Regenerative Therapy for Osteoarthritis: A Perspective

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Osteoarthritis (OA) is the most common type of arthritis and causes a significant deterioration in patients’ quality of life. The high prevalence of OA as well as the current lack of disease-modifying drugs led to a rise in regenerative medicine efforts. The hope is that this will provide a treatment modality with the ability to alter the course of OA via structural modifications of damaged articular cartilage (AC). Regenerative therapy in OA starts with the concept that administered cells may engraft to a lesion site and differentiate into chondrocytes. However, recent studies show that cells, particularly when injected in suspension, rapidly undergo apoptosis after exerting a transient paracrine effect. If the injected stem cells do not lead to structural improvements of a diseased joint, the high cost of cell therapy for OA cannot be justified, particularly when compared with other injection therapeutics such as corticosteroids and hyaluronic acid. Long-term survival of implanted cells that offer prolonged paracrine effects or possible engraftment is essential for a successful cell therapy that will offer durable structural improvements. In this perspective review, the history and current status of regenerative therapy in OA are summarized along with the conceptual strategy and future directions for a successful regenerative therapy that can provide structural modifications in OA.

Keywords: Osteoarthritis, Regenerative therapy, Chondrogenic, Mesenchymal stem cells

Introduction

Regenerative therapies in osteoarthritis (OA) began with the concept that administered cells may engraft to lesion sites and differentiate into chondrocytes. However, recent studies have shown that cells, particularly when injected in suspension, undergo apoptosis after exerting a transient paracrine effect (1, 2). While paracrine action may include the mobilization of endogenous stem cells that contribute to the formation of regenerative neo-cartilage, the anti-inflammatory effect of innate immunity has been shown to be a more prominent paracrine action than the chondrogenic effect (3, 4).

If injected stem cells disappear after exerting a brief anti-inflammatory effect and do not contribute to structural improvement, i.e., regeneration of articular cartilage (AC), the high cost of cell therapy for OA cannot be justified, particularly when compared with other injection therapeutics such as corticosteroids and hyaluronic acid. Long-term survival of implanted cells that offer a prolonged paracrine effect or possibly engraftment is essential for a successful cell therapy in OA that will offer durable structural improvements.

Osteoarthritis and the Need for Regenerative Medicine

OA is the most common type of arthritis. It is characterized by loss of AC, subchondral sclerosis, osteophyte
formation, and, ultimately, joint destruction (5). Quality of life significantly deteriorates in OA patients with increased pain and loss of joint function (6). The current treatments for early OA are weight reduction, exercise, braces, nonsteroidal anti-inflammatory drugs, and intra-articular (IA) injections of glucocorticoid or hyaluronic acid (HA) in advanced cases, joint replacement has been the mainstay treatment for decades (7, 8). Pharmaceutical treatment provides alleviation of symptoms such as pain and inflammation. There are currently no disease-modifying drugs that alter the natural history of OA and offer structural improvements in damaged AC. Joint replacements are frequently associated with serious life-threatening complications, including thromboembolism (9) and periprosthetic infection (10). The high prevalence of OA as well as the current lack of disease-modifying drugs has led researchers and physicians to explore regenerative medicine as a possible treatment modality that may alter the course of OA via structural modification of damaged AC.

The Meaning of Chondrogenic Induction from Stem Cells

Cell therapy for cartilage regeneration was first based on the belief that implanted cells regenerate damaged AC, thus bringing about structural modification of a diseased joint, and might eventually replace pharmaceutical and surgical treatments for OA. Autologous chondrocytes were the first cell candidates. However, shortcomings of the treatment, such as loss of chondrocyte phenotypes and additional morbidity associated with the process of harvesting chondrocytes, led researchers to consider other sources of therapeutic cells, mostly mesenchymal stem cells (MSC) (1, 2, 11).

Early experimental studies for stem cell-based cartilage regeneration focused on the induction of chondrogenic differentiation from stem cells. A number of studies attempted to define the appropriate combination of growth factors or gene transfers that would induce chondrogenesis from stem cells (12-18). Others attempted to apply biomechanical stimuli to enhance chondrogenic induction from stem cells (19, 20).

Early induction of hypertrophic markers such as type 10 collagen and runx-2 in MSC chondrogenesis revealed a prominent difference from articular chondrocytes, which never express these markers (17, 18). As a corollary, researchers made great efforts to devise methods of suppressing hypertrophy in MSC chondrogenesis. However, if IA-administered cells do not survive long enough to differentiate into articular chondrocytes, these efforts would be useless, not producing any improvement.

Transient Intraarticular Survival of Injected or Implanted Stem Cells

Notably, the inflammatory environment of an OA joint provides generally inhospitable conditions for tissue regeneration. Most IA-administered stem cells undergo rapid apoptosis. The survival of cells can vary from 3 days to several weeks depending on the mode of administration and the IA environment (1, 2). These cells secrete several paracrine factors before undergoing apoptosis. These factors were found to possess predominantly anti-inflammatory and immunosuppressive actions rather than chondrogenic effects. Murphy et al. demonstrated the absence of IA-injected MSCs 1 week after injection in an ovine model (21). Kolon Life Science developed cell therapeutics consisting of TGF-β-transduced chondrocytes. Those cells were observed to completely disappear from the injected joints within 2 weeks (22). When cells were focally implanted rather than injected, longer-term survival of stem cells was reported, as seen in the application of Cartistem® in advanced OA (23).

If a stem cell therapy aims to achieve structural improvement to lesion sites by regeneration of AC, prolonged survival of implanted stem cells that could exert prolonged paracrine effects and/or engraftment with chondrogenic differentiation are mandatory requirements. The author’s preliminary results show that adipose stem cells (ASCs) in spheroid form survive longer post-IA injection than do ASCs that are injected in a free single cell suspension. These findings mean that some communication/interaction between cells can promote IA cell survival, as in monolayer cell culture, in which a certain concentration of cells is necessary for survival. Also, ASCs that were fixed on the focal chondral defect using a strong bioadhesive (mussel adhesive protein) showed longer-term survival than those immobilized using fibrin glue. These results indicate that stem cells can survive longer when forced to stay at the site of implantation (Fig. 1).

Factors That May Affect Stem Cell Survival and Enhance Engraftment

Cellular aging naturally reduces the survival of stem cells. Oxidative stress promotes cellular aging. In aged MSCs, superoxide dismutase (SOD), an important antioxidant enzyme, is decreased (24). Conversely, hypoxic states or antioxidants such as ascorbic acid, N-acetylcys-
tein, erythropoietin, and sulforaphane increase stem cell survival (25, 26). The PI3K/AKT/mTOR/FOXO3 pathways play a significant role in modulating oxidative stress. An mTOR inhibitor, rapamycin, suppresses the production of ROS (27, 28). Aged MSCs secrete molecules that aggravate inflammation, including leptin, TGF-α, interleukin-8, eotaxin, interferon-γ, VCAM1, interferon-β, interleukin-4, and monocyte chemotactic protein-1 (MCP1) (29).

A vast wealth of knowledge has been obtained from the study of aging and survival of stem cells. Pre-treatment with substances known to promote cell survival may enhance IA survival of administered stem cell therapeutics.

**Future Directives for Successful Cell Therapy to Treat OA**

When cell therapy was first reported to treat cartilage defects and osteoarthritis, an optimistic view prevailed which held that implanted cells could be incorporated into defects and regenerate AC. The main focus was on how to ensure that the implanted stem cells possess the full properties of articular chondrocytes. As it became evident that almost all IA-administered stem cells rapidly undergo apoptosis and that their principal mode of action is paracrine, two strategies rose up to help enhance the effects of cell therapeutics: 1) enhance the survival of stem cells by pretreatment with factors known to promote cell surv-
vival or by administration of stem cells in physical states that favor longer-term survival, such as the spheroid form or encapsulated in a hydrogel, and 2) apply stem cells in a high concentration and prevent dispersal into the joint using a bioadhesive (Fig. 2).

Given that the mechanisms underlying necrosis versus survival of implanted stem cells are not well-established, future studies should focus on how the fate of IA-administered stem cells is affected by factors such as the physical status of the cells, mode of implantation, and adjuvant biomaterials.

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Potential Conflict of Interest
The authors have no conflicting financial interest.

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