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Perspective Article

Hylonome

Summary – Mechanisms of fracture healing and pharmacologic control

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Approximately 8 million skeletal fractures occur annually in the United States. Many of these fractures cause interruption of work and activities of daily living and many are associated with long-term, permanent disability or increased mortality. While the majority of fractures heal normally after fixation, approximately 10% heal more slowly (malunion) or fail to heal at all (non-union). Understanding the mechanisms of fracture healing has the potential to reveal why certain fractures or individuals fail to heal. Further, understanding the mechanisms of fracture healing can lead to the identification of new therapeutic strategies and molecular targets to improve and insure bone healing and potentially the disability, morbidity, and mortality of patients following a fracture.

Significant progress has been made in delineating the biological processes underlying fracture healing. Gerstenfeld (Boston, MA) summarized the cascade of bone healing at a fracture site including the spatial and temporal organization of callus development, and the molecular fingerprints that characterize the bone healing process. Pro-inflammatory cytokines and TGFβ family members including the TGFβ itself and bone morphogenetic proteins are important regulators of initial stages of bone healing. As illustrated by Gerstenfeld, a majority of the work in understanding the molecular events in fracture healing has been derived from the evaluation of the transverse femoral fracture model in rats and mice.

Bone, bone marrow, periosteum, surrounding muscle, and blood vessels each contribute to the bone healing process. What remains is to determine the contribution each tissue plays in the healing cascade. A failure in angiogenesis will contribute to impaired bone healing. One angiogenesis factor, vascular endothelial growth factor (VEGF) is believed to play a key role in bone healing. Endogenous VEGF is produced in the early days following fracture and inhibition of VEGF at fracture sites impairs bone healing. Further administration of exogenous VEGF in bone fractures or defects promotes angiogenesis and bone healing. These data support the critical role that angiogenesis plays in successful bone healing.

Significant progress has taken place in our understanding of the molecular, cellular, and tissue events in bone healing. From this understanding, targets for therapeutic intervention have emerged in an attempt to reduce malunions and non-unions of bone fractures. A notable case is the use of bone morphogenetic proteins (BMP-2 and 7), in which placement of a carrier plus BMP has demonstrated clinical benefit in accelerating bone healing and treating fracture nonunions. One of the limitations of the current BMP applications has been the need for delivery of the protein with collagen carriers. Seeherman et al. have extended the possible delivery vehicles to also include injectable BMP-2 to percutaneously deliver the protein to bone fractures. Thompson also demonstrated improved bone healing of long bone fractures and critical bone defects with an PGE2 EP-2 selective agonist. This small molecule, non-protein when given as a single administration effectively healed bones of rodents and canines. These studies provide new therapeutic approaches to enhance bone healing and reduce the number of malunions and non-unions thereby reducing morbidity and mortality.

In addition to enhancing bone healing, an important issue is the impact of concomitant medications taken by patients following fracture or prior to fracture on bone healing outcomes. The effect that COX-2 inhibitors has on bone healing is controversial. Also, the effects of SERMS and bisphosphonates have been evaluated in fracture healing. As more patients are treated with anti-osteoporotic agents, a certain percentage of these patients will go on to suffer from bone fractures. It is important to understand how these bone active compounds will affect the healing outcome.

In spite of our increasing understanding of the molecular and cellular events leading to fracture healing and emerging

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new therapeutic approaches to enhance bone healing, key questions emerge that require additional work. A significant body of literature has emerged in characterizing the fracture healing cascade in rodents including knockout and genetically modified mice and in rats using the transverse femoral fracture model. Are rodent fracture models good models for human fracture healing? Are there species differences in bone healing that make one species preferred over others in terms of their relevance to bone healing in humans? Do rodents, canines, primates, and humans respond to therapeutic interventions similarly? What is the "best" preclinical model of human bone healing? Does a model of diaphyseal fracture healing mimic healing at a metaphyseal site? Answers to these questions will likely enhance our understanding of bone healing to permit improved healing outcomes that will minimize the morbidity and mortality of patients suffering from fractures.