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Regenerative Medicine

Regenerative Treatments to Enhance Orthopedic Surgical Outcome

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Abstract

In orthopedic surgery there has been a never-ending quest to improve surgical outcome and the patient's experience. Progression has been marked by the refinement of surgical techniques and instruments and later by enhanced diagnostic imaging capability, specifically magnetic resonance. Over time implant optimization was achieved, along with the development of innovative minimally invasive arthroscopic technical skills to leverage new versions of classic procedures and implants to improve short-term patient morbidity and initial, mid-term, and long-term patient outcomes. The use of regenerative and/or biological adjuncts to aid the healing process has followed in the drive for continual improvement, and major breakthroughs in basic science have significantly unraveled the mechanisms of key healing and regenerative pathways. A wide spectrum of primary and complementary regenerative treatments is becoming increasingly available, including blood-derived preparations, growth factors, bone marrow preparations, and stem cells. This is a new era in the application of biologically active material, and it is transforming clinical practice by providing effective supportive treatments either at the time of the index procedure or during the postoperative period. Regenerative treatments are currently in active use to enhance many areas of orthopedic surgery in an attempt to improve success and outcome. In this review we provide a comprehensive overview of the peer-reviewed evidence-based literature, highlighting the clinical outcomes in humans both with preclinical data and human clinical trials involving regenerative preparations within the areas of rotator cuff, meniscus, ligament, and articular cartilage surgical repair.

Introduction

Regenerative adjunctive treatment is the next logical step in the progression of surgical intervention. Biologically augmented or regenerative techniques are at the very forefront of modern treatment and have the potential to transform the practice of medicine and surgery significantly in a very short period. Less than 20 years ago, one of the first applications of platelet-rich growth factors was successfully used to help augment dental implantation [1]. From this starting point progressive advancements have been made, but much remains to be learned. Although the basic science remains in its infancy, especially in the areas of signaling, regulation, and mechanism, regenerative knowledge has expanded significantly in volume and across disciplines. The purpose of this review is to provide a road map of the significant developments in preclinical and clinical results involving biological solutions to improve rotator cuff, ligament, meniscus, and articular cartilage surgical repair.

Discussion

Methodology

Searches via PubMed (through August 15, 2014) and Google Scholar (through August 15, 2014) were performed to identify both scientific investigations and review articles to ensure inclusion of pertinent data. Key words used included platelet-rich plasma (PRP), mesenchymal stem cell (MSC), stem cell, growth factor, basic science, cell signaling, paracrine, autocrine, anterior cruciate ligament (ACL), rotator cuff, meniscus, and cartilage. The articles were downloaded directly from publishers or other online resources when they were not available from the local medical library and/or through interlibrary loan. The articles were then

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reviewed for additional references and originality. Primarily, the methodology and results were extracted from each pertinent scientific article and categorized as either preclinical or clinical data and presented in the respective section.

Basic Science

Background

Orthopedic surgery and therapeutics have come a long way since the time of Aristotle, when the use of bone marrow for restorative procedures was described. Connolly and others [2-4] initiated the modern era of evidence-based medicine regarding the role of bone marrow in surgical treatments such as bone fracture reconstruction. Indeed, needle aspiration of the iliac crest to obtain autologous bone and marrow, especially for spinal fusions, became a standard procedure in the 1980s [5,6]. This later understanding that marrow could stimulate or add value to osteogenic reconstruction and the popularity of bone marrow transplantation for the past 50 years [7] has resulted in further scientific exploration into the cellular basis of marrow's therapeutic properties.

Based on this research, it has been proposed that bone marrow aspirate (BMA) contains multipotent progenitors, which Caplan [8] has named MSCs, as pictured in Figure 1. It should be emphasized that the understanding in the late 1980s and early 1990s was that adults had only one stem cell in marrow, the hematopoietic stem cell. Furthermore, the scientific community maintained that individuals were born with the requisite number of specific organ-specific cells (say, cardiac myocytes) and that those cells became bigger or smaller but did not increase in number [9].

The current scientific evidence has now provided evidence that *every* tissue in the body has tissue-specific progenitors and that MSCs are derived, totally or in part, from perivascular cells called pericytes [10-12]. Thus muscle has satellite cells (myogenic progenitors) and a separate yet distinctive class of MSCs that reside as functional pericytes in uninjured muscle, and tendons have tendon progenitors and pericyte-derived MSCs. The MSCs from bone marrow, muscle, and tendon have the same general properties, but their basic chemistries are quite different as controlled by both their tissue of origin and the genome of the donor.

PRP

Platelets are small non-nucleated bodies in peripheral blood that are involved in hemostasis. Platelets contain a number of proteins, cytokines, and other bioactive factors that regulate wound healing. Plasma is the fluid portion of blood and contains clotting factors, proteins, and ions. Several authors have suggested that the definition of PRP should include preparations that have a platelet concentration of at least 1 million platelets per microliter and a 3- to 5-fold increase in growth factor concentration and cytokines. Preparations of this composition have been associated with the enhancement of healing [13,14].

The basic cytokines from the alpha granules of platelets include transforming growth factor−β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor I and II, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor (VEGF), and endothelial growth factor. These growth factors have important regulatory effects on MSCs [15,16].

Bioactive factors are also found in the dense granules in platelets, including serotonin, histamine, dopamine, calcium, and adenosine. These non−growth factors affect aspects of wound healing such as inflammation proliferation and remodeling [17].

The platelets in PRP can be delivered in a clot that contains adhesion molecules such as fibronectin, fibrin, and vitronectin [18].

MSCs

Bone marrow MSCs can be isolated and expanded in culture [19,20]. These MSCs are a heterogeneous mixture of cells that have at least 2 different capabilities. Some of these cells are already committed to the osteogenic pathway and accelerate bone formation and regenerative repair [2-4,21,22], whereas other MSCs have the capacity to be immunomodulatory and trophic [23]. These MSCs are formed at broken and inflamed blood vessels where the local pericyte detaches from the vessel and becomes an activated MSC. This in situ MSC secretes a curtain of bioactive agents that locally inhibit the overaggressive immune system from sending in integrating cells. This is the body's first line of control and defense against establishing an autoimmune reaction against the antigens exposed by the injured tissue. This immunomodulatory capacity of MSCs can be harnessed to provide therapeutic effects against graft-versus-host disease, Crohn disease with its inflammation of the gastrointestinal tract, and a large array of other clinical situations (for more information, search for "mesenchymal stem cells" at clinicaltrials.gov).

The "trophic" effects of MSCs establish a regenerative microenvironment at the site of injury by (1) inhibiting ischemia-related apoptosis, (2) inhibiting scar formation, (3) stimulating angiogenesis by secreting large amounts of VEGF and by transforming some of the MSCs back into pericytes that function to stabilize the fragile, newly forming capillaries, and (4) secreting tissue progenitor-specific mitogens so that the slow process of tissue regeneration is enhanced [24]. Thus MSCs serve as "drug stores" [25] for sites of injury and/or inflammation by providing an array of bioactive molecules tailored for that site and the injury (Figure 1) [25,26].

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