Stem Cells in Osteoarthritis

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Introduction

Articular cartilage has significant limitations for repair or regeneration. It does not respond to an injury or disease with the normal inflammatory sequence of events that results in repair of most other tissues. The issues that preclude a functional repair in articular cartilage include its avascularity, the presence of cells (chondrocytes) that have a limited capacity to respond, and a complex structure that is difficult to reproduce. A plethora of approaches has been applied in an attempt to repair articular cartilage. Although short-term functional repair has been reported, a long-term biological regeneration has yet to be accomplished.

Cells and Cartilage Regeneration

Our laboratory has focused for the last two decades on cells as the central driver for functional long-term regeneration. The potential cells that could be used for cartilage regeneration are autologous or allogeneic chondrocytes and osteochondral progenitor cells defined as mesenchymal stem cells (MSCs). Autologous chondrocytes are not ideal since they are in limited supply and are generally unresponsive to the specific demands of their mechanical environment. Allogeneic chondrocytes invoke an immune response when transplanted into a host. Conversely, MSCs are ubiquitous in all tissues, are in unlimited supply, have a broad range of expression, and are responsive to their environment both biologically and mechanically. Further, they can recapitulate embryologic lineage and therefore have the potential to create a regenerative tissue.

MSCs can be isolated from the bone marrow. Human mesenchymal stem cells decline with age; a newborn has approximately one MSC in every 10,000 marrow cells, while someone in their 80s have one MSC in every 2,000,000 marrow cells. Several studies of MSCs isolated from osteoarthritis patients reported that these cells do not change their capability to form bone. Their proliferative and osteogenic potential, however, was significantly reduced with age. Murphy et al. [6] demonstrated that bone marrow-derived stem cells from osteoarthritis patients had a decreased proliferative capacity when compared to age-matched controls, as well as a decrease of their chondrogenic and adipogenic capacity. However, no decline in their osteogenic capacity was found.

The potential approaches to using stem cells in the treatment of osteoarthritis include their application in tissue engineering and their use alone in treatment protocols. Tissue engineering applications are discussed elsewhere in this symposium. The use of stem cells alone in the treatment of osteoarthritis depends upon the injury response cascade. After injury or onset of disease, an inflammatory response usually occurs. By providing the host with an enhanced number of stem cells in the biological regenerative phase, an acceleration of the functional repair of the tissue can occur. This treatment concept would either use MSCs for the direct repair of articular surfaces or for their trophic or immunomodulating function [5].

Strategies for the Use of Stem Cells in Cartilage Repair

One approach to the direct repair concept is the development of stem cell homing technology [2]. The MSC is manipulated to enable direct targeting of the cell to the cartilage defect for repair. The advantages of this concept are the elimination of the need for surgery except for the cell injection, the elimination of the need for a manmade scaffold, and the lack of an immune rejection because an autologous cell pool is used. The MSCs that are used are provided a transient coating on their surface with a matrix binding molecule to promote attachment to the specific repair sites. The coating is provided by a two-step method using palmitated protein G (PPG) initially attached to the cell membrane and then a second incubation

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with specific antibodies to cartilage matrix antigens linked to the PPG. This coating technique does not affect cell viability or inhibit cell proliferation or chondrogenic potential. Using fluorescently labeled cells with a vital dye, we demonstrated that these cells “target” to defects on the surface of articular cartilage (Fig. 1). The cell attachment is enhanced by the use of dual antibodies to chondroitin sulfate and type II collagen.

Stem cells have been used as a platform for genetic engineering. Gelse et al. [4] transfected MSCs isolated from rib perichondrium with BMP-2/IGF-1 expressing genes. The cells were then transplanted into rat femoral defects. The investigators reported a restoration of the surface with hyaline cartilage. This is another attractive approach to the treatment of articular cartilage destroyed by osteoarthritis.

The trophic functions of mesenchymal stem cells were recently reviewed by Meires et al. [5]. Studies indicated that MSCs have multiple functions including immunomodulation, anti-apoptosis, enhancement of angiogenesis, support of growth and differentiation of localized stem and progenitor cells, antiscarring, and finally providing a chemoattraction capability for cells. Stem cells in this functional mode act as enhancers and inducers of local MSCs to participate in the regeneration of a specific tissue. Recent work by Crisan et al. [1] demonstrated that stem cells are identical to perivascular cells (pericytes). This finding suggests that the pericyte in the specific tissue is capable of repairing or regenerating a deficiency in that tissue after being induced to become a repair cell by circulating MSCs.

Recent studies evaluated the potential of MSCs in the treatment of experimentally induced osteoarthritis. Frisby et al. [3] treated the carpal joints of horses with bone marrow-derived mesenchymal stem cells on day 14 after induction of osteoarthritis. The only positive finding was a decrease in the synovial PGE-2 level, but no real treatment value was noted in comparison with the control animals. Murphy et al. [7] induced osteoarthritis in adult goats by using a

combination of medial meniscectomy and transection of the anterior cruciate ligament. Ten million MSCs were injected in a hyaluronic acid vehicle at 6 weeks after induction of the disease. The animals were then observed for 3 and 6 months. Evidence of marked regeneration of the medial meniscus was observed, along with significant preservation of articular cartilage and reduction of osteophyte and subchondral bone changes in the cell treated joints when compared to joints treated with the vehicle alone. The investigators concluded that the local delivery of adult mesenchymal stem cells stimulated regeneration of meniscal tissue and retarded the progression of osteoarthritis.

Future Frontiers

Significant questions remain in defining the use of stem cells in the treatment of osteoarthritis: what type of stem cell should be used, what's the most effective manipulation of these cells, how many cells are required, what carrier should be used, and most importantly, what is the optimal treatment protocol, including the timing of cell treatment relative to the disease state? Finally, the overriding remaining issue is a complete understanding of the mechanism of mesenchymal stem cell function. Notwithstanding these issues, an understanding is emerging of how mesenchymal stem cells may be used in the treatment of tissue deficiencies in the musculoskeletal system. Stem cells in an undifferentiated state have significant trophic and immunomodulatory capabilities and can be used in treatment protocols that take advantage of these properties. The application of MSCs in tissue engineering requires the introduction of MSCs that are committed to a specific phenotype. Future basic and applied research will delineate the principles of both approaches and their applicability to clinical problems.

Fig. 1. Photomicrographs of the articular surface which demonstrate fluorescently labeled cells with a vital dye plus antibodies to chondroitin sulfate and type II collagen. Cell attachment is enhanced compared to control. Adapted from Dennis et al. [2], copyright 2004, with permission from John Wiley and Sons

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