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STEM CELLS IN ORTHOPAEDIC SURGERY (J DRAGOO AND K JONES, SECTION EDITORS)

Stem Cell Treatment for Ligament Repair and Reconstruction

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Abstract

Purpose of Review With the rapid and ongoing evolution of regenerative and sports medicine, the use of stem/stromal cells in ligament repair and reconstruction continues to be investigated and grow. The purpose of this review was to assess available methods and formulations for stem/stromal cell augmentation as well as review early pre-clinical and clinical outcomes for these recently emerging techniques.

Recent Findings Recent literature demonstrates promising outcomes of stem/stromal cell augmentation for ligament repair and reconstruction. Multiple groups have published animal models suggesting improved healing for partially transected ligaments as well as histologic re-approximation of native bone-tendon interfaces with the use of mesenchymal stem/stromal cells in reconstructive models. Human studies also suggest improved outcomes spanning from higher patient-reported outcome scores to magnetic resonance imaging evidence of ligament healing in the setting of anterior cruciate ligament tears. However, clinical studies are only recently available, relatively few in number, and not necessarily accompanied by standard-of-care controls.

Summary There is increasing availability and growing animal and clinical evidence demonstrating potential benefit of stem/stromal cell augmentation for tendon healing. However, to date, there is a relative paucity of high-level human evidence for the routine use of stem/stromal cells for ligament repair and reconstruction in the clinical practice. This field contains substantial promise and merits further, ongoing investigation.

Keywords Stem cells · Stromal cells · Ligament repair · Ligament reconstruction · Biologics · Orthopedics

Introduction

Ligament injury and subsequent repair and reconstruction efforts remain central themes in orthopedics, with substantial patient volumes and ongoing research for improved healing and joint mechanics restoration. An ongoing challenge in ligament surgery is the relatively avascular nature of the tissue being manipulated, with little innate ability for healing [1]. A prime example of this are initial efforts at anterior cruciate ligament (ACL) repair, which were described as early as 1895 and subsequently largely abandoned given a clinical failure rate of up to two-thirds of patients [2, 3]. More recently, primary ACL repair has generated renewed interest, especially in the setting of proximal tears. Previously overshadowed by the evolution of arthroscopic ACL reconstruction, the favorable outcomes of multiple groups in the late 1980s and early 1990s are now being revisited and made increasingly popular with modern techniques [4–7]. This represents a desirable return to ligament healing and restoration given that repair can assist with maintaining proprioception while preventing the comorbidities of graft harvest, tunnel preparation, and fixation [6]. With the rapid emergence and evolution of regenerative medicine and associated biologic therapeutics, stem (stromal) cells have created concurrent renewed and ongoing interest in cellular augmentation of ligament repair and reconstruction in hopes of achieving true ligament healing.

Stem/stromal cells represent a population of cells that demonstrate the ability for self-renewal, long-term viability, and

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multilinear culture [8•]. While embryonic stem cells have been under prolonged ethical discussion and consideration, adult stem cells from peripheral tissues such as bone marrow and fat (i.e., mesenchymal stem cells; MSCs) represent a clinically available source for biologic augmentation and implementation [9]. MSCs are derived embryonically from the mesoderm and have the capacity to divide into connective tissues including ligament, tendon, bone, muscles, and cartilage leading to ongoing and renewed interest in stem/stromal cell therapy for orthopedic care [8•, 10]. When evaluating therapeutics such as MSCs, our approach has focused on ensuring that the risks and benefits provided can be justified for both route of administration and material to be administered and subsequently reviewing available pre-clinical and clinical research.

Route of Administration

Augmentation of ligament repair and reconstruction is readily performable in terms of administration, given that stem cell application generally occurs at the time of pre-existing access from ongoing arthroscopic or open surgery. Furthermore, for those patients undergoing augmentation of otherwise natural healing processes through the injection of stem cells, injections into multiple intra- and peri-articular structures have long-standing clinical implementation and safety at the bedside [11–13]. It is noteworthy that 2.4–12% of patients may experience injection-related adverse events, most of which are mild and self-limiting and treated with observation and supportive measures such as ice and acetaminophen or ibuprofen [14].

Other delivery methods and vehicles for ligament healing augmentation are also worth discussing. Especially noteworthy is the ongoing Bridge-Enhanced Anterior Cruciate Ligament Repair (BEAR) trial which employs a bovine-derived extracellular matrix scaffold to augment primary ACL repair [15]. In the trial, the scaffold is seeded with autologous blood for growth factor delivery in the area of the repair and has demonstrated overall promising results, with 2-year outcomes now becoming available in the published literature. Of the 10 patients undergoing BEAR ACL repair, no failures were noted and the BEAR procedure demonstrated healed ligament morphology more similar to the contralateral intact ACL than patients undergoing ACL reconstruction with hamstring tendon autograft [16, 17]. Other efforts to deliver growth factors to ligament repair and reconstruction have focused on characterizing the transcriptional fingerprint of the involved tissues and subsequently generating functionalized suture constructs which can capture and locally concentrate endogenous growth factors along the span of healing tissues [18–20]. While animal models have demonstrated increased femoral and tibial tunnel bone formation using bone-morphogenic protein-2 (BMP-2) binding peptides, these methods could also be used to sequester stem/stromal and other signaling cells in the otherwise capacious intra-articular environment which averages 6.7 mL in healthy knees [21].

Stem Cell Preparations

Stem cell preparations exist in varying formulations spanning from point-of-care aspirates (i.e., bone marrow), concentrated isolates, and culture-expanded auto- or allogeneic cells (Table 1). Classic investigations into stem cells and their potential role in musculoskeletal repair were centered initially about bone marrow mesenchymal stem/stromal cells (BMSCs) and their role in skeletal repair and hematopoiesis [22]. More recently, the use of BMSCs has expanded into orthopedic applications, and recent investigations have suggested a role for BMSCs in hamstring tenocyte modulation and extracellular matrix remodeling, as notably occurs at the time of ACL reconstruction [23]. While bone marrow is enriched in MSCs as compared with other adult tissues, we caution efforts to employ bone marrow aspirate as a robust, functional source of stem cell augmentation given that stem cells comprise only 0.01–0.001% of the harvested cells [10, 24]. By contrast, the stromal vascular fraction (SVT) of adipose tissue contains approximately 500-fold the stem/stromal cell concentration of bone marrow given that approximately 1% of adipose cells are MSCs [25, 26].

Much like the MSCs found in bone marrow and its various concentrates, adipose-derived mesenchymal stem/stromal cells (AMSCs) have demonstrated promise in regenerative therapeutics. AMSCs differ from BMSCs in the relative ease of adipose-tissue isolation, both in clinic and in the OR, as well as the quantity of tissue that can be readily harvested in most patients depending on habitus. AMSCs have been demonstrated to differentiate into fibrocytes and tenocytes in addition to adipogenic, myogenic, and chondrogenic tissues and are therefore a natural target for tendon repair/regeneration studies [27, 28]. In a recent RNA sequencing analysis of AMSCs and BMSCs obtained from the same human donors, Zhou et al. found that AMSCs demonstrated lower expression of human leukocyte antigen I (HLA I) as well as higher immunosuppression capacity when compared with the BMSC population [29•]. This is desirable given that limitations in HLA effect can enable allogeneic stem cell application, easing logical preparations, especially as they relate to culture-expanded formulations [30, 31]. Furthermore, the immunomodulatory effect of stem cells may also play a key role in ligament healing given that multiple groups have proposed and reported on the positive histologic effects and recreation of native-like tendon-bone interfaces with immunosuppression and macrophage inhibition [32–34].

Table 1 Available stem cell formulations and associated reported advantages and disadvantages

Formulation	MSC content*	Advantages	Disadvantages
Bone marrow aspirate	0.01–0.001%	Easy to obtain Point-of-care harvest Inexpensive	Low stem cell content Bone progenitors present
Adipose-derived stem cells**	~ 1%	Generally abundant, readily accessible source More homogeneous, less immunogenic than BMSCs	Require enzymatic processing Availability varies by patient habitus
Culture-expanded B/AMSCs	100%	Homogenous Control of desired growth, volumes, and dosing	Expensive Lack of other modulatory cells

*Approximate and preparation dependent

**Enzymatic digestions and non-cultured preparations

Outcomes: from Bench to Bedside

Many efforts examining the effects of MSCs on tendon healing have focused on the anterior cruciate ligament (ACL) given the relatively high prevalence of ACL injury and the profound effects that ACL injury can have on subsequent cartilage and meniscus health, patient function, and well-being [2]. Given these factors, ACL research expenditure is amongst the highest in orthopedics and has been at the forefront in stem cell augmentation during repair and reconstruction [35–37].

Animal models have investigated the effects of MSCs at the time of ACL injury and repair and had generally positive results. Kanaya et al. reported that in the setting of partial ACL transection followed by intra-articular injection of BMSCs, Sprague-Dawley rats demonstrated healing tissues within the surgically created tissue gap and a higher ultimate load to failure at 4 weeks as compared with the contralateral side which underwent partial transection alone [38]. Similar outcomes were reported by Oe et al. who observed significantly improved biomechanics and histology when administering whole bone marrow aspirate or cultured mesenchymal cells in rats with partial ACL transection and comparing them with the saline control [39]. Furthermore, both Ju and Lim et al. have reported that ACL reconstruction in rats and rabbits augmented with synovial or bone marrow–derived MSCs led to the formation of native Sharpey's fiber-like bone-tendon interfaces as compared to usual fibrocartilage scarring [40, 41].

In terms of translational human studies, there is a relative paucity of available literature, with most studies published after 2017, highlighting the ongoing evolution of this field. Perhaps the highest level evidence evaluating the efficacy of ligament reconstruction augmentation with mesenchymal cells is provided by Wang et al. who performed a double-blinded, randomized controlled trial regarding a single intra-articular injection of 75 million allogeneic immature mesenchymal precursor cells (MPCs) in a hyaluronic acid vehicle for patients undergoing ACL reconstruction [42•]. Patients receiving MPCs demonstrated significantly higher improvements in Knee Injury and OA Outcome Score (KOOS) as well as SF-36 pain scores through 24 months of follow-up ($p < 0.05$). Furthermore, the MPC group was noted to have reduced lateral tibiofemoral joint space narrowing at 24 months of follow-up as compared with hyaluronic acid vehicle–only controls ($p < 0.04$). Of note, no cell-related serious adverse effects were observed in this allogeneic study, providing further evidence of the achievable safety of both auto- and allogeneic preparations. However, ACL healing specific measurements such as clinical laxity grading or graft incorporation on MRI were not assessed in this study.

Centeno et al. reported on 29 patients presenting with symptomatic, clinically and MRI-confirmed Grade 1–3 ACL tears with less than 1 cm of retraction [43]. Patients were treated using injected delivery of 2–5 cc of bone marrow concentrate generated from 60 to 120 cc of whole bone marrow aspirate combined with platelet rich plasma (PRP) and platelet lysate (PL) and injected under fluoroscopic guidance into the torn ACL and intra-articular space. At a mean of 8.8 months of follow-up, 77% of patients demonstrated significant improvement in ACL integrity, as measured my T_1 MRI ACL signal intensity ($p < 0.01$), with statistically significantly improved International Knee Documentation Committee (IKDC) and Numeric Pain Score (NPS) scores at 1–24 months post injection. Promising, long-term clinical outcomes were not reported and five patients underwent subsequent ACL reconstruction. The combination material injected raises the question of the relative efficacy and contributions of bone marrow concentrate, PRP, and PL in treatment effect.

For completeness sake, the role of MSCs in tendon healing also merits discussion given that ligament reconstructions often employ tendon auto- and allografts which subsequently undergo healing and ligamentization. Perhaps the most prolific subsection of the tendon-MSC literature exists about the rotator cuff. Overall, few human studies have been completed; however, general outcomes are promising, with one of the earliest reports being published by Hernigou et al., who observed improved healing rates (100% versus 67% at 6 months) and a lower subsequent tear rate (13% versus 22%) in a case-controlled study involving a mean of 51,000 ± 25,000

autogeneic bone marrow–derived MSCs applied at the time of full-thickness supraspinatus repair [44•]. Subsequently, groups including that of Kim et al. have demonstrated similar protective effects of AMSCs at the time of rotator cuff repair, with a 14% retear rate in the AMSC group and 39% retear rate for non-AMSC controls ($p < 0.01$) [45].

Conclusions

As regenerative medicine continues to rapidly evolve, the use of stem cells in ligament repair and reconstruction continues to be investigated and grow. Various stem cell preparations are available in clinical practice and include BMSCs, AMSCs, and culture-expanded allo- and autogeneic formulations. To date, there is a relative paucity of high-level evidence for the use of stem cells in ligament surgery and healing; however, early human and animal results support the reparative and immunomodulatory potential of stem cells as an evolving therapeutic meriting further investigation.

Compliance with Ethical Standards

Conflict of Interest Mario Hevesi, Matthew LaPrade, Daniel B. F. Saris, and Aaron J. Krych declare that they have no relevant conflicts of interest.

Human and Animal Rights and Informed Consent Any articles contained in this article performed by the authors were performed following Institutional Review Board (IRB) and Institutional Animal Care and Use Committee (IACUC) approval, as listed in the respective articles.

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