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Operative Techniques in
Orthopaedics

Overview on Small Molecule Biologic and Gene-Based Treatments in Sports Medicine

Alexander E. Weber, MD,[*] Ryan A. Mlynarek, MD,[†] Brian J. Cole, MD, MBA,[*] and Asheesh Bedi, MD[†]

The use of biologic treatment strategies in the nonoperative and operative care of orthopaedic and sports injuries continues to expand in parallel with our understanding of the healing response after injuries. This is in large part because of the growing number of basic, translational, and clinical studies investigating the use of biologic augmentation in musculoskeletal care. Platelet-rich plasma, growth factors, and cell-based and gene-based treatments are among the most commonly explored options, and they have found varying levels of success in promoting soft tissue and osseous healing. Preclinical studies have illustrated the potential for broad application of biologic treatment strategies in orthopaedics. However, many important questions remain regarding delivery, efficacy, and safety of biologic treatments. Additional well-designed basic and clinical studies are of paramount importance to create evidence-based guidelines for the implementation of biologic treatments in orthopaedics.
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Introduction

Orthopaedic and sports-related injuries are increasing in frequency in the United States and throughout the world. Injuries to cartilage, ligament, tendon, muscle, and bone are particularly difficult to treat. This is in part because of incomplete healing of the soft tissues or healing via scar rather than recapitulation of the native architecture and organization of the tendon, ligament, muscle, or enthesis. The aforementioned challenges with soft tissue injuries often lend to tissue reconstruction rather than repair, as is the case with arthroplasty for osteoarthritis or replacement with tendon graft for anterior cruciate ligament injuries. This paradigm has led to the investigation of alternatives, including biologic solutions for soft tissue healing and repair.

The umbrella of "biologics" in orthopaedic surgery refers to naturally available products that are implemented to alter or improve the biology of healing tissue.[1] The field of biologics in orthopaedic surgery can be grouped into 3 distinct categories on the basis of the relative size of the biologic intervention (Table). The 3 categories are small molecule therapies, cell-based strategies, and tissue-derived treatments. The purpose of this article is to provide an overview of small molecule and cell-based and gene-based biologic treatments. The specific clinical applications and outcomes would be presented in the following articles within this edition of Operative Techniques in Orthopaedics.

Rationale for Study and Use

Over the last 3 decades, there have been vast improvements in the technology available to diagnose and treat a wide spectrum of orthopedic injuries. These advances have led to safer procedures, mechanically improved surgical constructs, and decreased rehabilitation times. Despite these advancements, there has been relatively slow progress in altering the biologic environment of healing tissues. This is partly because of the innate properties of human healing, ie, healing with

*Division of Sports Medicine, Department of Orthopaedic Surgery, Rush Medical College of Rush University, Rush University Medical Center, Chicago, IL.
†Division of Sports Medicine, Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI.
*Address reprint requests to Alexander E. Weber, MD, Division of Sports Medicine, Department of Orthopaedic Surgery, Rush Medical College of Rush University, Rush University Medical Center, 1611 W Harrison St, Suite 400, Chicago, IL 60612. E-mail: weber.ae@gmail.com

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Table The Subdivisions of Biologic Treatments in Orthopaedics

Small molecules	**Growth factors**
	Cytokines
	Platelet-rich plasma
Cell-based treatments	**Chondrocyte implantation**
	Autologous
	Allogenic
	Bone marrow aspirate
	Concentrate
	Stem cells
	Autologous
	Allogenic
	Gene therapy
Tissue-based treatments	**Allograft transplantation**
	Xenograft tissue
	Synthetic

disorganized scar tissue rather than the regeneration of native preinjury or predegenerative tissue. Unfortunately, the complex biologic signaling at the molecular, cellular, and tissue levels remains incompletely characterized or understood. Each signaling step, at every level (molecular, cellular, and tissue), provides an opportunity to investigate therapeutic avenues for intervention.

Small Molecule

Growth Factors and Cytokines

The introduction of osteoinductive growth factors or cytokines into the healing environment is an area of ongoing research. There are numerous growth factors, and the most common ones are bone morphogenetic protein (BMP), transforming growth factor (TGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and granulocyte colony-stimulating factor. These small proteins have demonstrated potentially positive effects on soft tissue and osseous healing and repair.[2-6]

Inflammatory cells at the healing interface express FGF, a potent promoter of cellular migration and angiogenesis.[7,8] Depending on the isoform present, FGF can increase extracellular matrix production in the healing tissue. At physiological concentrations, FGF promotes anabolic pathways; however, at higher concentrations, FGF may promote proinflammatory processes detrimental to the healing tissue.[7,9] In addition to playing a role in soft tissue-to-bone healing, recent work has implicated FGF as a key mediator in bone density homeostasis.[10]

The activity of TGF in isolation has been studied for its effects on type-I collagen and fibronectin production. The quality of healing tissue may be related to the predominant isoform of TGF expressed. Scar-mediated healing is associated with TGF-β1 expression, whereas "scarless" healing or recapitulation of the native tissue is associated with TGF-β3.[11] In a rodent model, TFG- β3 has improved the structural and mechanical properties of the tendon-to-bone healing interface.[12]

The predominant fibroblast chemotactic growth factor in the healing response is PDGF.[13] The PDGF-β isoform is responsible for fibroblast chemotaxis and proliferation, macrophage activation, collagen synthesis, extracellular matrix synthesis, and angiogenesis of the healing site.[13] The chemotactic effects of PDGF-β have also been shown to promote bone cell migration and proliferation, which can improve the healing of soft tissue-to-bone and bone-to-bone interfaces.[14] Animal studies have demonstrated improvements in mechanical strength of tendon repairs and the biomechanical profile of achilles tendinopathy following the administration of recombinant PDGF.[15,16]

The isoforms of BMP are cytokines that are highly regarded for their effects on bone-to-bone healing; however, they also play a role in soft tissue-to-bone healing.[17-20] The BMP signaling pathway is turned on in embryogenesis to promote the formation of fibrocartilage, tendon, and bone. Specifically, BMP increases osteoclast proliferation and induces osteoblastic commitment of mesenchymal stem cells (MSCs).[21] The osteogenic BMPs are BMP-2, BMP-4, and BMP-7 (also known as osteogenic protein-1). Preclinical animal studies examining healing tissue augmentation with BMP isoforms have demonstrated promising results in rotator cuff repair, patellar tendon healing, fracture remodeling, and spinal fusion.[19,20,22] Recombinant BMP is currently approved by the US Food and Drug Administration for long bone fractures and lumbar spine fusion.[23] Unfortunately, concerns over clinical safety have limited BMPs current clinical use and further studies are needed to substantiate or refute the adverse profile of recombinant BMP.[23,24]

Platelet-Rich Plasma

Platelet-rich plasma (PRP) has garnered the greatest scientific and media attention to date. PRP is an autologous whole-blood derivative that contains a supraphysiological concentration of platelets. The premise behind its use in musculoskeletal injuries is that the concentrated plasma component of whole blood contains a variety of growth factors, cytokines, and interleukins, in theoretically appropriate proportions, all of which are important for tissue regeneration.[25,26] In addition to the growth factors named in the prior section, PRP contains insulin-like growth factor-1 and vascular endothelial growth factor. Benchtop and animal studies have found that PRP is effective as a chemotactic and mitogenic agent for osteoblasts and tenocytes in the healing environment.[27-30]

However, recent studies have demonstrated that not all PRP formulations are created equally.[31-34] Furthermore, leukocyte-poor formulations of PRP may be advantageous as compared with leukocyte-rich formulations.[34] Regardless of PRP formulation, an advantage over the individual growth factors is the ability to deliver physiological levels of multiple growth factors and cytokines to the healing tissue. Conversely, the disadvantage of this technique is the uncontrolled nature of applying numerous healing factors in concert with no ability to interpret which factor(s) is or are responsible for the improved healing response. Nevertheless, there is a large and ongoing effort to apply PRP in the clinical setting and better understand the