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Operative Techniques in
Orthopaedics

The Current State of Stem Cell Therapies in Sports Medicine ☆

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The theoretical clinical potential of stem cells in the orthopaedic sports medicine setting is unprecedented. The application of cellular-based treatments, such as stem cells, represents a fascinating and continuously evolving therapeutic approach into treating underlying pathologies. In recent years, technological advancements and innovation have shifted the mindset of clinicians from treating symptomatology to fundamentally altering the underlying disease process at the primordial molecular level. However, confusion created throughout the media and popular press, existence of unlicensed clinics throughout the world, ongoing regulatory debates, safety standards, and ethical concerns are among the many obstacles preventing the widespread clinical use of stem cells. Additionally, researchers and clinicians continue to struggle with identifying ideal dosage, timing, and frequency of treatments required for various indications to achieve maximum effectiveness in tissue-specific sites. Despite these barriers, the orthopaedic clinical application of stem cells has rapidly expanded from animal models to human clinical trials investigating various musculoskeletal conditions. Promising preclinical and clinical studies continue to provide critical insight necessary to fully elucidate the in vivo therapeutic effects of stem cells in the clinical application of orthopaedic sports medicine injuries and pathologies.
Oper Tech Orthop 26:124-134

KEYWORDS stem cell, orthopaedic, sports medicine

Introduction

The most fundamental and intriguing concept in the clinical application of stem cells to treat injury and disease is that every living cell in the body turns over. Dynamic signaling, occurring through programmed cellular death, injury, or infection, ultimately results in cellular material and tissues being replaced via innate regenerative mechanisms.[1] Stem cells' capacity to self-renew, accompanied by their ability to alter the regenerative microenvironment through anti-inflammatory, antiapoptotic, antifibrotic, proangiogenic, and immunomodulatory effects, has led to rapid advancements and innovations for the use of stem cells to treat orthopaedic sports medicine pathologies.[2,3]

Numerous obstacles have prevented the widespread clinical use of stem cells. Hype, controversy, and skepticism have vigorously surrounded stem cell use in sports medicine. Governmental regulations and ethical concerns have limited the clinical application of specific stem cell types and harvesting methods. Most treatments are deemed "experimental" and not reimbursed by medical insurance companies. This has led to safety concerns regarding patients seeking out potentially unregulated or unlicensed stem cell clinics throughout the world. As a result, safety and immunogenicity issues have warranted caution of less scrupulous stem cell providers exaggerating the benefits and undermining the risks of unproven stem cell therapies.

The theoretical clinical potential of stem cells in the orthopaedic sports medicine setting is unprecedented. However, efforts to determine their true efficacy remain immensely challenging owing to the complexity and existence of a multitude of variables. Isolation, preparation, and delivery methods are crucial elements under investigation to identify

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 http://dx.doi.org/10.1053/j.oto.2016.06.002
1048-6666//

ideal in vivo regenerative capacity. Additionally, deleterious in vivo conditions affecting the fragility of stem cells are also being determined. Other areas currently being explored in the literature include sex-related differences, tissue-specific properties giving rise to variable stem cell characteristics, plasticity and transdifferentiation properties, effects of aging and prolonged culture expansion of stem cells, and benefits of hybrid bioactive adjuncts combined with stem cells.

Orthopaedic clinical application of stem cells has expanded primarily from animal models to human clinical trials. Investigators are rapidly pressing forward to elucidate the effects of stem cells in a variety of musculoskeletal conditions such as fracture repair, osteonecrosis, cartilage regeneration, osteoarthritis (OA), meniscal pathology, tendinopathy, ligamentous injuries, and skeletal muscle restoration and function. Stem cell research and clinical use in orthopaedic sports medicine represents an exciting and promising time that continues to evolve to identify intrinsic means to enhance healing, expedite recovery, and prevent disease.

Basic Science

Stem cells are broadly defined as undifferentiated cells capable of self-renewal, with the ability to differentiate into some or all specialized cell types, and function to maintain and repair normal tissue. Stem cell potency can be categorized into 3 basic differentiation capacities: (1) Totipotent stem cells lines can form all types of cells in the body, including extraembryonic or placental cells and are able to give rise to an entire organism.[4] The only cells capable of totipotency are embryonic cells early in cell division after fertilization has occurred.[4,5] (2) Whereas, Pluripotent stem cell (PSC) lines can give rise to all embryonic germ layers (endoderm, mesoderm, and ectoderm).[4,6] Embryonic stem cells (ESC) are considered pluripotent.[6] (3) Lastly, multipotent stem cell lines can develop into more than a single cell lineage but give rise to a more restricted subset of cell lines of a particular organ or system.[6] Adult stem cells arising postnatally (including postnatal umbilical stem cells) are considered multipotent.[6]

Depending on the developmental stage, stem cells are generally classified as either embryonic stem cells or adult stem cells.[6] ESC for human use are restricted by the Food and Drug Administration (FDA) and are not currently used clinically in orthopaedics in the United States. Adult stem cell subcategories include the following: (1) hematopoietic stem cells (HSC), (2) induced PSC (iPSC), and (3) mesenchymal stem cells (MSC). HSC (also known as blood forming cells) are of mesodermal cell origin and primarily reside in the bone marrow and give rise to all types of mature blood cells within the hematolymphatic system (eg, erythrocytes, platelets, monocytes neutrophils, eosinophils, basophils, B and T lymphocytes, natural killer cells, and dendritic cells).[6,7] Contrary to belief, HSC (not MSC) are thought to be the main drivers of tissue regeneration because of their ability to upregulate cytokine release, recruit MSCs and other HSCs to the site of damage, and induce vasculogenesis and angiogenesis. In recent years, HSCs have also been shown to exhibit significant plasticity.[6] iPSC are adult stem cells that are altered or "manipulated" by enzymes or viral means that share similar properties with ES's but with less ethical concerns.[8] Importantly, there remains concern among the potential for teratoma formation when using ESCs and iPSCs for treatment.[8]

Regulations placed on manipulation of iPSCs and ethical concerns affecting ESCs have limited their orthopaedic clinical application and have led to increased interest in research and clinical use of MSCs.[8] MSCs have advantages of being relatively simple to isolate autologously and expanded in culture, possess important immunosuppressive properties when transplanting in an allograft setting, and are not derived prenatally.[9] MSC have been reported to be derived from perivascular cells[1]; thus, they are abundant and function in many types of adult tissues but the ideal source remains unknown.[10-12] MSCs have traditionally been derived from bone marrow but other common tissue sources for isolating MSC include synovium, periosteum, adipose, and postnatal umbilical cord tissues.[10-14] MSCs are precursors to cells of the mesodermal lineage, with chondrogenic, osteogenic, and adipogenic potentials and thus are believed to enhance the intrinsic regenerative and repair capabilities of "solid tissues" such as bone, muscle, cartilage, tendons, and ligaments.[1,10,15,16]

Trophic Effects

Human multipotent MSCs exhibit multilineage differentiation potential and have also been shown to secrete significant levels of trophic substances, such as cytokines, chemokines, and growth factors, to induce cellular proliferation and angiogenesis.[17] The induction of cellular proliferation and division of fibroblasts, epithelial, and endothelial cells may occur via MSCs expression of mitogenic proteins such as transforming growth factor-alpha and beta, hepatocyte growth factor, epithelial growth factor, basic fibroblast growth factor, and insulin-like growth factor-1.[17-19] Additional trophic effects may actually help reduce the formation of scar tissue though local paracrine secretion of factors such as keratinocyte growth factor, stromal cell-derived factor-1, and macrophage inflammatory protein-1 alpha and beta.[17] Additionally, angiogenic factors, such as vascular endothelial growth factor, insulin-like growth factor-1, epithelial growth factor, and angiopoietin-1, may be released to recruit endothelial lineage cells and initiate vascularization.[20]

Anti-Inflammatory and Immunomodulatory

Following trauma or long-standing chronic conditions, inflammatory modulators function to protect against invasion of toxic substances and microbes; however, these inflammatory modulators may persist and impede the intrinsic repair and regenerative mechanisms and lead to scarring.[17,1] MSCs may aid in faster recovery and improved chronic disease states via modulating the regenerative microenvironment with anti-inflammatory and immunomodulatory mechanisms.[17] Ultimately, through paracrine mechanisms, MSCs may enhance and speed up recovery by preventing proliferation and actions of key inflammatory and immunomodulators or effectors such