Genes & Diseases (2014) 1, 140—148

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REVIEW ARTICLE

Constructing the toolbox: Patient-specific genetic factors of altered fracture healing

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Received 2 July 2014; accepted 18 July 2014
Available online 27 July 2014

KEYWORDS
Bone repair;
Fracture healing;
Genetics;
Orthobiologics;
Patient factors

Abstract The multifaceted sequence of events that follow fracture repair can be further complicated when considering risk factors for impaired union, present in a large and growing percentage of the population. Risk factors such as diabetes, substance abuse, and poor nutrition affect both the young and old, and have been shown to dramatically impair the body's natural healing processes. To this end, biotherapeutic interventions such as ultrasound, electrical simulation, growth factor treatment (BMP-2, BMP-7, PDGF-BB, FGF-2) have been evaluated in preclinical models and in some cases are used widely for patients with established non-union or risk/indication or impaired healing (i.e. ultrasound, BMP-2, etc.). Despite the promise of these interventions, they have been shown to be reliant on patient compliance and can produce adverse side effects such as heterotopic ossification. Gene and cell therapy approaches have attempted to apply controlled regimens of these factors and have produced promising results. However, there are safety and efficacy concerns that may limit the translation of these approaches. In addition, none of the above mentioned approaches consider genetic variation between individual patients. Several clinical and preclinical studies have demonstrated a genetic component to fracture repair and that SNPs and genetic background variation play major roles in the determination of healing outcomes. Despite this, there is a need for preclinical data to dissect the mechanism underlying the influence of specific gene loci on the processes of fracture healing, which will be paramount in the future of patient-centered interventions for fracture repair.

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Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2014.07.006

Introduction

Fracture treatment relies on the timely principles of restoration of anatomy and appropriate osseous stabilization, which will lead to restoration of bone structure and function.[1,2] Despite the intrinsic ability of the body to heal fractures, patient risk factors can significantly impair skeletal repair.[3] The rate of delayed fracture healing or non-union is highest amongst subpopulations with specific risk factors such as smoking, advanced age, steroid use, use of certain pharmaceuticals (i.e. anti-cancer drugs) and metabolic diseases such as diabetes mellitus (DM).[3] An increased mechanistic understanding for impaired osseous healing associated with specific high-risk populations will provide fundamental information necessary to design a regenerative approach for fracture patients with specific risk factors for non-union. This complexity is further increased when "the patient factor" is introduced. Namely, each individual has a unique genetic makeup, which influences the processes of fracture repair. In addition, genetic mutations caused by external patient factors (comorbidities, environmental influences) may further distinguish healing processes amongst our world's population as truly heterogeneous.

Of the 6.2 million fractures sustained in the United States each year, these patient factors have resulted in a 10% incidence of delayed union or non-union.[4] To address these clinical concerns, there are a number of treatments available including autologous or allogeneic bone grafts and a variety of bone substitutes such as demineralized bone matrix (DBM).[5,6] Adjunctive measures such as low intensity pulsed ultrasound (LIPUS) to provide biomechanical stimulation[7] have also been used. More recently, biological factors including the bone morphogenic proteins (BMPs) have been successfully used to promote bone repair.[8] BMP2 (Infuse) in particular has been administered to patients with established non-union or risk of non-union due to the fracture location. While these and other currently available agents hold promise in accelerating fracture healing, they have limited usefulness or efficacy and do not account for the genetic component or "the patient factor".[9,10]

The development of a predictive "toolbox" to assess how individual patients will respond to particular treatment regimens should be the next leap forward in treating a growing global population, many of whom have comorbidities that increase the likelihood of compromised bone repair. The collection of preliminary data to construct this "toolbox" may be garnered through large-scale preclinical studies which examine the genetic influences of isolated point mutations on bone repair using models of closed fracture and established non-union. This information can be used to personalize therapeutic regimens for fracture repair, similar to existing personalized medicine for genetic screening for certain cancers (i.e. BRCA gene for breast cancer) and screening for risk of cystic fibrosis in expected parents.

In this review, we will begin with a brief discussion of fracture repair, followed by a description of patient factors, which have been shown to inhibit regenerative processes. Several clinically implemented biotherapeutics and promising gene therapy approaches for patients with these risk factors will be described and their use/effectiveness will be discussed. Finally, the potential of patient centered medicine will be presented, considering potential pitfalls and alternative paths forward.

Bone fracture healing

Following injury, bone has the unique ability to repair itself through mechanisms similar to its post-natal development process. Fracture healing involves two distinct but important mechanisms leading to bone formation, primary and secondary fracture healing. Primary fracture healing occurs when bones unite across the fracture site via direct bone formation to bridge the gap. This type of healing occurs in the presence of rigid internal fixation and a near absence of interfragmentary strain.[11] Secondary fracture healing (endochondral ossification) occurs when there is significant micro-motion at the fracture site. It is characterized by responses from the periosteum, marrow, and external soft tissue that lead to formation of a callus to bridge the gap, and occurs in three stages: inflammation, repair, and remodeling.[1,2] Despite the sequenced description of these processes, these phases actually occur in an overlapping spacial and temporal pattern.

Blunt trauma associated with a fracture results in an interruption of skeletal integrity, coupled with a disruption of the normal vascular structures and nutrient flow at the fracture site. This leads to reduced oxygen tension and disruption of bone marrow architecture (Fig. 1A). The inflammatory phase of fracture healing proceeds with inflammatory cell, macrophage, and degranulating platelets infiltration of the fracture site during hematoma formation.[2,12] Platelets and inflammatory cells within the hematoma release several factors that are important for chemotaxis, proliferation, angiogenesis and mesenchymal stem cell differentiation into osteoblasts or chondroblasts.[13,14] The early events that take place during the inflammatory phase set the stage for the cartilaginous phase and the progression of endochondral ossification.

During the cartilaginous phase of healing in a long bone fracture, two discrete crescent shaped cartilage tissue masses develop, symmetric to the fracture line (Fig. 1B). Cartilage, which provides initial stability to the healing fracture, is produced through a process beginning with signaling molecule directed differentiation of mesenchymal cells into chondroblasts. Once chondroblasts become embedded in the extracellular matrix, they mature to become chondrocytes. Non-hypertrophic chondrocytes are capable of proliferation and continue to synthesize cartilage matrix. Maturing chondrocytes which previously expressed aggrecan and type II collagen undergo hypotrophy, terminal differentiation, and characteristically express type X collagen.[15] The matrix is subsequently calcified and remaining cartilage is resorbed, setting the stage for the bony phase of fracture repair.

Following calcification, the callus is invaded by newly formed blood vessels. The vasculature provides a conduit for the recruitment of osteoblastic progenitors, as well as chondroclasts and osteoclasts needed to resorb the calcified tissue and early mineralized tissue (Fig. 1C). The