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Stem cell-based therapies for osteoarthritis: Challenges and opportunities

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Abstract

Purpose of review—Regenerative medicine offers the exciting potential of developing alternatives to total joint replacement for treating osteoarthritis (OA). In this article, we highlight recent work that addresses key challenges of stem cell-based therapies for OA and provide examples of innovative ways in which stem cells can aid in the treatment of OA.

Recent findings—Significant progress has been made in understanding the challenges to successful stem cell therapy, such as the effects of age or disease on stem cell properties, altered stem cell function due to an inflammatory joint environment, and phenotypic instability in vivo. Novel scaffold designs have been shown to enhance the mechanical properties of tissue-engineered cartilage and have also improved the integration of newly formed tissue within the joint. Emerging strategies such as injecting stem cells directly into the joint, manipulating endogenous stem cells to enhance regenerative capacity, and utilizing stem cells for drug discovery have expanded the potential uses of stem cells in treating OA.

Summary—A number of recent studies have greatly advanced the development and pre-clinical evaluation of potential stem cell-based treatments for OA through novel approaches focused on cell therapy, tissue engineering, and drug discovery.

Keywords

mesenchymal stem cells; arthritis; tissue engineering; inflammation; induced pluripotent stem cells

Introduction

Articular cartilage exhibits little or no ability for self-repair, resulting in progressive tissue loss and dysfunction following isolated cartilage injuries. The lack of effective repair also contributes to the widespread degeneration of the joint associated with osteoarthritis (OA). Stem cells have extraordinary potential to contribute to novel treatment strategies for both clinical situations. For the repair of chondral or osteochondral defects, stem cells may be able to provide an abundant cell source, preventing the iatrogenic damage associated with the invasive isolation of chondrocytes used in autologous chondrocyte implantation (ACI) strategies. Additionally, the continued development of tissue engineering strategies has sought to combine stem cells with various scaffolds and chondrogenic signals (e.g., growth factors, bioreactors) to produce a functional tissue that could be used to repair focal cartilage defects. However, new challenges arise when transitioning such therapies from filling a small defect in an otherwise healthy cartilage surface to treating a severely degraded

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osteoarthritic joint. This recognition is important for aligning research goals with societal need, as the clinical impact of generalized cartilage degradation with OA far surpasses that associated with focal cartilage defects [1].

Total joint replacement with artificial components remains the definitive treatment for end-stage OA, but the limited lifespan of these prostheses may be unable to meet the growing demand from younger and more active patients [2], providing an opportunity for the development of new therapeutic approaches. However, in order for stem cell-based therapies to emerge as viable alternatives, the unique challenges associated with using stem cells to treat OA patients must be identified and addressed (Figure 1). In this article, we highlight current work that is addressing these challenges in innovative ways. Some approaches fall into the cartilage tissue engineering paradigm of transplanting newly formed cartilage to resurface the joint, while others seek to expand the horizons of how stem cells can be used to combat OA by enhancing the body's endogenous regenerative capacity or by aiding in drug discovery.

The effects of age and disease on stem cell properties

Adult stem cells such as bone marrow-derived mesenchymal stem cells (MSCs), adipose-derived stem cells (ASCs), and synovium-derived stem cells (SDSCs) have demonstrated chondrogenic potential when treated with chondroinductive agents such as transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs). However, the stem cells typically used in these studies are from young, healthy donors and may not reflect the expansion and differentiation characteristics of stem cells from OA patients requiring autologous stem cell therapy. Given previous indications that the presence of OA may reduce the chondrogenic capacity of stem cells [3], it was important that several recent studies have confirmed that MSCs from OA patients are able to be isolated, expanded, and differentiated toward the chondrocyte lineage [4, 5]. However, patient characteristics other than OA itself may serve as important selection criteria for stem cell-based repair strategies. For example, increased age and obesity are both significant risk factors for OA and may affect the quality of stem cells. For patients failing to meet the criteria for autologous stem cell therapy, allogeneic therapy has been shown to be a safe alternative in clinical trials for other indications [6].

To study the effect of age on stem cell characteristics, Dexheimer et al. [7] characterized MSCs from 28 patients with an age range of 5–80 years. The single cell cloning efficiency and proliferation rate were reduced with age, but no significant correlation was found between age and chondrogenic differentiation. Importantly, nearly half of the donors failed to synthesize significant type II collagen in pellet culture, and these donors typically displayed slow proliferation during expansion. Although not strictly correlated to age in this study, the striking donor variability reinforces the concept that patient selection is likely to be an important feature of stem cell-based therapies.

ASCs and other stem cells from obese patients may be compromised by the presence of low-grade systemic inflammation that is associated with obesity. Indeed, ASCs derived from the visceral fat of morbidly obese patients showed a reduced proliferation rate, greater cell senescence, and a reduced differentiation to multiple lineages including chondrogenesis [8]. In addition to functional outcomes, the authors provide evidence of a dysregulated stemness network in ASCs from obese patients, with alterations in the Wnt, Notch, and Sonic Hedgehog pathways as well as aberrant miRNA regulation. Recent evidence from our lab using lean and obese mice indicate that obesity also alters the differentiation potential of stem cells isolated from subcutaneous fat, infrapatellar fat pad, and bone marrow [9]. Further analysis of how obesity affects stem cell properties such as prevalence, proliferation,

and multipotency may lead to methods for adapting differentiation protocols to counteract the reduced chondrogenic potential of stem cells from obese patients.

The effects of joint inflammation on stem cells

In contrast to the misconception that OA is simply a “wear and tear” disease, it is now clear that pro-inflammatory cytokines and mediators play an important role in the onset and progression of this disease [10]. In this respect, the potential impact of inflammatory cytokines present in the joint space must be considered when evaluating stem cell-based treatments. For tissue engineering strategies, this involves the recognition that newly implanted constructs may be subjected to a similar inflammatory environment that led to degradation of the original cartilage. It is clear that inflammatory cytokines such as interleukin-1β (IL-1β) and transforming necrosis factor-α, as well as conditioned medium from OA synovium, can interfere with chondrogenic differentiation if present early in the tissue maturation process [11]. This observation threatens the paradigm of utilizing the joint as a bioreactor to guide chondrogenesis of transplanted stem cells without prior differentiation. However, it appears that more mature tissue-engineered constructs are also susceptible to degradation after exposure to inflammatory cytokines. With just three days of high dose IL-1β treatment, cartilaginous pellets of differentiated MSCs demonstrated significant aggrecanase enzyme activity that was absent during the differentiation process [12]. Interestingly, exposure to inflammatory cytokines may have lasting effects on stem cell differentiation, as the inflammation associated with anterior cruciate ligament surgery in sheep was enough to reduce the in vitro chondrogenic potential of stem cells derived from the inflamed synovium [13]. These observations highlight the need to test tissue engineered constructs in an inflammatory environment and to use advances in scaffold design or genetic engineering to alter the manner in which engineered tissue will be resistant to inflammatory cytokines.

Maintaining stability of the chondrocyte-like phenotype

One of the most difficult aspects of controlling the chondrogenic differentiation of stem cells is achieving phenotypic stability over long periods of time following implantation. The loss of chondrocyte-specific features can occur by either transition to a fibrocartilage phenotype with increased type I collagen production or transition to the hypertrophic chondrocyte phenotype with increased type X collagen synthesis. Vinardell et al. illustrated this point well by showing that stem cells from synovium and adipose tissue tended towards the fibrocartilage pathway whereas stem cells from bone marrow were susceptible to hypertrophic chondrocyte conversion after subcutaneous transplantation [14]. However, several studies have shown that recapitulation of the natural environment of cartilage by reducing the oxygen tension limits the potential for differentiation towards the hypertrophic chondrocyte phenotype [15, 16].

Scaffolds and signals to enhance tissue mechanical properties

Cartilage primarily serves a biomechanical function, and therefore tissue engineering strategies must ultimately produce a construct that is able to recapitulate the most essential mechanical properties of native cartilage. This significant challenge can be addressed by either promoting abundant matrix synthesis during an in vitro culture period or by seeding cells in scaffolds that provide initial mechanical integrity. In this regard, several recent studies have developed methods that greatly accelerate cartilage matrix formation and accumulation in vitro. To stimulate high rates of glycosaminoglycans (GAG) and collagen production, hyaluronic acid hydrogels containing a high density of bovine MSCs were subjected to dynamic culture conditions in the presence of TGF-β3 [17]. After nine weeks, the resulting tissue demonstrated an equilibrium modulus similar to that of native cartilage,

with values in excess of 1 MPa. Complementary approaches using bioreactors to provide a chondroinductive mechanical environment may help speed up the process of matrix formation by stem cells [18].

An emerging approach is to design scaffolds with mechanical properties close to those desired in the final tissue-engineered product. This approach opens up the possibility of resurfacing the joint with a biologic implant even without prior matrix synthesis, as the scaffold provides sufficient functional properties at the time of implantation. For example, our lab developed 3-dimensional woven scaffolds with fully controllable mechanical properties in order to replicate the complex mechanical behavior of cartilage [19]. Recent developments have used composite scaffolds to combine features that are cell instructive while simultaneously providing mechanical integrity [20]. A related approach used electrospun fibers embedded in a hydrogel to form a composite scaffold, demonstrating that the proportion of fibers determines both the initial mechanical properties and the chondrogenic response of MSCs during culture [21].

Composite constructs to facilitate osteochondral integration

The difficulty in achieving cartilage-to-cartilage integration has frustrated attempts to integrate tissue-engineered constructs with surrounding native cartilage tissue in focal defects. In this regard, the approach of resurfacing a completely degenerated joint surface has an advantage in that the need for lateral integration with cartilage is obviated. However, challenges may still remain with integrating the tissue-engineered cartilage with underlying bone. One potential strategy is to take advantage of superior bone-to-bone integration by incorporating a layer of tissue-engineered bone to create osteochondral composite constructs. The use of a single stem cell source to create both cartilage and bone layers requires controlling the spatial distribution of chondrogenic and osteogenic induction agents. This approach was accomplished by seeding MSCs in gene-activated scaffolds that delivered the chondrogenic growth factor TGF-β1 to the top layer and the osteogenic factor BMP-2 to the bottom layer [22]. Layers were then combined with fibrin glue and pre-cultured for two weeks before transfer to an osteochondral defect, exhibiting convincing repair over the course of 12 weeks. Other work using umbilical cord-derived stem cells employed a single scaffold with a graded distribution of microspheres delivering chondrogenic and osteogenic signals instead of distinct layers to enhance the integrity of the osteochondral junction during defect repair [23]. Future studies are needed need to validate the integration between osteochondral constructs and the OA joint, as changes to the bone during disease progression may affect the quality of integration.

Intra-articular stem cell injection to modify the progression of OA

Thus far this review has focused on stem-cell based cartilage tissue engineering strategies for end-stage OA, but emerging evidence indicates that the direct injection of stem cells to the joint can boost the normally limited repair and limit destructive processes. A limited clinical trial using ASCs for knee OA showed encouraging early results with regard to improved functionality, but further work is needed to confirm a specific effect of the stem cells [24]. MSC injection to equine joints was effective when delivered during early chemical-induced OA, but the cartilage loss at later stages was too drastic for significant repair even with MSC therapy [25]. Future work will need to continue to improve the specific targeting and retention of MSCs at the cartilage surface in order to maximize the potential effect [26].

One motivation for direct stem cell injection is that the anti-inflammatory function of stem cells may be effective at preventing or delaying OA if delivered at early stages in the disease process. This is consistent with the role of MSCs altering the balance of inflammation and

regeneration in numerous other injury models [27, 28]. In a recent study, we observed that a single intra-articular injection of purified MSCs could prevent the degenerative changes caused by an articular fracture of the tibial plateau in mice [29]. Similarly, injection of hMSCs into rat joints after meniscectomy prevented the development of subsequent OA at least in part by enhancing meniscal repair by rat cells [30]. Other work also supports the concept that stem cells protect joints from OA by acting on numerous joint tissues, as conditioned medium from stimulated MSCs reduced the gene expression of inflammatory mediators in both cartilage and synovium explants [31].

Manipulating endogenous stem cells to aid in cartilage repair

An intriguing approach that is gaining traction in the field is to use acellular implants that can manipulate endogenous stem cells to provide regenerative treatments for OA [32, 33]. Building on their previous work showing regeneration of the articular surface by providing a scaffold to guide the homing and differentiation of endogenous stem cells [34], Mendelson et al. performed in vitro work to determine which of the candidate stem cell types are most chemotactic, and whether incorporating additional chemotactic factors would enhance cell infiltration into the scaffold [35]. Studies on a cartilage defect model showed that a bilayered instructive scaffold incorporating TGF-β1 in the top layer and BMP-4 in the bottom layer induced appropriate chondrogenic and osteogenic differentiation of endogenous stem cells in a spatially controlled manner [36].

In an alternative approach to enhance the regenerative environment in an osteochondral defect, modified hydrogels that bind hyaluronic acid were delivered to the site of injury. These hydrogels were able to retain newly synthesized matrix as well as guide the differentiation of stem cells from blood or marrow present in the defect site [37]. The same group also showed that nanofiber scaffolds modified to present chondroitin sulfate preferentially encouraged the synthesis of type II collagen by native cells that infiltrate the scaffold during defect repair [38]. As these approaches are further developed, it will be essential to develop a better understanding of the how the properties of endogenous stem cells are altered in response to different manifestations of OA. For example, OA may allow stem cells from the bone marrow to migrate into cartilage due to a compromised tidemark [39] and the overall number and proportion of MSCs in the joint space may be affected by joint injury and OA progression [40, 41].

Stem cells for the development of in vitro models for OA drug discovery

The recognition that stem cells offer a valuable resource for establishing in vitro models has motivated the use of stem cells to aid in the discovery of disease modifying osteoarthritis drugs (DMOADs). With the hypothesis that regulators of chondrogenesis in stem cells might also enhance native cartilage regeneration, Johnson et al. successfully discovered a novel candidate drug by performing a screen for small molecules that induced the chondrogenic differentiation of MSCs [42]. The group then went on to show that this molecule was effective in several animal models of OA. MSCs have also be used to study features of cartilage development, such as the effects of cartilage oligomeric matrix protein on cartilage morphogenesis [43], which may be important for harnessing the developmental programs that can recur during early OA.

The ability to derive induced pluripotent stem cells (iPSCs) from adult somatic cells [44, 45] has provided a new opportunity to create virtually unlimited numbers of patient-specific stem cells for drug discovery. Chondrogenic differentiation of iPSCs from patients with specific risk factors or manifestations of OA may therefore be useful for guiding high throughput studies on cartilage tissue for DMOAD discovery. Importantly, two recent studies demonstrated that joint-derived cells from OA patients can be reprogrammed to

iPSCs and subsequently differentiated to cells that synthesize cartilaginous matrix [46, 47]. Our lab sought to advance cartilage tissue engineering with iPSCs by developing a system for purification of differentiated chondrocyte-like cells from murine iPSCs to engineer scaffold-free tissues with robust GAG and type II collagen content [48]. The use of murine iPSCs takes advantage of the extensive knowledge of mouse genetics and OA for drug discovery by generating cartilage tissue matched to mouse strains with unique phenotypes, but clearly this cell selection strategy could be used with human iPSCs for patient-specific tissue models as well. Interestingly, a recent study has shown that the use of a subset of the iPSC reprogramming factors can be used to induce chondrogenesis of dermal fibroblasts in the absence of a pluripotent state [49, 50]. This approach may provide cells that can not only be used as drug screening tools, but may also have the potential for in vivo implantation for OA therapies due to a reduced risk of teratoma formation.

Conclusions

The development of stem cell-based therapies for OA is at a critical juncture. The extensive literature on stem cell isolation, chondrogenic differentiation, and scaffold design has empowered researchers and clinicians to consider the possibility of using stem cells to modify the progression of OA and use tissue engineering to resurface an entire osteoarthritic joint surface and prevent or delay the need for a total joint replacement (Figure 2). However, critical challenges specific to OA threaten to prevent successful translation of stem cell therapies to the clinic. Recent work has greatly enhanced understanding of the key issues and has made significant progress in improving the mechanical properties and integrative potential of newly formed cartilage. Studies have sought to harness endogenous stem cells for regeneration and have also utilized intra-articular injection of stem cells to delay OA progression. A novel approach using stem cells to guide drug development led to a candidate OA therapeutic, and the use of iPSCs will likely further capitalize on this strategy. Future work should continue to consider the OA context in order to maximize the likelihood that stem cells will provide much needed alternative treatment options for OA patients.

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Key points

- The primary cartilage disorder affecting patients is osteoarthritis (OA), and stem cell-based strategies appropriate for small cartilage defects in otherwise healthy joints may not sufficiently address the specific challenges of the osteoarthritic joint.
- Efficacy of stem cell therapies may necessitate screening patients for stem cell quality, addressing altered stem cell function due to age or an inflammatory joint environment, and utilizing environmental cues to maintain phenotypic stability in vivo.
- Composite scaffolds designed to provide initial mechanical function and supply instructive cues may help promote regeneration from endogenous stem cells and produce osteochondral tissues that facilitate integration with the joint surface.
- In addition to cartilage tissue engineering approaches, stem cells directly injected into the joint space appear to have an anti-inflammatory effect that inhibits OA.
- Stem cells can guide drug discovery by providing opportunities for high throughput screening and cartilage tissue engineering with iPSCs will allow for further progress by incorporating genetically matched tissues into this approach.

The challenges and opportunities with stem cell-based therapies for osteoarthritis

Challenge	Opportunity
OA is not a focal defect	Resurface entire joint surface
Aged or diseased patients may have compromised stem cells	Selection based on patient characteristics or stem cell function
Inflammatory environment in OA joints	Utilize native or engineered anti-inflammatory properties of stem cells
Maintaining chondrocyte-like phenotype of differentiated stem cells	Biomimetic environmental conditions to control phenotype
Inadequate mechanical properties of tissue-engineered constructs	Advanced scaffolds with biomimetic function; bioreactors to enhance matrix synthesis
Lack of integration between new tissue and native cartilage	Multi-layered tissue-engineered constructs to enhance osteochondral integration
Preventing disease progression before extensive cartilage loss	Intra-articular stem cell injection to alter balance of regeneration and degeneration
Complexity of stem cell isolation, in vitro culture, and transplantation	Manipulating endogenous stem cells to enhance regeneration
Developing novel disease-modifying OA drugs	High throughput drug screens; patient-matched induced pluripotent stem cells

Figure 1. The challenges and opportunities with stem cell-based therapies for osteoarthritis

The specific context of the osteoarthritic joint presents numerous challenges for stem cell-based therapies. Addressing these challenges provides opportunities for stem cells to aid in the treatment of osteoarthritis.

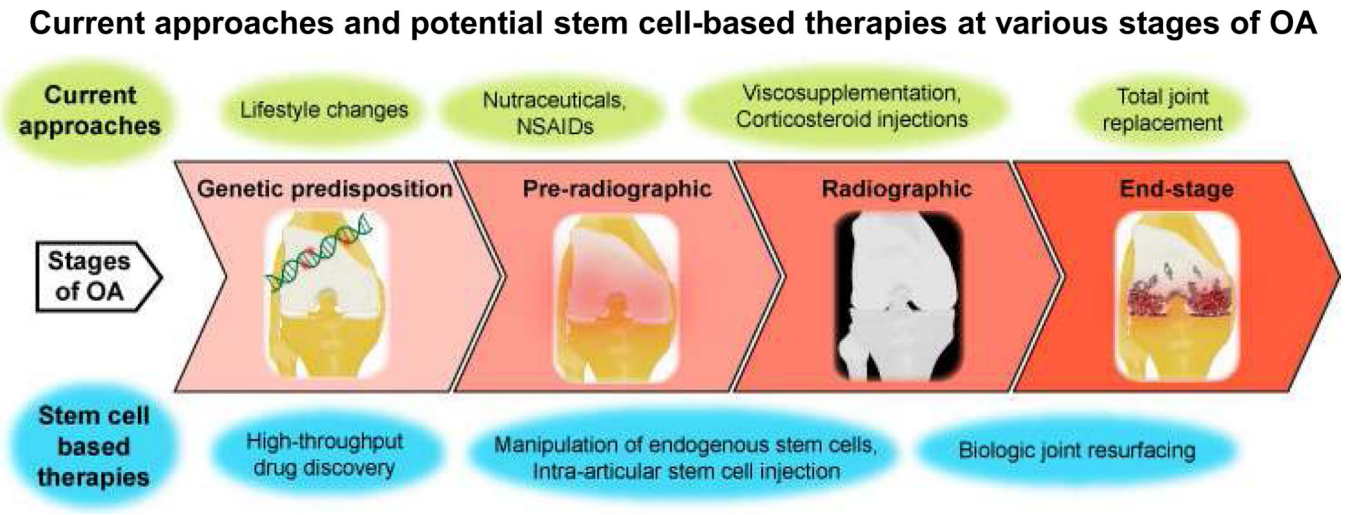

Figure 2. Current approaches and potential stem cell-based therapies at various stages of OA

Treatments for OA vary with the stage of the disease. Current therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) or nutraceuticals are unable to alter the course of disease and in many cases a total joint replacement is required. Stem cells may be able to contribute to the discovery of drugs to prevent OA for some patients, delay or prevent OA progression before or after extensive cartilage degradation, and generate cartilage tissue for joint resurfacing after complete cartilage loss.