Augmentation of Meniscus Surgery with Cartilage Progenitor Cell Treatment May Stimulate Healing and Improve Repair Efficacy

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ABSTRACT

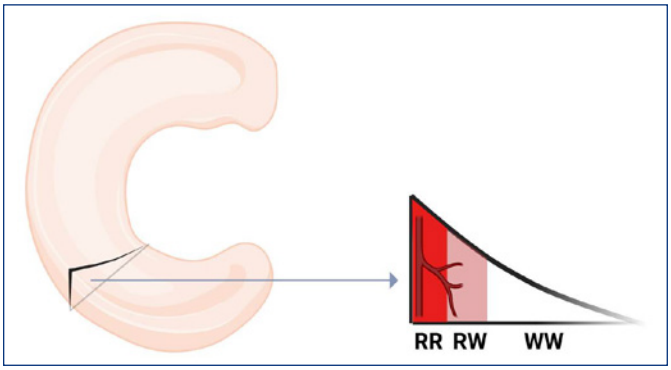
Meniscal tearing is one of the most common knee injuries. Meniscus tears seldom heal, making partial meniscectomy the primary surgical option for patients seeking quick relief. Unfortunately, removal of meniscal tissue impedes loadbearing in the knee, which can lead to accelerated post-traumatic osteoarthritis. It is hypothesized that implementing stem/progenitor cells in the treatment of orthopedic soft-tissue injuries may improve the rate of healing. This article discusses the progress made by our research group in the Department of Orthopedics at Brown University Health, with funding and logistical support from Advance RI-CTR, to develop a novel cell-based strategy for stimulating meniscal fibrocartilage healing. We detail the clinical need that fueled (and continues to fuel) our research efforts, our justification for cell selection, and our published studies that have tested the efficacy of this approach using both *in vitro* and *in vivo* models of meniscal injury.

KEYWORDS: meniscus; cartilage; osteoarthritis; stem cells

BACKGROUND

Tearing of the meniscus is one of the most common knee injuries seen by orthopedic surgeons today. It is also an injury that doesn't have an ideal clinical solution for long-term relief. The lateral and medial menisci are crescent-shaped fibrocartilage soft tissues that sit inside the knee joint, with the primary function being load absorption and displacement, which fundamentally protects the more rigid articular cartilage from being damaged during physical activity.[1,2] Meniscal tearing leads to about one million surgeries annually in the U.S. alone.[3] A 2025 study by Bergstein et al found that 94% of 2,053,884 million meniscus surgeries were meniscectomies—a procedure where entire portions of the torn meniscus is excised and removed to resolve chronic inflammation in an effort to stop further damage to the joint.[4] Unfortunately, even partial removal of meniscal tissue results in increased load placement on articular cartilage, thereby making it more vulnerable to injury and increasing the risk of post-traumatic osteoarthritis (PTOA).[5,6]

Figure 1. Illustrated diagram of the different zones of the knee meniscus. The cross-sectional diagram shows three different regions that constitute the meniscus, from left to right. The red-red (RR) zone is the thickest and most vascular region. The red-white (RW) zone has limited vascularity. The thinnest and most avascular region is the white-white (WW) zone, which does not heal on its own.



The loadbearing inner two-thirds of the meniscus consist of fibrochondrocytes that are well-dispersed and entrenched within a dense, collagen-rich extracellular matrix with little to no vasculature [**Figure 1**].[7] Meniscal tears in this region seldom heal, helping to explain why meniscectomy is the predominant intervention today. Finding ways to support meniscus healing stands to revolutionize the clinical landscape with respect to how meniscal tears are treated. For the past eight years, our group has been developing and optimizing a cell-based intervention to help stimulate meniscus healing following arthroscopic meniscal repair. Our central strategy is to repurpose mesenchymal progenitor cells originating from articular cartilage, which have a natural propensity for producing proteoglycans and type 2 collagen, to support matrix anabolism and reintegrative healing of the tear channel.

In 2017, we received pilot research support from the (then) newly formed and National Institutes of Health (NIH)-funded program, Rhode Island Clinical and Translational Research (Advance RI-CTR), to investigate whether (and how) cartilage progenitor cells (CPCs) can be used to stimulate meniscal healing. This article will detail the findings of the initial project and summarize the overall progress that our group at Brown University Health has made in translational, cell-based tissue engineering since its completion.

METHODS

CPC isolation and stabilization

Human CPC isolation and culture experiments are described in our original publications.[8,9] Briefly, human cartilage tissue was obtained with approval from the Rhode Island Hospital Institutional Review Board (IRB). Cells were separated from chondrocytes using differential adhesion to fibronectin. Cell lines were generated by introducing Large T-Antigen using pRetro-E2 SV40 infection.[8]

Explant culture meniscal injury model

Explant culture experiments are described in the original publication.[8] Briefly, menisci were collected from three-month-old Lewis rats, with approval from the Rhode Island Hospital Institutional Animal Care and Use Committee (IACUC). A radial tear was created in the anterior horn and treated with CPCs, bone marrow-derived stromal cells (BM-MSCs), or left untreated as a negative control. The menisci were cultured for four weeks. Menisci were imaged at different time points. Menisci were sectioned and stained with trichrome at the four-week mark.

In Vivo meniscal injury model

Studies in live rats are fully detailed in the original work.[9] Briefly, skeletally mature RNU athymic male rats were used in the study, with approval from the Rhode Island Hospital IRB. A 1.0 mm meniscal tear was surgically created using micro scissors, ensuring that the meniscus did not detach into two separate pieces. Cells were administered by intraarticular injection through the patellar tendon at Weeks 1 and 4, post-surgery. Repair efficacy was evaluated by sectioning the menisci, staining with Saf O/Fast green, and measuring the mean area of the open tear channels in each experimental group, seven weeks following treatment. Articular cartilage was also stained with Saf O/Fast green and Modified Mankin scoring was used to evaluate cartilage quality.

Statistical Analysis

Statistical analyses are detailed in our original publications.[8,9] To summarize, analysis was performed using a student's t-test, when comparing only two groups. When comparing more than two groups, a one-way analysis of variance (ANOVA) was used, followed by post-hoc analysis. For live rodent experiments, when examining the effects of the treatments on meniscus defects and Mankin scores, generalized linear models were used, as detailed in the original published work. P-values smaller or equal to 0.05 were considered statistically significant. Sample sizes were always greater than or equal to 3 and error bars represent ±1 standard deviation of the mean.

RESULTS

Progenitor cells native to articular cartilage exhibit phenotypic specificity for rebuilding inner meniscus tissue.

The tissue microenvironment of the inner meniscus is remarkably similar to that of articular cartilage. Much like the inner meniscus, articular cartilage has a dense tissue matrix that is rich in type II collagen and proteoglycans. These proteins form networks that contribute to the resilient mechanical properties of both tissues. Specifically, aggrecan is a proteoglycan that is abundant in both tissues and functionally important because it is negatively charged and attracts water molecules. Hyaluronic acid (HA) is another proteoglycan that aids in holding the Aggrecan core proteins together, while the type II collagen network prevents excessive expansion that comes with water retention, which helps to build the compressive tension within the extracellular matrix (ECM) that is the essential functional feature of these loadbearing tissues.

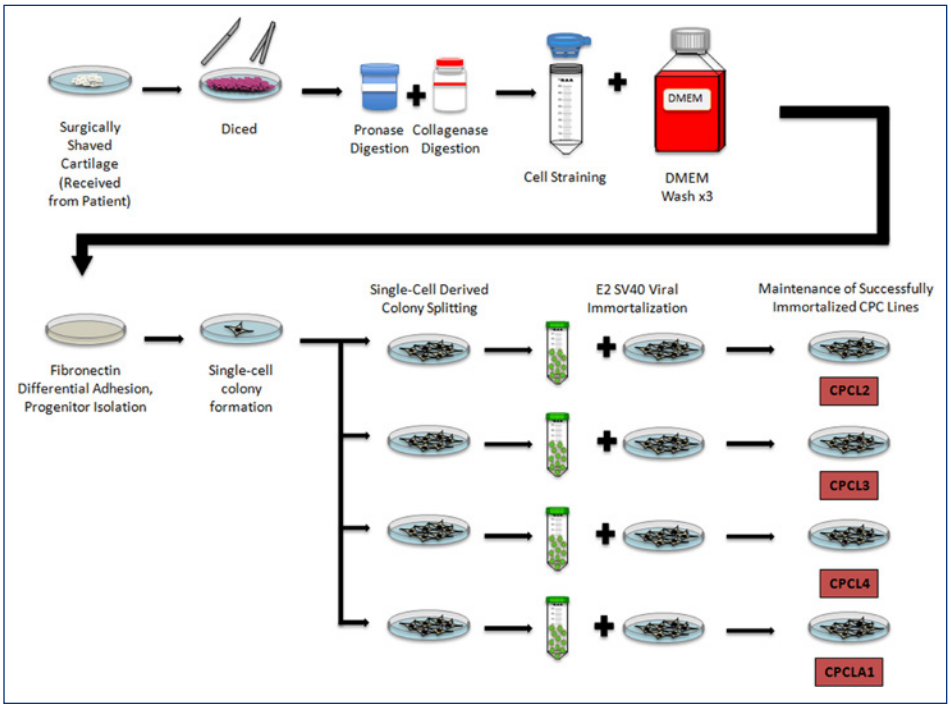
Another similarity is that unlike the elongated spindle-like fibrochondrocytes that are native to the outer third of the meniscus, cells in the inner meniscus are round and resemble chondrocytes—the resident adult cell population in articular cartilage. Hence, in our pursuit to identify a source of cells that are well-suited to help rebuild damaged inner meniscal tissue, we first considered utilizing chondrocytes. However, despite their well-reported capacity for producing an ideal ECM, rich in type II collagen and aggrecan, chondrocytes have several features that make them unideal for our needs. Chondrocytes are fully differentiated adult cells that, while immune-privileged compared to other mature cell populations,[10,11] no longer exhibit the extensive immunosuppressive capabilities characteristic of less committed cells like mesenchymal progenitor/stem cells.[12,13] This feature helps cells to evade a host recipient's immune system so that they can function properly while minimizing the chance of rejection and/or immune reaction. Fortunately, there is a satellite cell population within cartilage that fits this description. Cartilage-derived progenitor cells are a sparce population of mesenchymal progenitors that are native to articular cartilage.[14] They exhibit all the important key features we were looking for, including a high chondrogenic capacity for essential ECM protein synthesis, immunosuppressive capabilities, and high proliferative capacity (for *in vitro* expansion).[15,16]

Human cartilage progenitor cells stimulate mending of meniscal tears in *ex vivo* culture.

In our 2017 pilot study funded by Advance RI-CTR, the primary goal was to find a bioavailable source of CPCs and test their efficacy for stimulating meniscal healing, *ex vivo* and *in vivo*. We isolated these cells from cartilage using fibronectin adhesion. Compared to chondrocytes, CPCs exhibit high expression of CD49e (receptor for fibronectin), which makes enriching these cells relatively easy and cost effective, by

Figure 2. Illustrated diagram of procedure used to establish human cartilage progenitor cell lines. Healthy human cartilage was diced into small pieces and digested using pronase and collagenase. Released cells were washed and strained to remove clumps. Cells were seeded at low density and individual single-cell derived colonies were separated and stabilized using SV-40 mediated delivery of Large-T antigen.

[Figure 2 panels and legend are reprinted from *Jayasuriya et al. 2019. Human Cartilage-Derived Progenitors Resist Terminal Differentiation and Require CXCR4 Activation to Successfully Bridge Meniscus Tissue Tears. Stem Cells 37:102-114.* with permission from publisher.]



taking advantage of their high propensity for binding to fibronectin. Since CPCs are a rare, satellite cell population that make up less than 1% of cells within cartilage, we engineered stable CPC cell lines by introducing Large T Antigen [**Figure 2**].[8] We selected two of these engineered cell lines to validate that their differentiation potential, most importantly their chondrogenicity, was not impeded as a result of immortalization.[8]

Using an *ex vivo* meniscal injury model, we tested our hypothesis that CPC treatment can stimulate meniscal healing.[8] A radial tear was created in the white-white zone of rat menisci and treated with a fluorescently labeled CPC line in explant culture [**Supp. Figure 1**]. The control groups consisted of tears that were either left untreated or treated with fluorescently labeled bone marrow-derived stromal cells (BM-MSCs). Veritably, CPC treated meniscal tear channels exhibited complete filling by 20 days post treatment, whereas BM-MSC-treated menisci did not achieve this end. Histology analysis performed four weeks following CPC treatment demonstrated bridging at the tear channel [**Supp. Figure 2**]. [*Editor's note: Email author for supplementary figures 1,2*].

Human cartilage progenitor cells stimulate meniscal healing and delay onset of post-traumatic osteoarthritis in athymic rats.

Encouraged by these findings, we next tested whether CPC treatment could have the same effect in a live animal model of meniscus repair. We worked closely with Janine Molino, PhD, MS, of the Advance RI-CTR Biostatistics, Epidemiology, and Research Design (BERD) Core to design this study. We used a rat medial meniscus tear model to evaluate CPC-stimulated meniscus healing [**Figure 3**] in comparison to treatment with BM-MSCs [**Figure 4**] or treatment with saline/vehicle as a negative control [**Figure 5**]. A 1.5 mm longitudinal tear spanning the full thickness of the meniscus was created on the medial meniscus of 15-week-old skeletally mature rats. Fluorescently labeled human CPCs (1.6 million cells) were administered via intra-articular injection twice (at day 7 and at day 28 post-meniscal injury). There were two control groups: BM-MSC injected animals and vehicle (PBS) only injected animals. Rats were sacrificed and their medial menisci were evaluated using fluorescence imaging of the tear site seven weeks post-surgery. Localization and engraftment of injected cells (labeled fluorescent red) to the tear site was confirmed on tissue sections. Analyses showed that CPC-treated animals exhibited increased tear filling compared to the group treated with BM-MSCs [**Figure 6**].[9] These experiments suggested that CPC-treatment stimulates fibrocartilage healing in an animal model.

We also analyzed the articular surface of the medial knee compartment as a secondary outcome measure of success.[9] Animals treated with CPCs exhibited less cartilage damage in the medial compartment of the tibial plateau, which sits directly below the injured medial meniscus. The medial femoral condyles and medial tibial plateaus were sectioned and stained with Safranin-O/fast green. Mankin histopathology scores demonstrated that the CPC-treated group exhibited a significant improvement over the vehicle only treated saline control group, whereas the BM-MSC-treated group did not.

Figure 3. CPC-mediated healing of isolated medial meniscus tears in rats 46 days following treatment with CPCs. 3.2 million fluorescently labeled CPCs were injected into the joint capsule following meniscus injury. CPCs from the treatment are fluorescently labeled (red). Nuclei of all cells (both native meniscus cells and injected cells) are labeled with Dapi (blue). Yellow lines and arrows signify areas that remain open without healing, with yellow dotted lines inscribing the unfilled areas. Scale bar = 100μm

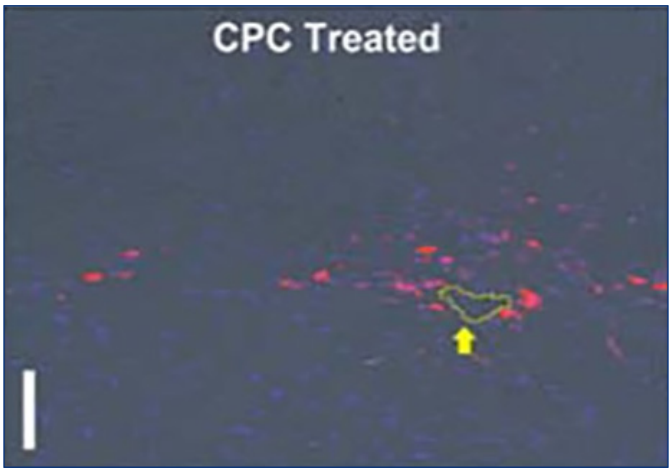


Figure 4. BM-MSC-mediated healing of isolated medial meniscus tears in rats 46 days following treatment with BM-MSCs. 3.2 million fluorescently labeled BM-MSCs were injected into the joint capsule following meniscus injury. This was used as a control group to compare against the CPC-treated group. BM-MSCs from the treatment are fluorescently labeled (red). Nuclei of all cells (both native meniscus cells and injected cells) are labeled with Dapi (blue). Yellow lines and arrows signify areas that remain open without healing, with yellow dotted lines inscribing the unfilled areas.

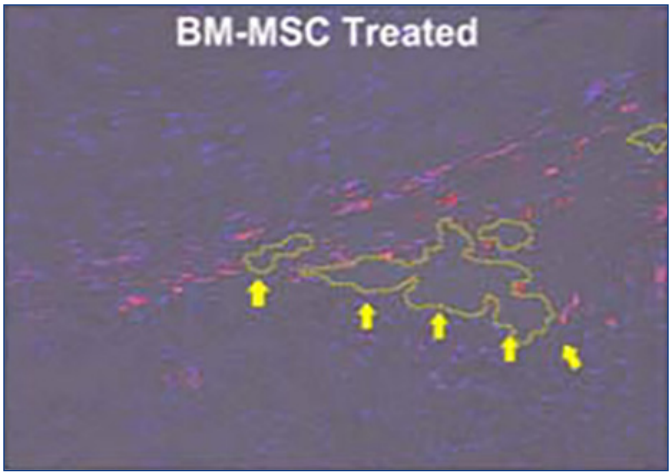


Figure 5. A medial meniscus tear in rats 46 days following treatment with no cells. This group was the negative control group. Nuclei of all native cells meniscus cells are labeled with Dapi (blue). Yellow lines and arrows signify areas that remain open without healing, with yellow dotted lines inscribing the unfilled areas.

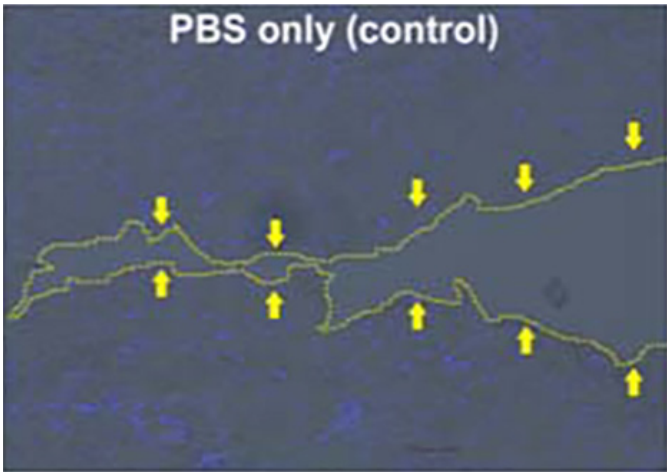
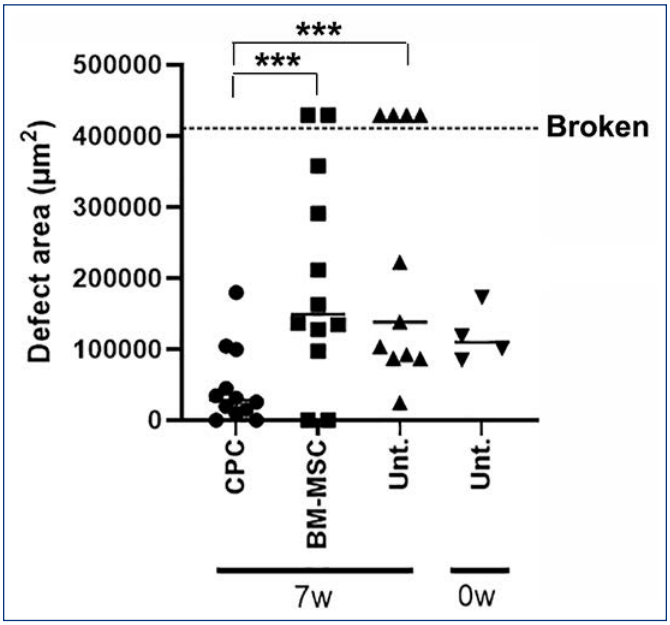


Figure 6. Open areas remaining within the meniscal tear channel was quantified by image analysis and compared across experimental groups. A 0-week control group was used to determine the open area of the meniscal tear before healing, or further tearing due to the *in vivo* environment, can take place. Data points above the dotted line indicates menisci that were broken in two at the time of harvest. N≥8 per group. ***, P≤0.005.

[Figure 5B and corresponding part of the legend are reprinted from *Desai et al. 2022. Stable human cartilage progenitor cell line stimulates healing of meniscal tears and attenuates post-traumatic osteoarthritis. Front Bioeng Biotechnol 10:970235.* with permission from publisher.]



DISCUSSION

Our goal is to develop a novel cell-based treatment to stimulate healing in the meniscus. The studies detailed in this article are the first to demonstrate the efficacy of administering CPCs as a means of accelerating meniscal healing. We have shown that CPCs can maintain a highly chondrogenic phenotype without the need for exogenous growth factors. We have shown that these cells can migrate to areas of fibrocartilage injury and accelerate the integration of tears, both in *ex vivo* culture and in live animals that have compromised immunity.

Since completing these studies, we have explored ways that CPC might be implemented to treat tears in fully immunocompetent live animals,[17] and to treat human meniscus tissue using an explant injury model.[18] We have also investigated the molecular mechanism(s) that constitute the anabolic and anti-catabolic effects of CPCs that may contribute to their propensity for musculoskeletal tissue repair,[19,20] as well as their potential to be further primed for chondrogenesis using commercially available small molecules.[21] Based on our findings, we expect that augmenting the standard clinical procedure of meniscus suture repair with adjuvant CPC therapy has practical potential for significantly improving repair efficacy in the near future.

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Disclosures

Dr. Jayasuriya is a co-founder of EnkaBio Inc. and holds equity in the company.

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