18 Future Trends in Ligament Surgery: The Role of Biology

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18.1 Introduction

There have been numerous treatments developed to address ligament injury, given the functional impact of such injury on lifestyle and participation in physical activities at all levels of recreational and competitive endeavors. With regard to commonly diagnosed knee injuries, anterior cruciate ligament (ACL) insufficiency is a frequently encountered pathology that often requires surgical treatment to restore the desired level of function. Considering that ligament injuries most commonly affect active individuals who tend to be younger, such injuries can lead to substantial alterations in lifestyle, and therapeutic treatments that restore near-anatomic function of damaged ligaments have the potential to overcome some of the shortcomings associated with current methods of reconstruction, particularly in the case of ACL insufficiency. The incidence of complete injury to the posterior cruciate ligament (PCL) is considerably lower than that of the ACL and is estimated to occur at a rate of 2 per 100,000; however, the prevalence of asymptomatic PCL injury is considered to be not ably higher [1]. Injury to collateral ligaments represents a significant proportion of knee injuries that present to emergency rooms, and high rates of medial and collateral ligament injuries are associated with collegiate sporting activities, with many of these cases involving noncontact competition [2].

Despite advances in sports medicine, there remains controversy in the treatment of ligament injury, particularly when there is functional insufficiency associated with partial ligament injury. For instance, reconstruction of the ACL is the current gold standard treatment for symptomatic ACL insufficiency, irrespective of injury pattern, and high rates of return to sport are expected [3, 4]. Disadvantages of ACL reconstruction include donor site morbidity, inability to restore normal joint kinematics, and an increased incidence of premature degenerative joint changes [5–8].

There are challenges associated with restoring anatomic function in cases of ligament injury, and biologic therapies have great potential to address some of these concerns. Therapeutic interventions that utilize bioactive growth factors and cellular elements may be used to augment ligament repair processes and can be used in

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conjunction with surgical treatment modalities. These biologic treatments may be a prominent feature of treatment algorithms as these technologies develop and understanding of reparative processes at the cellular level advances.

18.2 Basic Science and Anatomic Considerations of Ligament Healing and Repair

The ACL and PCL receive vascular supply from the middle genicular artery, after branching from the popliteal artery. There are synovial sheath vessels that are associated with the cruciate ligaments, as well as capsular vessels that supply the distal fibers of the PCL, which branch from the popliteal and inferior genicular arteries [9]. While the ACL and PCL both share blood supply arising from the middle genicular artery, anatomic differences in the vascular supply may impact the improved healing capacity of the PCL. Anastomosing branches of the middle genicular artery and infrapatellar fat pad are an important vascular contributor to the ACL, whereas the PCL derives a more direct arterial supply. Moreover, there is greater synovial encapsulation of the PCL.

Collateral ligaments have a greater inherent healing potential, and there are anatomic factors related to vascular supply that should be considered. Differences in the healing capabilities of the ACL and MCL have been examined in animal models that have highlighted the positive impact of vascular supply on the healing potential of these ligaments [10]. There are multiple branching vessels about the medial collateral ligament (MCL), and several vessels directly supply the ligament tissue [11, 12], whereas the vascular supply of the ACL consists of one or two branches of the middle genicular artery that course beneath the synovial sheath [12, 13]. The body of the ACL has sparse or no direct vascular supply and is relatively hypovascular, and this may be a major contributor to the reduced healing capacity of the ACL as a result of the diminished physiologic and metabolic response to injury.

There are anatomic and physiologic factors related to the intra- or extra-articular location of ligaments that impact the healing potential. Processes of cell signaling, migration, proliferation, and differentiation, as well as the proficiency of collagen production, affect the inherent capacity for ligamentous repair and regeneration. Fibrin clot formation at the site of ligament injury sequesters reparative cells and provides a microenvironment that favors healing and repair. Due to the intra-articular position of the ACL, the process of fibrin clot formation is deficient, and tissue repair processes are impaired. Moreover, circulating plasmin within the intra-articular space can inhibit fibrin clot formation, and synovial fluid may inhibit fibroblast proliferation and migration [14, 15].

18.3 Growth Factors and Platelet-Rich Plasma (PRP) in Ligament Repair

Numerous bioactive substances coordinate the complex processes of cellular regenerative activation and response after tendon injury [16]. Certain growth factors are capable of directing cellular proliferation, migration, and differentiation while also enhancing collagen production. Bioactive growth factors are upregulated in response to ligament and tendon injury and act at several phases of the regenerative cascade, of which transforming growth factor beta (TGF-β), insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), bone morphogenetic protein (BMP), and vascular endothelial growth factor (VEGF) have been shown to have particularly considerable contributions to processes critical to ligament healing [17–20]. PDGF could also play a significant role in the early stages of healing as the application of PDGF-BB has been shown to improve the structural composition of rabbit and rat ligaments [21, 22].

Platelet-rich plasma is generally defined as an isolate of plasma that has a concentration of platelets above the baseline concentration in whole blood. Autologous PRP can be prepared after venous blood extraction using a variety of commercially available preparation systems. Within platelets, there are important regulatory bioactive factors that coordinate processes of ligament repair, including cellular proliferation,

chemotaxis, differentiation, and deposition of extracellular matrix. Applying PRP to a site of tissue injury is performed to provide a concentrated release of platelet-derived growth factors to stimulate and augment reparative processes. There is variability in the protocols used for PRP preparation, and there is debate as to the ideal constituency. Plasma isolates can generally be categorized as platelet-poor plasma (PPP) or platelet-rich plasma (PRP). PRP can then be further categorized as either leucocyte-poor platelet-rich plasma (LP-PRP) or leucocyte-rich platelet-rich plasma (L-PRP) [23]. When PRP is applied to injured tissue, thrombin or intra-articular collagen will activate the platelets, leading to sustained release of regenerative growth factors capable of augmenting repair processes. A variety of biologic growth factor preparations have been studied to treat ligament and tendon injury, and these treatments are being increasingly utilized in the clinical setting [24, 25].

The application of growth factors contained within platelets has been studied in several animal models. TGF-β1, bone morphogenetic protein 2 (BMP2), and growth differentiation factor 5 (GDF5) have shown increased collagen synthesis and healing in response to ligament injury [26, 27]. There continues to be contrasting findings in the literature related to the use of growth factors in ACL repair. The application of basic fibroblast growth factor (bFGF) has shown enhanced vascularity and ligament healing in cases of canine ACL injury [28], whereas other research examining the use of PRP for ACL injury in animal models has failed to demonstrate superior ligament repair. In examining the clinical use of growth factors to treat ligament injury in humans, preliminary research has demonstrated that the use of such therapy in partial ACL injury may enable high rates of return to pre-injury activity levels. There is, however, inconsistency in the literature, and there may be important differences in the expected outcome of biologic treatments depending on the concentration of bioactive factors, the type of ligament treated, and also the specific injury pattern. Recent work by LaPrade et al. [29] examined the use of PRP to treat complete MCL disruption in a rabbit model. While treatment with a PRP isolate of two times the baseline platelet concentration did not improve healing, it was actually found that treatment with a PRP isolate containing four times the baseline platelet concentration negatively impacted the quality of repair tissue compared to controls.

18.4 Cellular Therapy in Ligament Repair

Mesenchymal stem cells (MSCs) are multipotent cells that have an inherent self-renewal capability and contain a large assortment of growth factors that direct regenerative processes. These cells can be isolated from a number of readily accessible tissues that include the bone marrow and fat tissue [30] (Fig. 18.1). There has been increasing interest in the clinical use of such cells in recent

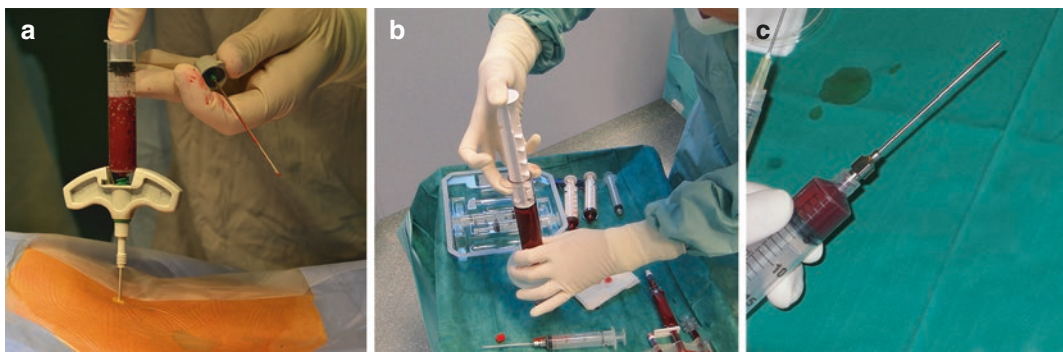

Fig. 18.1 Bone marrow aspiration from the iliac crest (**a**). Processing of bone marrow aspirate in a commercially available system to isolate bone marrow aspirate concentrate (**b**). Final preparation of bone marrow aspirate concentrate (BMAC) for clinical application (**c**)

years due to the wide range of potential therapeutic applications [31, 32]. These multipotent cellular isolates have been used successfully to restore healthy and functional tissues for a variety of pathologies, including challenging cases of high-grade articular cartilage injury [33–35]. Therapies that utilize MSCs have the capacity to coordinate regenerative processes at the molecular level, and there are similar cellular characteristics with ligament outgrowth cells that are important for ligament repair [6, 36]. Intra-articular injection therapy of multipotent cells sourced from bone marrow aspirate concentrate to treat ligament injury has demonstrated improvement in tissue integrity according to MRI examination [37].

18.5 Scaffolds and Cell-Scaffold Composites in Ligament Repair

Scaffolds may be used to provide structural biomechanical support to healing ligamentous tissue and to contain concentrations of endogenous cells, while extracellular matrix is deposited and remodeled, thereby contributing to stability of the repair and optimizing the local regenerative microenvironment. Scaffolds may be used to facilitate cellular proliferation and differentiation and can encourage growth factor attachment while promoting extracellular matrix production and remodeling into ligament repair tissue [38].

Combining cellular isolates with biologic scaffolding has demonstrated promising clinical utility in the treatment of chondral and osteochondral lesions [39–42], and there are great potential advantages for this treatment in cases of ligament injury. Biologics such as PRP and MSC preparations contain regenerative growth factors and cellular elements important for ligament repair, and combining these bioactive isolates with scaffolding can provide a supportive matrix to facilitate cellular processes while also providing biomechanical support to the destabilized injured tissue. Moreover, when undertaking primary repair of injured ligament tissue, such scaffolding can act to protect the repair site from the effects of plasmin, thereby stabilizing the microenvironment for tissue regeneration to proceed. Randomized controlled trials are needed to further study the extent of expected clinical benefits of such techniques, as there has been limited critical evaluation of outcomes in human trials.

18.6 Surgical Techniques of Ligament Repair

There continues to be debate among clinicians regarding treatment of ligament injuries, particularly in cases of partial tears that are associated with instability. Noyes et al. determined that conservative treatment of partial ACL injury would lead to complete ACL insufficiency in 50% of those treated where more than 50% of the ligament was injured [43].

Historical data indicates that surgical repair of the ACL leads to a failure rate that is excessively high for this method to be considered a preferential treatment [44, 45]. Short-term follow-up in a military cohort of patients by Feagin demonstrated good outcomes; however, 94% of these cases suffered from knee instability 5 years postoperatively [46]. There have been cohorts of patients treated with primary ACL repair that have had successful outcomes and maintained knee stability long-term [45], and so it is thought that a subset of injury types could benefit from a primary repair procedure, when properly indicated.

Reconstruction of the ACL is widely considered the gold standard surgical treatment to restore stability and enable return to physical activity in cases of complete or partial ligament instability that is associated with functional limitation [3, 4]. Reconstruction of the ACL is associated with a number of complications that include donor site morbidity, altered proprioception, bone tunnel widening, the inability to replicate anatomic joint kinematics, and degenerative changes to the articular cartilage [6–8]. With reconstructive methods, the incorporation of the graft is typically slow due to the hypovascular and hypocellular characteristics of the graft tissue [47].

18.6.1 Biologic Augmentation of Surgical Ligament Repair

Regeneration of the ACL and restored stability after primary repair procedures that have been augmented by biologic growth factors and cellular therapy has been demonstrated [48–52]. Augmenting the healing processes of ligament repair with multipotent cellular elements provides an array of regenerative growth factors to support healing processes. Early methods of providing such augmentation have been described by Steadman and involved releasing marrow elements from the bone marrow to assist with ligament repair [51, 53]. Phenotypically, these cells are capable of great plasticity, and several methods have been developed to strategically isolate and proliferate cell lines with these capabilities to treat a growing number of musculoskeletal disorders, including ligament injury. These regenerative cells can be readily isolated from tissues such as bone, synovium, fat, muscle, connective tissue, and skin.

Our center has used bone marrow stimulation to augment primary repair for certain injury patterns of the ACL and PCL for over a decade [54–56] and has demonstrated in clinical series that partial tears of the ACL can successfully be treated by primary repair with biologic augmentation, in lesions that are indicated appropriately [48, 57]. The most recent clinical outcomes after long-term follow-up of up to a 14-year duration in a series of patients who underwent treatment of symptomatic partial ACL injury with primary ligament repair with biologic augmentation demonstrated good to excellent outcomes and restored knee stability, and these benefits were maintained at a high rate over the course of follow-up.

18.6.2 Preferred Technique of Primary ACL or PCL Repair with Biologic Augmentation

Patient positioning and perioperative setup are performed according to surgeon preference for ligament reconstruction. In cases where bone marrow aspirate concentrate (BMAC) will be isolated to provide biologic augmentation, the ipsilateral iliac crest is included in the prepared surgical field. Examination under anesthesia of the operative knee and diagnostic arthroscopy are performed to determine the degree of ligamentous instability and to identify associated lesions that are treated concurrently. Partial ligament tears are visualized and probed while varying the degree of knee flexion and with the knee aligned in a figure-of-4 position. Jerk and Lachman tests are also performed during diagnostic arthroscopy to supplement the examination of ligament sufficiency. To repair the torn ligament fibers, PDS no. 1 suture is passed through fibers of the distal stump followed by fibers of the proximal stump using a standard clever hook or other suture passing devices. Two or three sutures are typically passed, and a Duncan loop is tied to reapproximate the injured ligament tissue, thereby restoring continuity and eliminating gapping between injured fibers (Fig. 18.2a).

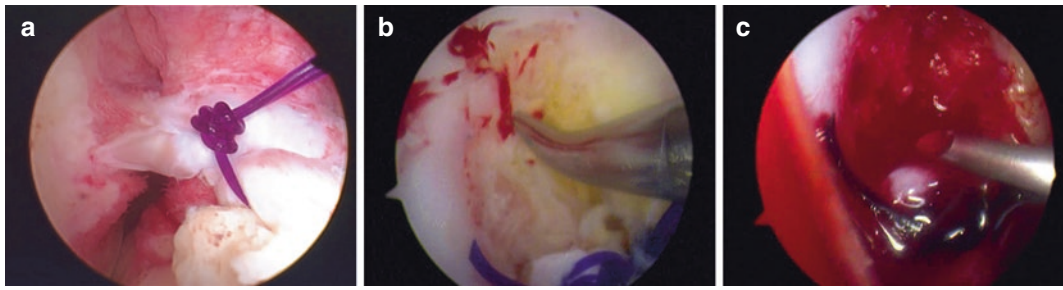

Fig. 18.2 Partial anterior cruciate ligament (ACL) arthroscopic suture repair of torn anteromedial bundle (**a**). Microfracture of intercondylar notch to release marrow elements about the repair site (**b**). Biologic augmentation of primary ACL repair with clot-activated bone marrow aspirate concentrate (**c**)

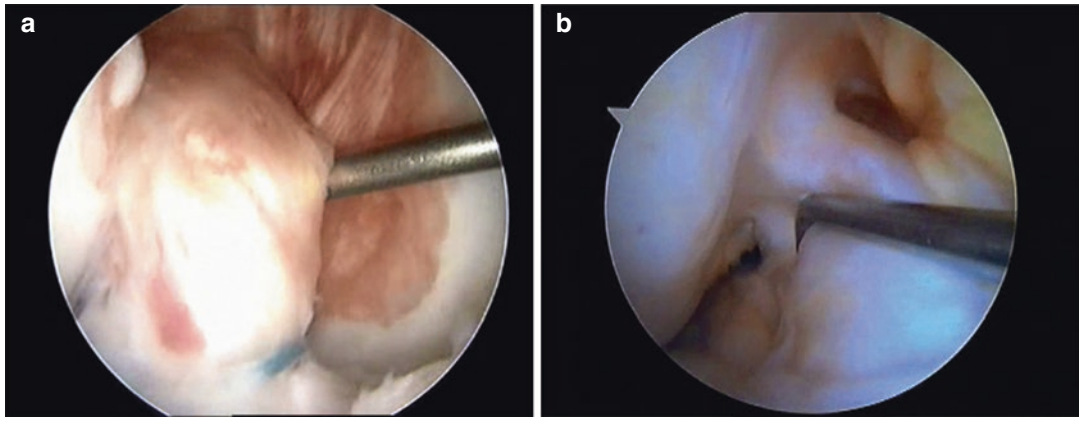

Fig. 18.3 Second-look arthroscopic examinations of healed anterior cruciate ligaments after treatment by primary repair and biologic augmentation depicted 4 months postoperatively (**a**) and 6 months postoperatively (**b**)

Bone marrow elements are then released by performing microfracture perforations within the intercondylar notch about the anatomic origin of the injured ligament (Fig. 18.2b). Careful examination of remaining tissue about the footprint ensures that residual ligament fibers are protected while performing marrow stimulation. The available reparative biologic factors are then supplemented with PRP or BMAC. The chosen biologic is isolated using a commercial system and is then activated with batroxobin enzyme or autologous thrombin to create an adhesive biologic gel. Intra-articular fluid is removed to provide a working space for dry arthroscopy. The biologic gel is then applied over and about the ligament, further enhancing the regenerative microenvironment and minimizing the effects of plasmin at the repair site (Fig. 18.2c). Second-look arthroscopic examination of primary ACL repair with biologic augmentation is depicted in Fig. 18.3.

18.6.3 Postoperative Rehabilitation

Mechanical stimulation is an important consideration during rehabilitation and physical therapy. Mechanotransduction provides stimuli to the cellular elements that act synergistically with this surgical repair technique. Bracing is used initially postoperatively, with continuous passive motion and weight bearing recommended early in the rehabilitation. Running activities are usually allowed 3 months postoperatively, with more intense activities and contact sports avoided until at least 4 to 5 months, depending on the extent of ligament repair and the rehabilitation progression.

18.7 Conclusion

The understanding of tissue healing processes is progressing at a rapid pace, and there has been increasing interest in treatments that are capable of retaining functional ligament tissue and optimizing the regenerative environment, particularly in cases of partial ligament injury. There are several important advantages of therapies that restore native ligament anatomy, with restoration of anatomic joint kinematics being of crucial importance. A number of biologic isolates have been developed for clinical application that have the potential to enhance ligament repair by providing growth factors and cellular elements, and there is also continued development of biologic scaffolding that can be used in conjunction with biologics to sequester a regenerative microenvironment. There has been an acceleration in the publication of literature that examines the clinical outcomes of ligament repair procedures over recent time. In the case of ACL insufficiency, initial findings have been most supportive of primary repair and biologic augmentation in the setting of acute, partial, and proximal

ligament injury. This ongoing work will have great clinical importance in the identification and characterization of specific injury patterns that would benefit most from these regenerative treatments.

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