor-alpha in fracture healing

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ABSTRACT

This review presents a summary of basic science evidence examining the influence of tumor necrosis factor-alpha (TNF-α) on secondary fracture healing. Multiple studies suggest that TNF-α, in combination with the host reservoir of peri-fracture mesenchymal stem cells, is a main determinant in the success of bone healing. Disease states associated with poor bone healing commonly have inappropriate TNF-α responses, which likely contributes to the higher incidence of delayed and nonunions in these patient populations. Appreciation of TNF-α in fracture healing may lead to new therapies to augment recovery and reduce the incidence of complications.

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Introduction

The healing pathway of a broken bone is primarily dictated by the mechanical relationship and position of the two fracture ends [1]. The initial stability achieved within the first days dictates the trajectory of the entire healing process and the final quality of the repair tissue [2]. Absolute stability with compression across a fracture gap induces primary bone healing, which seals the two bone fragments together using a remodeling process and occurs independently of an inflammatory reaction. Inadequate immobilization between the fracture fragments results in a higher percentage of mechanically inferior fibrous repair tissue with decreased mineralization and angiogenesis in the early stages of healing [3]. Fractures without absolute stability progress

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through a series of coordinated and predictable steps, known as secondary bone healing. The general paradigm for secondary bone healing follows the same pattern seen in soft tissue repair including hemostasis, inflammation, mesenchymal cell migration/proliferation, angiogenesis, and remodeling [4]. Specifically, secondary fracture healing progresses through the following phases: (1) acute inflammatory response with mesenchymal stem cell recruitment, proliferation, and differentiation, (2) production of a cartilaginous fracture callus, (3) ossification and revascularization of the fracture callus, and (4) remodeling of the deposited trabecular bone [4,5]. This process also contributes to osseous recovery in surgical procedures including arthrodesis, osteotomies, and bone grafting and therefore has a wide impact on the success of most orthopedic procedures.

A significant body of basic science literature offers valuable insight into the role of the targeted chemical messengers (cytokines) in secondary bone healing. Of specific interest is tumor necrosis factor-alpha (TNF-α), which is recognized as a primary mediator in the inflammatory reaction that initiates the reparative process. After injury, TNF-α is elevated in a bimodal temporal distribution within the fracture site. The peri-fracture concentrations are elevated in the initial inflammatory phase, then diminish to normal physiologic levels for the majority of the reparative process, but are later elevated in the remodeling phase [6]. Deviations from this schedule may produce inferior or more robust repair tissues [7,8]. The interaction between TNF-α and bone is not limited to reparative states, but also extends to normal physiologic homeostasis.

Poor bone integrity common in elderly, osteoporotic, diabetic, or obese patients as well as in individuals abusing alcohol or those on chronic doses of corticosteroids may arise from local and systemic deviations from the physiologic TNF-α equilibrium. The development of atrophic nonunions may be driven by interruptions in the spatial and temporal patterns of elevated TNF-α concentrations within the fracture site. This review summarizes the role of TNF-α at specific time points along the course of fracture healing, presents evidence suggesting its role in common metabolic bone diseases, and speculates on the likely physiological responses to TNF-α modulation for both. Understanding the role of TNF-α in physiologic response to injury is important as it provides the foundation for exploration of potential treatments that facilitate recovery from injury or surgery as well potential interventions in metabolic bone disease [9].

Bone healing progression

The stages of bone healing and the role of TNF-α at each stage are summarized in Fig. 1 and Table 1.

Days 1–3: acute inflammatory response and mesenchymal cell recruitment (elevated TNF-α)

Disruption of the osseous cortex tears periosteal and endochondral vessels, creating a peri-fracture hematoma. Cytokines, fibrin, platelets, and cellular degradation products within the collected blood induce an inflammatory reaction [6,10] and stimulate angiogenesis [11]. Removal of the collected blood between the second and fourth day following injury results in mechanically inferior bone quality four weeks later [12], suggesting that factors within the hematoma are osteogenic. Furthermore, the hematoma itself does not contain the osteogenic cell precursors, but rather stimulates cells within the periosteum to initiate endochondral ossification [13]. TNF-α is one of the initial inflammatory cytokines within the hematoma and is first produced by resident macrophages and recruited inflammatory cells [6]. Its concentration peaks at 24 h and resolves to baseline levels within 72 h after the injury [6,14–17]. The TNF-α receptors p55 and p75 are found on immune

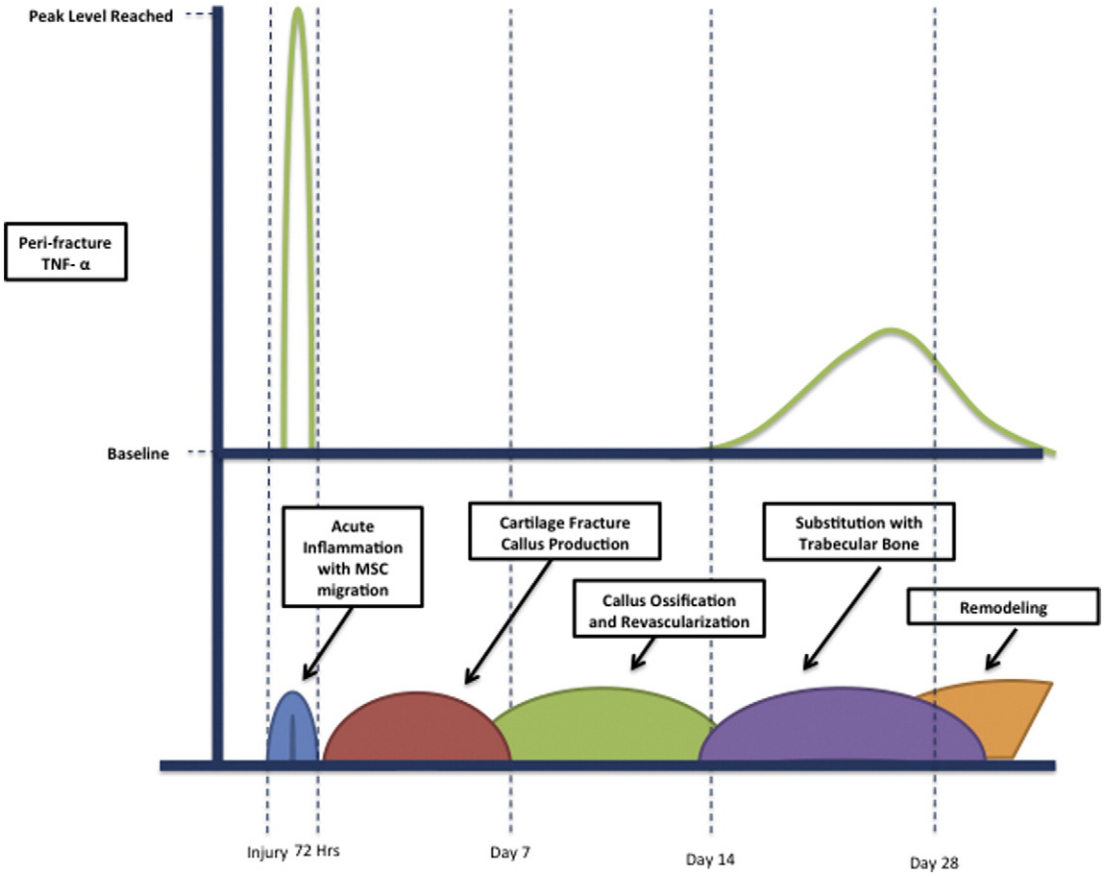

Fig. 1. .Stages of bone healing and the peri-fracture TNF-α concentration at each stage.