Editorial

New technologies for the enhancement of skeletal repair: Challenges and opportunities

The abilities to stimulate fracture repair, enhance spinal arthrodesis, heal nonunions, or regenerate lost segments of bone are common goals among orthopedic surgeons, craniofacial surgeons, and other medical professionals who deal with skeletal wound healing. While in most clinical settings these processes are biologically optimized, many patients continue to experience delayed or impaired healing. Methods to enhance or accelerate these healing responses are greatly needed in order to ensure a patient's rapid recovery and return to work, recreation, and family life. Moreover, as bone graft harvesting procedures are still associated with surgical morbidity, the ability to heal skeletal injuries without the use of autologous iliac bone is highly desirable. Methods for the enhancement of skeletal repair can be divided into biophysical and biological strategies, and then further divided into local and systemic approaches. Biophysical strategies such as electromagnetic fields and ultrasound stimulation have undergone substantial scientific review including the use of systematic meta-analyses. Recent data on electromagnetic fields suggest there is no significant impact of this technology on delayed unions or un-united long bone fractures but that methodological limitations and high inter-study heterogeneity leaves the impact of electromagnetic stimulation on fracture healing uncertain.[1] With regard to low intensity pulsed ultrasound, evidence in support of an effect on the healing of fractures is moderate to very low in quality and provides conflicting results.[2] Thus, while these two forms of biophysical stimulation are currently available worldwide, the evidence to support their use is weak and further study is required. Local strategies for the repair and regeneration of bone include the use of osteogenic materials such as autologous bone or bone marrow, osteoconductive materials such as calcium-phosphate- or calcium-sulfate-based bone graft substitutes, human demineralized bone matrix, and emerging biological materials such as recombinant protein growth factors. At this time, autologous bone remains the standard against which all new technologies are compared. Calcium-phosphate- or calcium-sulfate-based bone graft substitutes do not induce new bone but may enhance osteoconduction by providing an adequate scaffold or attachment surface for osteoblasts. The use of recombinant growth factors to enhance or accelerate healing remains an exciting field and possibly represents the future of skeletal trauma surgery. Based on the concept that the healing of a fracture is initiated at the time of injury when a clot is formed at the fracture site, several investigators have suggested that the degranulation of platelets in the fracture callus clot elaborates active components such as platelet-derived growth factor.[3,4] A recent randomized controlled trial using recombinant human platelet-derived growth factor to enhance the healing of ankle arthodeses led to a recent food and drug administration panel review in the United States. The panel recommended approval of this new growth factor for the enhancement of ankle fusion; the actual data which supported that decision have yet to be released to the public.[5] Another recent technology that has emerged is the local application of recombinant human fibroblast growth factor-2 (FGF2). This molecule is a known stimulator of angiogenesis and osteogenesis and a recent randomized controlled trial in tibia fractures showed enhancement of radiographic union with FGF2 treatment.[6]

Over the past decade, many studies have been reported on the use of recombinant human bone morphogenetic protein-2 (rhBMP-2),[7,8] recombinant human bone morphogenetic protein-7 (rhBMP-7; OP-1),[9] and their various combinations of BMPs with collagen-based delivery vehicles. At this time, there is regulatory approval in many countries around the world for the use of these materials in the enhancement of fresh fracture healing, nonunion, and spinal arthrodesis. Several concerns have been raised regarding their safety in the cervical[10,11] and, indeed, lumbar spine[12] and other concerns have been expressed regarding their efficacy in skeletal trauma settings as well as their ability to stimulate heterotopic bone at various skeletal sites.[13] There is no doubt that these molecules are extremely potent and potentially efficacious but their association with adverse events and their application in settings where appropriate stability has not yet been achieved has led to results that have been unfavorable at times. Moreover, results may vary depending on the operative fixation used as a recent

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report noted lack of an effect of rhBMP-2 on the healing of open tibia fractures treated with an intramedullary nail.[14] Much more work is needed in order to find optimum ways to utilize the biological potential of these BMP's.Most recently, strategies have emerged that may set the stage for developing drugs and/or devices that could stimulate skeletal healing in a systemic manner. Although many medical conditions are treated with oral or parenteral medications that enhance a healing response or correct a physiological deficit, no such strategies are available for the healing of skeletal injuries. Potential candidates for further scientific exploration include growth hormone, parathyroid hormone, and inhibitors of Wnt signaling antagonists. Although growth hormone may also be an effective agent for systemic enhancement of fracture healing, a recent placebo controlled dose escalating randomized controlled trial in open and in closed tibia fractures failed to meet the primary outcome measure of acceleration of time to healing.[15] However, a subgroup analysis of only the closed fractures did show acceleration of healing with the highest dose of human growth hormone suggesting that a more extensively powered study or a further evaluation of appropriate dosing may lead to better results. The data on the use of parathyroid hormone (PTH) in the enhancement of skeletal repair is extensive. Numerous animal studies have demonstrated enhancement of fracture healing with PTH[16-18] and recent clinical trials in distal radius fracture healing (with the use of PTH 1-34)[19] and pubic ramus fractures (with PTH 1-84)[20] have demonstrated significant beneficial effects. These findings, coupled with reports of enhancement of osseous regeneration in the oral cavity with PTH 1-34[21] strongly suggest that PTH may be an anabolic therapy for skeletal healing.

Perhaps the latest technological advance upon which to develop a systemic strategy for the enhancement of skeletal repair is in the area of inhibiting the Wnt signaling pathway antagonists. The Wnt signaling pathway, like the BMP signaling pathway, leads to the expression of target genes that enhance bone formation.[22] The pathway is triggered by an interaction between the extra-cellular Wnt protein and both a receptor and co-receptor complex. Two antagonists of this co-receptor binding, DKK-1, and sclerostin modify signaling events and inhibit bone formation. This is a normal physiologic process. However, the development of monoclonal antibodies against these modifying antagonists may up-regulate target gene expression by interfering with normal physiological antagonism. In doing so, systemic enhancement of bone healing may occur. Although only a small number of advanced technologies are likely to make their way into widespread clinical use after extensive development and testing, the opportunities that exist are exciting. To achieve success, it will be necessary to develop better delivery systems for cells, growth factors, and osteoinductive substances, explore systemic applications of osteogenic agents, and identify appropriate experimental settings and measurable, meaningful clinical endpoints for human clinical trial design. Although animal studies and *in vitro* data provide cause for optimism, a new idea or new technology is only as good as our ability to test it clinically.

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