Biologic Approaches for the Treatment of Partial Tears of the Anterior Cruciate Ligament

A Current Concepts Review

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Background: Anterior cruciate ligament reconstruction (ACLR) has been established as the gold standard for treatment of complete ruptures of the anterior cruciate ligament (ACL) in active, symptomatic individuals. In contrast, treatment of partial tears of the ACL remains controversial. Biologically augmented ACL-repair techniques are expanding in an attempt to regenerate and improve healing and outcomes of both the native ACL and the reconstructed graft tissue.

Purpose: To review the biologic treatment options for partial tears of the ACL.

Study Design: Review.

Methods: A literature review was performed that included searches of PubMed, Medline, and Cochrane databases using the following keywords: partial tear of the ACL, ACL repair, bone marrow concentrate, growth factors/healing enhancement, platelet-rich plasma (PRP), stem cell therapy.

Results: The use of novel biologic ACL repair techniques, including growth factors, PRP, stem cells, and bioscaffolds, have been reported to result in promising preclinical and short-term clinical outcomes.

Conclusion: The potential benefits of these biological augmentation approaches for partial ACL tears are improved healing, better proprioception, and a faster return to sport and activities of daily living when compared with standard reconstruction procedures. However, long-term studies with larger cohorts of patients and with technique validation are necessary to assess the real effect of these approaches.

Keywords: anterior cruciate ligament repair; partial anterior cruciate ligament tear; stem cell therapy; platelet-rich plasma; healing enhancement; bone marrow aspirate concentrate

The anterior cruciate ligament (ACL) is one of the most studied structures of the human musculoskeletal system, being the subject of many anatomic and biomechanical studies. While treatment options for complete ruptures of the ACL are well studied, partial ACL tears remain more nebulous in their postinjury treatment course. Partial ACL tears were first described almost 5 decades ago.[91] However, since the initial description, there remains no consensus on the classification for these injuries, and the optimal treatment continues to be a subject of considerable debate.[71] Complete tears of the ACL can result in immediate anteroposterior and rotational knee instability. Anterior cruciate ligament reconstruction (ACLR) has been reported to achieve a near-native biomechanical function in symptomatic patients.[34] However, when the ACL is partially torn, the natural evolution of these lesions is poorly understood and thus, the evidence regarding treatment options is limited.[69]

Unlike other ligaments of the knee, such as the posterior cruciate ligament (PCL) and medial collateral ligament

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(MCL), the ACL possesses limited intrinsic capacity for spontaneous healing after an injury.[83-89] Early reports of direct suture repair of the ACL culminated in failure in 40% to 100% of cases.[47] In part, the poor healing capacity of the ACL has been speculated to be a consequence of its intra-articular location and a thin synovial membrane. Generally, ligamentous injuries trigger the release of proinflammatory cytokines that initiate formation of a fibrin-platelet clot scaffold that is rapidly replaced by granulation tissue, and weeks later by immature, parallel collagen fibers.[83] However, several studies have demonstrated the inhibitory properties of the intra-articular synovial fluid of the knee on fibrin-platelet clot formation and ACL fibroblast migration in patients suffering ACL injury.[47,68,83] Thus, the capacity for spontaneous repair and remodeling after ACL injury is relatively poor, thereby requiring surgical reconstruction or augmentation to recover stability in many cases.[89]

This clearly induces a dilemma in the treatment of partial ACL injuries. Despite being the historical standard of care for complete ACL disruptions, ACLR procedures have been reported to potentially result in diminished proprioception, postoperative muscular weakness, inability to fully restore normal kinematics, donor site morbidity, and possible premature osteoarthritis (OA).[8,30,37,44] Biau et al[10] reported in a meta-analysis that only 40% of patients who had an ACLR achieved full recovery independent of the surgical technique, and Kartus et al[37] reported that 65% of patients had anterior knee pain and disturbance of anterior sensitivity caused by intraoperative injury to the infrapatellar nerve(s) after ACLR with patellar tendon autograft. These findings are of particular concern in combination with the findings of Barenius et al,[8] which showed that 57% and 18% of patients will develop osteoarthritis at 14-year follow-up in the ACL reconstructed knee and in the contralateral knee, respectively. Zhou et al[93] evaluated knee proprioception with a passive reproduction test and isokinetic strength in 36 patients who had their ACL reconstructed with semitendinosus/gracilis grafts (reconstructed group: 6 months after surgery) and 13 healthy adults without any knee injury. They reported a significant difference in proprioception between the reconstructed and control groups and concluded that impaired knee proprioception is observed 6 months after ACLR.

Many studies have shown significantly greater translational and rotational laxity of the reconstructed knees relative to the contralateral uninjured sides, regardless of the graft type.[9,78] Additionally, high-demand activities among patients with ACLR reportedly lead to increased tibial rotation and impaired neuromuscular control that potentially results in an increase of cartilage load and thus higher risk of reinjury.[27] Shah et al,[70] in a case series of 49 National Football League (NFL) athletes who had undergone primary ACLR, concluded that the return to play after ACLR in NFL football players was lower than previously perceived; only 63% of NFL athletes returned to NFL game play at an average of 10.8 months after surgery. In contrast, a higher rate of return to play was found in recreational athletes; Ardern et al[6] in a systematic review found that an average of 82% of athletes returned to sports in this group.

Thus, due to the evolving understanding of tissue engineering and regenerative medicine, there has been a recent interest in the development of new biological treatment techniques to address partial injuries of intra-articular structures, such as the ACL. The use of biologic approaches, including different growth factors, platelet-rich plasma (PRP), stem cells, biological scaffolds, and augmented ACL primary repair, has been the focus of current research in ACL accelerated repair and healing. These alternatives to the current surgical reconstruction techniques have the potential to preserve the native insertion site of the remaining fibers and therefore its proprioceptive function, which may in turn lead to biomechanics that are more natural.[42,53] As biologic approaches appear to be one possible future treatment for a subset of orthopaedic injuries, the purpose of this article was to review the current biologic treatments of partial tears of the ACL.

HISTORICAL OUTCOMES OF ACL REPAIR

The first ACL repair was reported in 1895.[67] In Europe, in 1927, Wittek[86] described and illustrated the different types of tears of the ACL. Later, in 1935, Wittek[87] published a technique to surgically treat ACL tears using a distally based strip of extensor retinaculum and the medial border of the patellar tendon, brought into the joint through a tibial tunnel and secured against the anterior-superior aspect of the PCL with sutures. In the 1970s, Feagin and Curl[24] began to further evaluate the possibility of ACL repair in isolated and acute tears utilizing a polyglycolic acid suture woven through the tibial stump and passed up through bone tunnels in the femur. Postoperatively, patients were immobilized for 6 weeks at 30° of flexion, and then allowed to begin a motion program with progressive return to activity. The authors reported that 25 of these 30 active patients had good results at a minimum of 2 years' follow-up. However, at 5 years' follow-up the results showed that 71% of patients had pain and 94% had knee instability.[23] These findings led to the conclusion that primary ACL repair had good outcomes in only one-third of patients treated in this cohort. However, the patients who initially had good outcomes at 5 years (one third) preserved the good outcomes at 30 years postoperatively.[79]

This seemed to suggest that there was a small subset of patients that could progress well after ACL repair if indicated appropriately. It should be noted that long-term clinical studies that reported ACL repair as ineffective were based on these original "failed" cohorts from the 1970s and 1980s and thus may not accurately reflect modern surgical acumen.[80] ACL repair has been abandoned in favor of ACLR largely because of the unpredictable results of the procedure. Historically, it was suggested that suture techniques alone may be useful for ACL injuries in which the ends of the torn tissue can be reapproximated under compression. Not surprisingly, a lower-demand subset of patients experienced better results than high-demand patients when this technique was utilized.[65] Long-term follow-up studies of primary repair reported poor results in nearly 30% of the patients,[76] high rates of additional

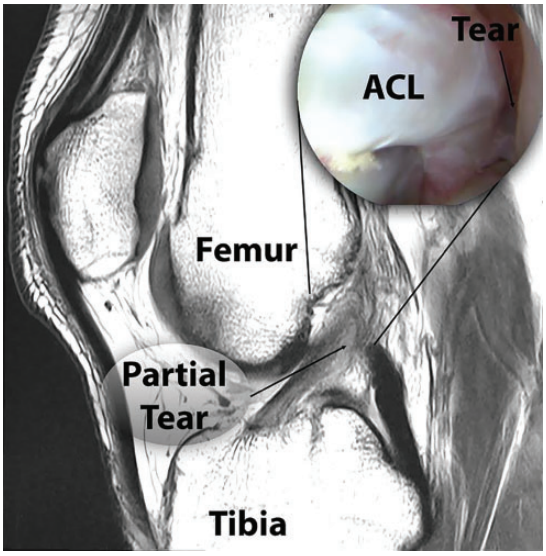

Figure 1. Magnetic resonance imaging (sagittal view) demonstrating a partial anterior cruciate ligament (ACL) tear. On the upper-right corner, the corresponding arthroscopic view (through the anterolateral portal) shows the posterolateral bundle tear of the ACL in a left knee.

surgery needed (64%),[79] and revision to ACLR for instability (13%-24%). In addition, objective laxity >5 mm by KT-1000 assessment was reported in 21% of these patients.[76] Modern surgical options and advancements in biological understanding have led researchers to reconsider the repair of ACL ruptures. However, longer follow-up with larger cohorts are needed to assess the real efficacy of this approach.

Partial ACL tears (Figure 1) must be treated early enough to prevent a large number of secondary instability-derived events, particularly meniscal damage, accelerated cartilage degenerative changes and functional disability.[71] Preserving native ACL remnant fibers, when partially torn, may provide several theoretical advantages over reconstruction, including preservation of the natural anatomy, physiology, proprioception, and intrinsic cell populations, as well as some of the complex biomechanical properties of the knee.[65] There are several basic research studies and surgical techniques published on preservation of the nondamaged fibers in cases of partial ACL tears. However, there are few published studies on the short- and medium-term clinical outcomes.[71]

BASIC SCIENCE AND ANATOMY

When considering partial tears of the ACL, understanding the anatomy and properties of this ligament is vital. The ACL is an intra-articular and extrasynovial ligament with a multifilament structure consisting of 2 separate bundles that maintain different tensions according to the degree of flexion of the knee joint.[2,38] These distinct anteromedial (AM) and posterolateral (PL) bundles act in concert during both flexion and extension moments of the knee with the

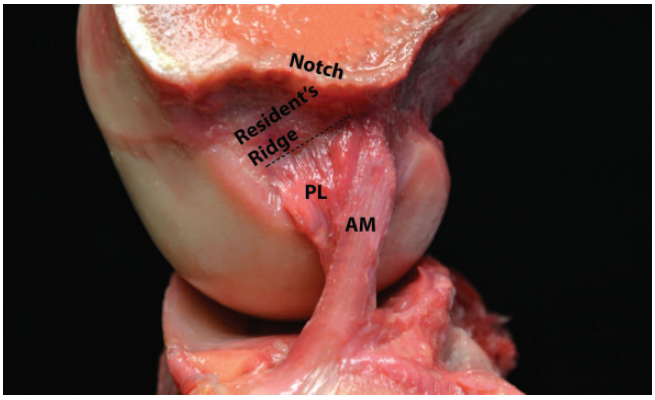

Figure 2. Lateral view of a right knee with the medial femoral condyle removed to reveal the insertion of the anterior cruciate ligament (ACL) on the medial wall of the lateral femoral condyle. This image demonstrates the insertion of the ACL posterior to the lateral intercondylar ridge (resident's ridge), and the positions of the posterolateral (PL) and anteromedial (AM) ACL bundles.

AM bundle tight in flexion and the PL bundle tight in extension.[3,4,81,92] These bundles attach proximally at the posterior aspect of the medial wall of the lateral femoral condyle posterior to the lateral intercondylar ridge, and are similar in size at the femoral insertion[94] (Figure 2). The length of the ACL has been reported to be between 22 and 41 mm, and the midbody width has been shown to be 7 to 12 mm.[29,58]

The ACL is a collagen composite structure, mostly composed of type I collagen, and presents an elastic behavior that reveals the ability of the ligament to alleviate sudden deformations and characteristic relaxation of tension to reduce the risk of injury in the event of a prolonged deformation.[41] The stress-strain behaviors of the ACL are nonlinear.[33] Woo et al[88] reported that the ultimate failure load of the ACL averaged 2160 N, while the mean ACL stiffness was 242 N/mm. A partial tear would be considered a "plastic" deformation, where the tissue has been stretched to the point where it cannot elastically recover. According to a recent systematic review, noncontact ACL injuries are most likely to occur when landing on a slightly flexed knee that is loaded by moments in 3 orthogonal planes. An internally directed tibial torque and knee valgus moment, combined with a quadriceps muscle contraction to resist the flexion moment. These forces appear to be particularly detrimental to elastic properties of the ACL.[66] Partial tear occurs when the forces through the ACL surpass the yield point.[41] When the ultimate strength is reached, the ACL fibers start to break until a complete rupture takes place at the so-called break point. The toe region represents the first non-linear region where collagen fibers are sequentially recruited to bear load, and it is followed by the linear region where collagen fibers temporarily deform.[84]

Because of its importance in ligament viability in both the native state and during reparative treatments of an ACL tear, the vascularity of the ACL has also been studied.[1,28] The blood supply to the cruciate ligaments

originates from the middle genicular artery, which provides 4 branches to the PCL and only 1 branch to the ACL. At the femoral and tibial insertions of the ligaments, the middle genicular vessels anastomose with a vascular subcortical network. These anastomoses are scant and therefore unlikely to be able to support the repair of a torn ligament. Injection and immunohistochemistry studies have confirmed these avascular areas.[62,63]

CLASSIFICATION OF PARTIAL ACL TEARS

Limited literature exists regarding the definition and classification of partial ACL tears and subsequent therapeutic algorithms. A partial ACL tear combines a positive Lachman's test with a firm endpoint. Panisset et al,[61] in a prospective study of 418 cases clinically, reported that a significant degree of laxity was detected between a population with complete ACL tears (98% of the patients had a positive Lachman test and 80% had a positive pivot-shift test) and a group with partial tears (30%-64%) had a hard or delayed stop in the Lachman test and had a negative pivot-shift test.

Important characteristics of partial ACL tears are a hyperintense signal within the ACL fibers on magnetic resonance imaging (MRI), arthroscopic findings of a partial tear, and a side-to-side difference in KT-1000 criterion (<5 mm).[43,71] Noyes et al[59] defined these injuries according to the percentage of uninjured ACL tissue remaining at the time of arthroscopy. Using a nerve hook, the authors carefully probed the ligament and removed overlying synovium to finally assess the residual ligament present. The region of the tear, the fiber bundles in relationship to the tibia, and the estimated amount of the gross tearing was assessed. They recognized that although not totally objective, direct visualization of the gross disruption remains the only means available to quantify ACL tissue. DeFranco and Bach[19] categorized partial tears based on a combination of knee laxity on physical examination and the arthroscopic appearance. Gobbi et al[32] classified partial tears into 4 separate grades based on MRI findings of the affected bundle, which were confirmed at the moment of the arthroscopic surgery. Grade 1 injuries involved a partial lesion of the AM bundle, while grade 2 lesions involved a similar partial lesion of the PL bundle. Grade 3 injuries represented incomplete injury of both bundles, and grade 4 was found to be a complete tear of both bundles.

BIOLOGIC TECHNIQUES FOR ACL REPAIR OR REGENERATION

Few reports documenting spontaneous healing of partial ACL tears are available in the literature.[17,35] While ACLR has demonstrated good results with different graft options for complete ACL ruptures, nonsurgical treatment and primary repair of the partial and complete tear of the ACL has been reported to fail to heal in the majority of patients.[24] Recent clinical and animal studies suggest a possibility of ACL healing after primary suture of the ligament augmented with the use of growth factors and bone marrow–derived mesenchymal stem cells (BMSCs).[54,74] This might be clinically important in the treatment of partial ACL tears, because growth factors and bioactive proteins play an important role in tissue healing as they can regulate key processes in tissue repair, including cell proliferation, chemotaxis, migration, cellular differentiation, and extracellular matrix (ECM) synthesis.[31]

ACL Repair by the Healing Response

First described by Steadman et al[72] the "healing response technique" was proposed to treat tearing or avulsion of the ACL from its proximal insertion on the femur. This technique involves a microfracture of the medial wall of the lateral femoral condyle performed close to the femoral ACL footprint. This reportedly leads to the formation of a blood clot and subsequent hematoma formation at the anatomic location of the ACL insertion, causing scarring and potential attachment of the proximal ACL.

Steadman et al[72] evaluated 13 skeletally immature athletes with proximal ACL tears who underwent a healing response procedure. Three (23%) patients had a reinjury 30 to 55 months after surgery. Subjective follow-up on the remaining 10 patients demonstrated resolution of pain without subjective instability or giving way, and all patients considered their knee function to be normal. At 69 months, the average Lysholm score was 96 and Tegner score was 8.5 (range, 7-10). Patient satisfaction at follow-up was 9.9 (1 = very dissatisfied and 10 = very satisfied). Clinical examination was performed on 7 of 10 patients at 35 months postoperative (range, 12-63 months). Five patients had a negative pivot-shift and 2 had a 1+ pivot-shift. KT-1000 measurements improved to 2 mm (range, 0-3 mm).

More recently, the same group evaluated 48 active middle-aged patients who underwent the healing response procedure with an average follow-up of 7.6 years (range, 2.2-13.4 years).[73] The average preoperative Lysholm score was 54 (range, 10-82) and improved to an average score of 90 postoperatively ($P = .001$). Median Tegner activity scale at follow-up was 5 (range, 2-9). Median patient satisfaction was 10 (range, 4-10).

Wasmaier et al[85] showed contrary results, demonstrating no differences between patients treated by the healing response technique or conservatively (nonsurgical) with regard to clinical scores, joint laxity, and rate of revision surgery. However, more recently, in an interesting histological study investigating spontaneously reattached tibial ACL remnants, Nguyen et al[57] concluded that the human proximal one-third ACL has an intrinsic healing response with typical characteristics similar to the MCL, which can heal spontaneously.

The recent findings of ACL healing in animal models[56] stimulate the interests in future translational studies to develop and evaluate the bioenhanced suture repair of torn ACLs in humans.

ACL Repair Augmented With Growth Factors

Growth factors, such as transforming growth factor beta1 (TGF-β1),[90] fibroblast growth factor–2 (FGF-2),[45] growth

and differentiation factors 5 and 7,[18] and basic-FGF (bFGF),[39] have been reported to regulate and improve cellular activities and proliferation, ECM deposition, and influence the differentiation of mesenchymal stem cells (MSCs) into fibroblasts in the repair process of torn ligaments. Particularly, the growth factors outlined below have exhibited positive effects on various biological processes needed to improve ACL healing. TGF-β is a key regulator during embryologic tendon development and also plays a significant role in the early modulation of scar tissue formation during connective tissue healing.[50]

In Vitro Studies. Marui et al[46] reported that the application of TGF-β1 resulted in increased collagen synthesis up to 1.5 times greater than controls in both MCL and ACL fibroblasts. Madry et al[45] showed the enhanced healing of the human ACL by overexpression of FGF-2 via direct recombinant adeno-associated virus (rAAV) vector–mediated gene transfer.

Animal Models. In a recent study, Takayama et al[77] assessed the effects of angiogenesis in ACLRs in a mice model. Angiogenesis blocking (thorough a virally transduced sFLT1 [soluble FMS-like tyrosine kinase–1]) reduced graft maturation and biomechanical strength; however, overexpression of vascular endothelial growth factor (VEGF) did not result in improvements in biomechanical strength. Kobayashi et al[39] reported on the positive effect of bFGF in improving ACL tissue healing in a canine model by increased vascularity compared with the control. In the bFGF group, a bFGF-impregnated pellet was sutured to the infrapatellar fat pad close to the defect. In the control group, the same pellet without bFGF was used. More recently, Kondo et al[40] studied the effect of TGF-β1 in an in vivo model of ACL injury in rabbits (n = 36). Different concentrations of TGF-β1 were utilized against no treatment acting as controls. They reported significant improvement of biomechanical and histological healing properties of injured ACLs treated with TGF-β1 compared with controls.

In vitro and animal studies using specific growth factors such as TGF-β, bFGF, VEGF, and FGF-2 demonstrated to stimulate cell proliferation and ECM synthesis and influence the differentiation of MSCs into fibroblasts in the repair process of torn ligaments.

ACL Repair Augmented With PRP

In a similar manner, PRP is known to contain several growth factors and has been the center of attention regarding noninvasive therapies. The combination of bioactive agents can mediate the tissue healing process after an injury through both the inflammatory and remodeling phases.[16] Platelets are involved in homeostasis, aggregation and clot formation steps, which finally leads to enhanced tissue healing.[49] These processes are mediated by the release of platelet-derived growth factor (PDGF), TGF-β1, VEGF, bFGF, and epidermal growth factor through degranulation of alpha granules. Among these growth factors, PDGF and TGF-β1 have been reported to be the most critical modulators in the healing process by contributing to increased fibroblast proliferation and collagen production.[22,48]

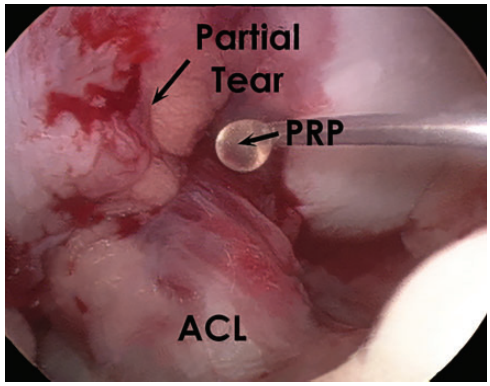

Figure 3. Arthroscopic view of partial tear of the anterior cruciate ligament (ACL) in a right knee treated with an injection of platelet-rich plasma (PRP) as viewed through the anteromedial portal.

Animal Models. Murray et al[52] reported on a porcine model using clotted PRP in the gap of a transected ACL and concluded that there was no beneficial effect of adding PRP. It was theorized that the fibrin clot containing the platelets may have been prematurely dissolved in the intra-articular environment, leading to the failure of isolated PRP as a system for localized growth factor delivery. These observations led to the exploration of scaffolds to hold the PRP at the wound site of the ACL and protect it from early degradation. Cheng et al[15] showed that the addition of PRP to the collagen hydrogel resulted in a significantly increased cellular metabolic activity, reduced apoptotic rate, and stimulation of collagen production in the cells from the immature and adolescent animals but had less effect on adult cells animals.

Clinical Studies. Seijas et al[69] reported a high return to sport in 19 professional soccer players with a partial ACL tear treated with intraligamentous placement of platelet-derived growth factors into the intact bundle (Figure 3). Platelet-rich growth factors (PRGF-Endoret) were applied using the technique described by Anitua (PRGF-Endoret)[5] with a spine needle in both the proximal origin of the bundle and in the middle portion thereof in an amount of 4 mL. The average time between the injury and the time of surgery was 5.8 weeks. At the end of the surgery, when the joint had been dried and all surgical instruments had been removed, another injection of PRGF-Endoret was administered (6 mL) in the articular space. Fifteen patients returned to play at an average of 16.20 weeks (1 rerupture at 7 months), while the 3 patients returned in 12.33 weeks. However, 1 patient was not able to return to sport due to the extent of their cartilage lesions. No notable complications were reported in any patients in the series, as well as no obvious bleeding or infections. A postoperative MRI study was performed in all patients and showed the remnant ACL bundle with complete ligamentization at 1 year postsurgery and good anatomic arrangement.

While a paucity of evidence in clinical studies on the use of PRP on partial ACL tears exists, the safety and versatility of PRP injections has inspired and stimulated its therapeutic use for other pathologies. It is used extensively on a

number of other orthopaedic injuries. Podesta et al[64] reported on 34 athletes with a partial-thickness ulnar collateral ligament (UCL) tear confirmed on MRI; 30 of 34 athletes (88%) returned to the same level of play without any complaints at an average follow-up of 70 weeks. They concluded that this study indicates that PRP was an effective option to successfully treat partial UCL tears of the elbow in athletes.

Animal models using PRP alone for ACL tears may have failed because the main structural protein within PRP was degraded by the active plasmin within the joint and the PRP was unable to remain in the ACL wound site. More studies are needed in animals to understand further the effect of PRP on the healing process in the intra-articular knee environment. While clinical studies showed a higher rate of return to sport and ACL ligamentization at 1 year follow-up when combined with PRP, further studies and longer follow-ups are required with the use of PRP in partial ACL injuries to draw definitive conclusions.

Cell Therapy

Cell therapy has been widely studied in vitro and in preclinical studies.[11-13] MSCs are adult stem cells from various sources, being multipotent and having the capacity of self-renewal. MSCs can differentiate into mesoderm-associated cell types such as chondrocytes, adipocytes, or osteoblasts. In vivo, they are often located in the perivascular area.[11]

Animal Models of MSCs ACL Repair

In a rat model of partial ACL tear, Kanaya et al[36] reported that intra-articular injection of MSCs resulted in a healed ligament with superior histological scores and a greater failure load compared with nontreated control knees. In a more recent study, Oe et al[60] used intra-articular injection of either fresh BMSCs or cultured MSCs at 1 week after ACL transection in a rat model. They showed that the donor cells were located within the wound site and the ACL exhibited almost normal histology, with more mature spindle cells with higher levels of TGF-β in the BMSCs group. They concluded that the direct intra-articular BMSCs injection was an effective option for the treatment of partial ACL tears.

ACL Repair MSCs Clinical Studies

In the only clinical study in humans, Centeno et al[14] reported on 10 patients with ACL tears treated with an intra-ligamentous injection of autologous bone marrow concentrate and PRP using fluoroscopic guidance. ACL laxity and MRI evidence of grade 1, 2, (partial), or 3 (complete) tears was documented including patients with partial and complete ACL tears with less than 1-cm retraction. ACL tears were analyzed by MRI images pre- and postinjection. A software was used to objectively quantify changes through 5 different types of measurements of ACL pixel intensity for ligament integrity. Seven of 10 patients showed improvement in at least 4 of 5 of these objective MRI measures. The mean visual analog scale change was a decrease of 1.7 ($P = .25$), the mean Lower Extremity Functional Scale change was an increase of 23.3 ($P = .03$), and mean reported improvement was 86.7%.

Scaffolds + Suture + PRP

Animal Models. The use of collagen-based scaffolds has been shown to be effective. ACL fibroblasts have been previously shown to effectively attach, proliferate, and express collagen on collage-based scaffolds.[21] Porcine small intestinal submucosa (SIS) was among the first scaffolds used to enhance the regeneration and repair of ligaments and tendons.[7,20] SIS is a collagen-based (90% of dry weight) bioabsorbable scaffold that contains cytokines and growth factors such as FGF and TGF-β.[55] Fisher et al[25] reported significant improvement in tissue mechanical and histological properties using a primary repair technique supplemented with SIS bioscaffold and hydrogel. There was no excessive hypertrophy of the ECM-treated ACLs, and the cross-sectional area was comparable to the sham-operated control group.

Recent in vivo work by Fleming et al[26] reported no significant improvement of suture repair when supplemented with a collagen scaffold alone used for complete ACL tears in a porcine model. However, by combining a collagen scaffold with autologous platelets, Vavken et al[82] demonstrated significantly improved ACL repair outcomes in a series of large animal studies, which showed superior tissue mechanical properties using primary repair augmented with a collagen-PRP hydrogel compared with suture repair alone. Additional studies have also now demonstrated that the combination of an ECM-based collagen scaffold and PRP is substantially more effective than the application of each of these factors alone.[52] The mechanism behind this remains unclear, but it may be due to a synergic effect between the collagen, PRP, and other ECM molecules.

Clinical Studies. Gobbi et al[32] evaluated the clinical results of suture repair of the ACL plus microfracture of the intercondylar notch and adjunctive PRP injection with 5-year follow-up in 58 athletes. They reported that 78% of the patients returned to their sports activities. A significant decrease in the side-to-side difference in anterior translation was also reported, from 4.1 mm (SD = 1.6) preoperatively to 1.4 mm (SD = 0.8) postoperatively at the 5-year follow-up. This difference was statistically significant ($P < .05$). Four patients had a retear during sporting activity and underwent ACLR within 2 years from the primary repair surgery. In this case series, they concluded that ACLR was an effective technique to restore knee stability and function in young individuals with acute partial ACL tears.

FUTURE DIRECTIONS

Biological Enhancement of the ACL

Newer approaches using scaffolds loaded with cells and growth factors could probably lead to improved rates of healing of ACL tears.[75] After many years of preclinical

studies, Murray et al[51] introduced the use of a collagen scaffold soaked with whole blood to deliver platelets in combination with a novel bioenhanced primary repair technique using a suture stent, called bridge-enhanced ACL repair (BEAR technique) and reported that it resulted in biomechanical properties of the repaired ACL equivalent to an ACLR after 3, 6, and 12 months of healing in an animal model.[82] Furthermore, this novel technique of bioenhanced repair prevented the development of cartilage lesions, which were seen 12 months after untreated ACL transection and ACLR in an animal model.[51]

CONCLUSION

ACLR can be associated with muscle weakness, biomechanical limitation, loss of proprioception, donor site morbidity with the use of autograft tissue, graft failure, and early posttraumatic osteoarthritis. Advancements in tissue engineering and regenerative medicine have resulted in a new interest in the biologic treatment of partial tears of the ACL. The use of novel biologic ACL repair techniques, including growth factors, PRP, stem cells, and bioscaffolds, have been reported to result in promising preclinical and short-term clinical outcomes. Further studies are necessary to define the role of these approaches in the treatment of the partial tears of ACL, to better understand the biology of the healing process, and to assess long-term outcomes.

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