

Repair of Injury to Articular Cartilage with Chondrocyte Progenitor Cells

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Osteoarthritis (OA) is a musculoskeletal disease of diarthrodial synovial joints that results from a constellation of genetic and environmental factors and altered metabolic function of articular cartilage, synovial tissue and subchondral bone cells [1-3]. The pathogenesis of OA is now considered to arise from the convergence of abnormal biomechanics with these genetic and environmental factors leading to fundamental changes in the composition and integrity of extracellular matrix (ECM) proteins of articular cartilage [1]. It is indeed the composition and integrity of ECM proteins that regulate the capacity of articular cartilage to appropriately respond to abnormal compressive forces and tensile stress [4]. When biomechanical abnormalities ensue they cause cartilage injury or OA which is generally accompanied by the gradual development of inflammatory responses in synovial joint tissues. Thus, inflammation appears to be the critical component permitting OA to progress to joint failure [5]. Inflammation may also be an important cartilage response affecting intrinsic repair properties after acute injury.

Presently, surgical intervention may be required to prevent further cartilage damage after acute injury. For OA patients, physical therapy is employed to improve joint motion. However, the pharmacotherapy of OA is rather restricted to old drugs. The OA therapeutic paradigm generally consists of administering intra-articular corticosteroids to affected joints to quell swelling, pain and inflammation; oral administration of Type I non-steroidal anti-inflammatory agents (NSAIDs) (e.g. naproxen and diclofenac) or Type II NSAIDs (e.g., celecoxib, etoricoxib and lumiracoxib), drugs designed to reduce prostaglandin biosynthesis via inhibition of cyclooxygenase-1 (i.e., COX-1) and COX-2 activity, respectively [6] and acetaminophen also used for pain relief [7]. In addition to these drugs, a host of nutritional supplements (i.e., nutraceuticals), include glucosamine, chondroitin sulfate [8], chondroitin as well as botanicals and other natural products [9] along with various injectable formulations of hyaluronic acid [10,11] are employed for the therapy of OA. These agents should always be considered complementary medicines in the OA therapeutic armamentarium. They have widespread use and purportedly possess anti-inflammatory properties. However, the efficacy of many of these alternative therapies and their effects on limiting the progression of OA remains highly controversial.

From an epidemiologic perspective, OA is associated with the ageing process [4,12,13]. Thus, as longevity increases OA will become even more of a seriously burdensome medical disorder which is likely to have significant effects on health care economics. As such it would be prudent for the biopharmaceutical industry to place their considerable research and financial resources into developing drugs that specifically target molecules which have been identified to promote the progression of OA. This target molecule approach has been rigorously defined through numerous studies using chondrocyte, synoviocyte and bone cells from human OA joints the results of which were, in general, then compared to results obtained with cells isolated from non-arthritic age-matched joints. The results of studies related to molecular targets pertinent to OA have also been identified from well-validated animal models of OA [reviewed in 14].

It is also germane to a consideration of future OA therapies that significantly elevated levels of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1) and IL-6

were found in the synovial fluid of OA patients [15] and these pro-inflammatory cytokines promote matrix metalloproteinase gene up-regulation [16] and apoptosis [17] to name only two of the many cellular events relevant to the progression of OA. Despite these findings, only an IL-1 receptor antagonist (IL-1Ra) [18] has been rigorously assessed in a phase II double-blinded non-controlled clinical trial of 13 patients with knee OA. In this study [19] patients received intra-articular injections of 150 mg of a recombinant form of human IL-1Ra. The results indicated a significant improvement in pain (using a visual analog scale) and in the Western Ontario and McMaster Universities (WOMAC) OA index over a 3-month period. However, assessments relative to the extent to which IL-1Ra altered the pathology of OA remain to be fully evaluated.

Recently, anti-Nerve Growth Factor (NGF) receptor monoclonal antibodies were evaluated for their capacity to reduce pain in clinical trials involving patients with advanced hip and knee OA and in patients with chronic back pain [reviewed in 20]. These NGF receptor antagonists were efficacious for reducing pain, but these agents were also associated with serious adverse effects including the development of osteonecrosis in some patients treated with anti-NGF and NSAIDs. NGF is a neurotrophin having strong regulatory activity towards peripheral nociception. In that regard, the expression of Substance P, calcium-related peptide and serotonin are the expected targets for NGF-receptor blockade. However, it remains to be determined whether the blocking of metabolic pathways by these anti-NGF receptor monoclonal antibodies can alter the progression of OA pathology. Importantly, the number of recent studies focused on testing anti-NGF receptor antagonists in OA pale by comparison with the targeted approaches employed by the biopharmaceutical industry in developing and successfully marketing for use in the clinic a multitude of biological agents designed to block the immune-mediated inflammation of rheumatoid arthritis [21,22].

In view of the relative paucity of drug development strategies designed to treat cartilage injury and OA, the Special Issue of *Rheumatology: Current Research* devoted to "Chondrogenic Progenitor Cell Response to Cartilage Injury" [23] reviewed the relatively novel approach of employing chondrocyte progenitor cells to suppress the destruction of articular cartilage after tissue injury and/or in OA. This cell-therapy paradigm is also envisioned to promote the local repair of affected joint cartilage. Thus, this experimental cell-based strategy may eventually compliment any newly developed pharmacotherapeutic interventions for OA, going forward. Cell-based therapy may delay and even allay joint replacement surgery for OA.

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The fundamental underpinnings for considering a cell-based therapy for the treatment of injured articular cartilage and OA stems from the discovery of a synovial joint stem-cell population with chondrogenic potential. In an editorial accompanying the Special Issue, Dr. Caroline Dealy [24], the lead editor of the Special Issue, critically discussed much of the evidence that stem-like cells with the potential to develop into chondrocytes could be localized within or adjacent to articular cartilage. In support of this contention, Dealy cited the work of Karlsson et al. [25] who localized a population of proliferating cells in the perichondrium as well as at the border of the growth plate. These cells were considered to be potential progenitor cells for articular cartilage renewal. In another study cited by Dealy, Adachi et al. [26] found that synovial cells harvested from the transitional zone between articular cartilage and synovial membrane of the femoral condyle had a greater proliferation potential and chondrogenic differentiation properties compared to synovial cells from an area 5 mm medial to the transitional zone of the femoral condyle. In addition, Adachi et al. [26] found that synovial cells from this transitional zone strongly expressed anti-ATP-binding cassette G-subfamily member 2, a biomarker for mesenchymal stem cells, suggesting that these cells would be preferable for expansion in culture to produce authentic articular chondrocytes.

What other sources of cells besides those isolated from synovial joints could potentially be employed for chondrocyte transplantation to repair injured or OA cartilage? To address this question, Gelse et al. [27] reviewed several alternative sources of chondrocyte progenitor cells for their potential use in transplantation. The most prominent of these alternative tissue sources appears to be stem cells isolated from bone marrow (BMSCs). However, BMSCs are compromised as potential cartilage repair cells because they exhibit a tendency to undergo ossification characterized by the formation of intralaminar osteophytes. Thus, in-growing BMSCs would likely undergo exuberant endochondral ossification and terminal differentiation precluding their use in cartilage repair. To overcome this problem, Gelse et al. [27] suggested that epigenetic factors involving regulation and modification of DNA methylation and histones of cartilage-relevant genes may be necessary to induce gene modifications which could alter the genomic imprinting of adult BMSCs and thus enable them to be employed in chondrocyte transplantation. In that regard, it seems relevant to these arguments that Malemud et al. [28] recently showed that monosodium urate (MSU) or TNF- α were capable of increasing the frequency of apoptosis *in vitro* by cartilage-constructs composed of human juvenile chondrocytes. However, these pro-inflammatory mediators could not induce apoptosis in cartilage-constructs composed of chondrocytes expanded from the lineage of human BM-mesenchymal stem cells (BMMSCs). Interestingly, the BMMSCs-derived cartilage-constructs expressed Type X collagen, a biomarker for chondrocyte terminal differentiation as well as Type II collagen, whereas cartilage-constructs from juvenile chondrocytes expressed only Type II collagen.

A standardization procedure for collecting stem-cells and the required quality assurance for using mesenchymal stromal cells (MSCs) for cartilage repair is yet another important issue that eventually will have to be addressed if chondroprogenitor cells are to be used in the clinic. To address these concerns, Müller and colleagues [29] reviewed several issues affecting the standardization process for using MSCs in the clinical setting. They posited that presently, the protocols for acquiring MSCs varies from tissue to tissue whereby acquisition of MSCs is the starting point for expanding these cells *in vitro*. This is a genuine problem because although this procedure may be sufficient for the molecular characterization of MSCs, these protocols clearly do not adhere to the standards and practices required for employing them

in the clinical setting. Thus, human subject's experimentation review boards will expect that the 'identity, purity, and potency' of MSCs be verified for each application, and most critically, that these cells be phenotyped as precisely as possible before they can be employed in individual patients.

One of the major stumbling blocks in employing stem-cell technology for cartilage repair and for OA is the extent to which adult stem cells versus embryonic stem cells (hESC) versus inducible pluripotent stem cells (iPSC) will become the standard choice for clinical applications. In a comprehensive analysis of this issue, Fisher et al. [30] pointed out that protocols are now being developed where the differentiation of hESCs into chondrocytes can be rigorously monitored. However, even if these protocols are successful, the comprehensive testing of hESCs for repairing cartilage lesions in preclinical animal models of cartilage injury or animal models of OA will have to be performed and the results systematically analyzed. Moreover, cartilage repair using these cells will have to be optimized. Optimization may involve employing 'pro-chondrogenic factors,' or 'bioactive scaffolds' capable of being seeded with growth factors, or other "cartilage-repair molecules." Not only will the safety issue need to be critically addressed if hESCs or iPSCs are used for cartilage repair, but also the possibility that transplanting chondrocytes derived from hESCs (or iPSCs) for cartilage repair might result in the loss of immune tolerance and potential autoantibody production.

A different theme was developed in discussing whether articular cartilage-derived (ADC)-stem cells were a better choice for promoting 'spontaneous' repair of injured cartilage. To address this point, Archer et al. [31] analyzed the replication capacity of articular cartilage-derived (ADC)-stem cells and showed that these cells had high replication potency. This response was associated with evidence that immature bovine-derived ADC-stem cells exhibited detectable telomerase activity with a delay in 'telomeric erosion' during *in vitro* monolayer culture. By contrast, "dedifferentiated" chondrocytes derived from full-depth articular cartilage samples had significantly lower levels of telomerase activity while also exhibiting telomeric erosion at approximately 20 population doublings [32]. Of note, ADC-stem cells from adult normal cartilage also displayed greater telomerase activity than chondrocyte isolates from full-depth tissue sites and chondrocytes produced from ADC-stem cells expressed the chondrocyte "signature" molecules, sox9, Notch-1, aggrecan and proliferating cell nuclear antigen. Thus, Archer et al. [31] and Khan et al. [32] envision that repair of articular cartilage lesions could be accomplished by employing ADC-stem cells with high replication potency. The use of these cells could improve on results obtained thus far employing currently available standardized articular cartilage implantation techniques.

In addition to the sources of chondroprogenitor cells previously discussed, Chu and Friel [33] critically analyzed whether synovial cells or adipose tissue contained chondroprogenitor cells populations which could eventually be used for cartilage repair. As far as synovial cells are concerned, Chu and Friel [33] highlighted the results of a study by Mochizuki et al. [34] who compared cells from fibrous synovium, adipose synovium (i.e., infrapatellar fat pad) and subcutaneous fat pad to determine which tissue contained the optimal number of chondroprogenitor cells. Mochizuki et al. [34] found that cells from fibrous synovium and adipose synovium had a greater chondrogenic potential than cells from subcutaneous fat, but cells from fibrous synovium and adipose synovium showed "comparable chondrogenic potential." In discussing the value of adipose-derived cells Mochizuki et al. [34] further commented that they were far more readily obtainable than BMSCs and, in contrast to procedures required to obtain BMSCs,

did not involve bone marrow aspiration with its documented risk and medical complications. They also pointed out there has been far less exploration of muscle, perichondrium and periosteum as sources of chondroprogenitor cells compared to other tissues and cell sources.

In conclusion, considerable progress has been made in defining molecular biomarkers required to establish the phenotype of chondroprogenitor stem-cells from various tissue sources. However, one major stumbling block which must be overcome to allow for more extensive use of these chondroprogenitor stem-cells to produce chondrocytes for eventual use in the clinic is the lack of standardized protocols for characterizing the chondrocyte “molecular-signature.” Based on the extensive number of ongoing studies in this field there is every reason to expect that developing such standardized regimens will provide the impetus for their eventual use in the clinic for repairing articular cartilage lesions resulting from acute tissue injury, and eventually in a cell-based therapy of human OA.

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