Biological Augmentation of Meniscal Repairs

13

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Contents

13.1 Introduction

Basic scientists, orthopedic clinicians, and the lay public have all recently become fascinated with biologic therapies. The interest has been stoked by the pursuit of science in animal studies and early clinical studies and by clinicians utilizing a broad spectrum of predominantly underdeveloped biologic treatments. The term biologics refers to natural products which are harvested and used to augment a medical process and/or the biology of healing. Biologics can be divided into three categories: growth factor therapies, which leverage chemokine and cytokine function such as point-of-care blood-based products; cell-based therapies which leverage cell function such as bone marrow aspirate; and tissue-based therapies, which utilize the structure of tissue to produce function such as allograft meniscal transplant. Investigators have been studying the biology of meniscal healing for many years, examining mechanical methods, methods involving growth factors, point-of-care blood-based augments, scaffolds, and stem cell therapies. This chapter will review the orthopedic pursuit of improving the healing of the meniscus.

13.2 Healing and Vascular Anatomy

Healing is divided into three phases: inflammation, repair, and remodeling. These phases are dependent on the delivery of cells and mediators

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R.F. LaPrade et al. (eds.), *The Menisci*, DOI 10.1007/978-3-662-53792-3_13

of healing, the removal of injured tissue, and a structural framework for the wound healing process. The movement and components of blood provide the building blocks necessary to start and complete the healing process, a premise which has been observed in meniscal healing studies in animals [1, 2]. Platelets and fibrin are both vital, because fibrin provides a scaffold for the healing process. Platelets are important signaling molecules, providing chemotactic and mitogenic stimuli for the repair process [3–5]. When exposed to these normal mediators of healing, meniscus fibrochondrocytes are capable of proliferation and extracellular matrix synthesis [5].

While first described by Policard in 1936, Arnoczky and Warren produced the most widely recognized study on the blood supply of the meniscus [6, 7]. Blood arrives via two mechanisms: a perimeniscal capillary plexus which penetrates the meniscus with radial branches and areas of synovial covering which are highly vascular. These sources provide blood supply to roughly the outer 25 % of the meniscus [7]. This peripheral supply tapers to an avascular internal section. Meniscal healing studies in canines have illustrated good healing potential in vascular areas and little healing potential in avascular sections [2]. The structure of the vascular anatomy and clear lack of healing in the avascular zones have led surgeons to divide the meniscus into three anatomic sections when evaluating tears: an outer peripheral one-third with excellent to good healing potential, a middle one-third with moderate healing potential, and an inner central one-third with poor healing potential.

13.3 Vascular Access Channels and Synovial Abrasion

Studies quantifying the vascular supply and illustrating healing in vascular regions were followed by studies into techniques aimed at increasing the blood supply available to the entire meniscus. Initial canine studies focused on creating vascular access channels from the central avascular portion to the peripheral vascular portion and illustrated improved healing potential [2, 8]. A needle, blade, or trephine was a simple method to make a vascular access channel from the central region to the peripheral region. In 1993, a prospective study evaluating trephination of incomplete tears with an 18-gauge needle found 90 % of 30 patients were determined to have a good to excellent outcome based upon a subjective patient assessment score [9]. A next theoretic step to improve vascular presence was to create a larger vascular access channel with an implanted, absorbable porous structure. Preclinical animal study around a cylindrical device composed of poly-L-lactic acid illustrated promise with a 71 % healing rate of avascular tears in canines [10, 11]. However, after acquisition of the technology by an orthopedic implant company, developmental steps in humans were stopped after beginning a clinical study for undisclosed reasons.

In addition to creating conduits for blood flow, increasing the synovial attachment to the meniscus also increases the blood supply. Synovial abrasion involves roughening the synovium with an instrument such as a rasp adjacent to a meniscal tear (Fig. 13.1). In animal studies, this improves the healing potential of the middle third of the meniscus which normally has a marginal blood supply but does not improve the healing potential of the central avascular third [12, 13]. A clinical comparative study with this method includes one case-control study, illustrating a decrease in failure rate from 22 to 9 % after the authors began adding synovial abrasion to their

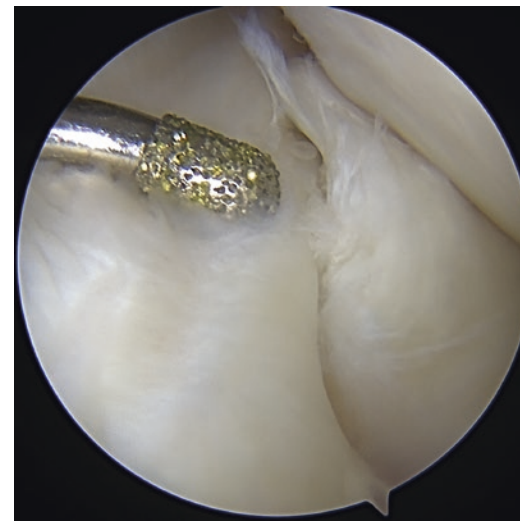

Fig. 13.1 Synovial abrasion performed arthroscopically

meniscus repairs [14]. It has been theorized that synovial abrasion is effective by itself to heal meniscus tears rather than as a method to augment meniscal suture repair [15]. A retrospective cohort study evaluating 47 patients who underwent synovial abrasion without suture repair found 71 % of the patients had complete meniscal healing, 21 % incomplete healing, and 8 % no evidence of healing when the sites were evaluated with second-look arthroscopy. The authors reported that stable tears illustrated the highest healing rate with this method [16].

13.4 Point-of-Care Blood Products

In addition to improving the blood supply of meniscal tissue, delivering various components of blood to meniscal tissue has also been studied including fibrin and platelets. Fibrin carries two properties which can be leveraged to improve meniscal healing: structural support of a clot and the chemokine properties of fibrin degradation products. Animal studies have varied; initial study of a fibrin clot in canines involved 2 mm meniscal defects, which when filled with fibrin clot healed with the formation of fibrocartilage [17]. Further study with a goat model of longitudinal tears found no benefit of a fibrin clot upon healing [13]. Tears repaired with sutures found a healing rate of 17 % with a fibrin clot augment and a healing rate of 87.5 % with synovial abrasion augment [13]. Low-level clinical studies have supported the use of fibrin clots to improve meniscal healing rates [18–20]. However, a randomized prospective study of horizontal tears reported that fibrin clot as an adjunct to repair produced inferior results when compared to repair with vascular access channels and when compared to a partial meniscectomy [21]. Synthesizing these studies suggests that fibrin clot can be useful when used as a scaffold or to protect healing tissue from the caustic healing environment of the joint but should not be interposed when adequate tissue is available for repair (Fig. 13.2).

While isolated and combined growth factors have proven effective for the enhancement of meniscus tissue regeneration in benchtop and animal studies [22–24], growth factors are not commercially available for clinical use with the exception of bone morphogenetic proteins, which have not been studied clinically in meniscus repair. However, point-of-care blood products such as platelet-rich plasma (PRP) are available to clinicians. Platelets contain a number of chemokines and cytokines which are released upon activation, including both anti-inflammatory and pro-inflammatory molecules [25–27]. While the exposure of tissues to pro-inflammatory molecules, such as TNF-alpha and IL-1, has inhibitory effects upon healing [28, 29], studies exposing cells from the

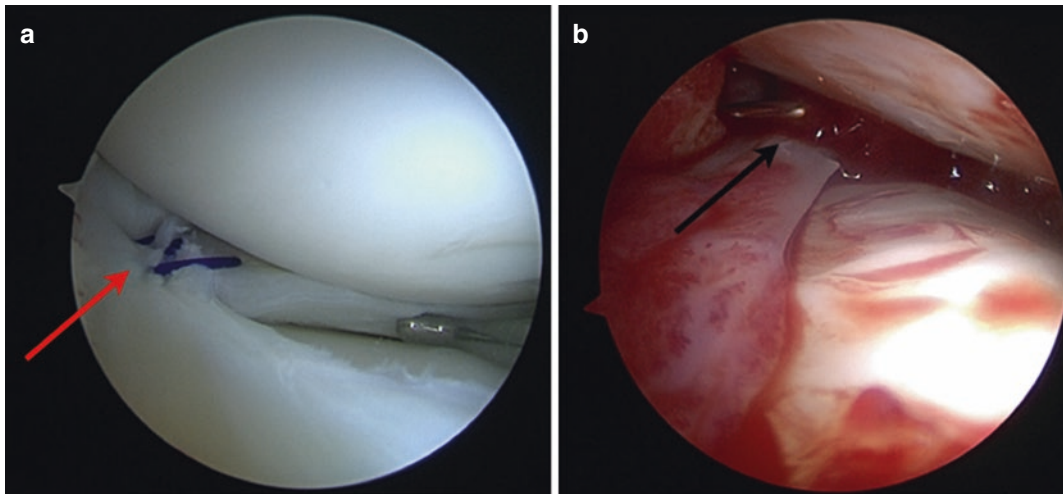

Fig. 13.2 A radial tear is repaired (**a**), protected by a fibrin clot loaded with bone marrow aspirate (**b**)

avascular meniscus zone to IGF, FGF, and PDGF have illustrated new matrix formation and fibrochondrocyte proliferation [30–32]. In a benchtop study, cell proliferation and extracellular matrix synthesis were stimulated by exposing cultured fibrochondrocytes to PRP [33]. These same authors investigated a PRP gelatin hydrogel (GH) which eluted PRP in a slow fashion, 4 weeks on average, in a rabbit model. Comparison included GH alone, GH with PRP, or GH with platelet-poor plasma to treat a punch defect. The group treated with the GH with PRP illustrated the best tissue upon histologic review [33].

Clinical data evaluating the efficacy of PRP to augment meniscal repair is limited to two studies. In a retrospective comparative study, the clinical outcomes of 15 isolated meniscus repairs augmented with a leukocyte-rich PRP matrix were compared to 20 repairs performed without PRP augmentation. Outcomes were similar regarding reoperation rate and clinical outcome scores. This study was underpowered with a post hoc power calculation suggesting that a similar study with approximately 200 patients in each arm would be necessary to answer the clinical question [34]. Another study evaluated 17 patients treated with open meniscal repair of a horizontal meniscus tear alone to 17 patients treated with open meniscal repair and an in injection of leukocyte-rich PRP into body of the meniscus repair. Outcomes assessed with MRI and clinical outcome scores were similar with the exception of a significant difference between two subsets of KOOS scoring, pain, and sports activities. These two subsets of the KOOS score favored the PRP group [35]. These studies suggest that the clinical benefit of current PRP technologies to meniscal repair at this time is marginal.

13.5 Scaffolds

For tissue regeneration to occur, it is theorized that three principle components are necessary: a scaffold, cells, and the appropriate cell signaling molecules. Meniscal injury can permanently damage tissue such that repair is not always possible, and tissue may not be available to provide cell incorporation and extracellular matrix formation. In some instances replacement tissue is necessary. For meniscal applications, replacement scaffolds come in three types: allograft meniscal tissue, xenograft collagen-based scaffolds, and synthetic scaffolds. Allografts are covered in a subsequent chapter and are indicated in scenarios of near-complete meniscal injury. Collagen-based scaffolds and synthetic scaffolds are typically used to fill segmental meniscal deficits.

The Collagen Meniscus Implant (CMI) (Ivy Sports Medicine LLC, Montvale, NJ) is a xenograft collagen-based scaffold manufactured from highly purified type 1 bovine collagen. In a developmental histologic study, the CMI was implanted in nine canines [36]. The implant underwent an active integration in the majority of cases over the course of 18 months, with four cases illustrating a mild chronic inflammatory response and one giant-cell engulfment of the scaffold in 3 weeks [36]. In clinical application, outcomes at 5 years and 10 years have illustrated superiority when compared to partial meniscectomy for medial meniscus injury [37–42]. Monllau et al. reported on a case series of 25 patients with 10-year follow-up. At final follow-up, clinical scores sustained improvement including Lysholm scores and mean pain scores on a visual analog scale (VAS). MRI analysis with Genovese scores found 64 % of cases as nearly normal and 21 % of cases as normal. There was an 8 % implant failure rate [37]. In a case-control study of 33 patients, Zaffagnini et al. compared CMI implantation with partial meniscectomy alone for medial meniscal injury [42]. Lower VAS scores and higher objective IKDC, Tegner index, and SF-36 scores were observed in the CMI group. Radiographs revealed less medial joint space narrowing in the CMI group [42]. A lateral meniscus study has recent 2-year outcomes which mirror the results of the medial meniscus experience [43]. Despite improvement in clinical outcome scores, implant absorption has been observed in 6–12 % of cases [42–44].

Synthetic meniscal scaffolds are under development with early encouraging results. Implant design involved optimizing pore number, pore

size, inter-pore connectivity, compressibility, ingrowth, and degradation time [45–47]. Development has continued with biomechanical analysis of a degradable synthetic porous scaffold, illustrating improvement in contact mechanics after implantation [48]. Implantation studies in canines and humans have illustrated replacement of the scaffold with vital material with limited to no signs of inflammatory reaction [49, 50]. Twenty-four-month data was encouraging, with significant improvements in all clinical outcome scores and an incidence of treatment failure of 17.3 % [51]. At 5 years, the clinical improvement maintained, but only 62.2 % of the implants survived upon MRI evaluation, questioning the complete efficacy of the implant [52].

13.6 Stem Cell Therapy

Cells are integral to tissue healing and regeneration, because they are necessary for the production and maintenance of extracellular matrix. Stem cells have garnered an exploding interest primarily due to their ability to self-renew and to differentiate into distinctive end-stage cell types. Potential mechanisms of action applying stem cells have focused on the ability of these cells to differentiate into a number of different cell types of orthopedic interest, i.e., cultured cells from bone marrow can be differentiated into chondrocytes, adipocytes, or osteocytes. Recent interest has grown concerning the additional abilities of these cells to mobilize, monitor, and interact with their surrounding environment [53–55] (Fig. 13.3). Stem cells are able to release a broad spectrum of macromolecules with trophic, immunomodulatory, and anti-inflammatory potential, which allows them to participate in injury response, tissue healing, and tissue regeneration. These cells are innate to the body's maintenance, repair, and stress response systems. Basic science and animal study have illustrated the potential of cells with stem potential regardless of their environment/source of harvest, and the interplay of cells

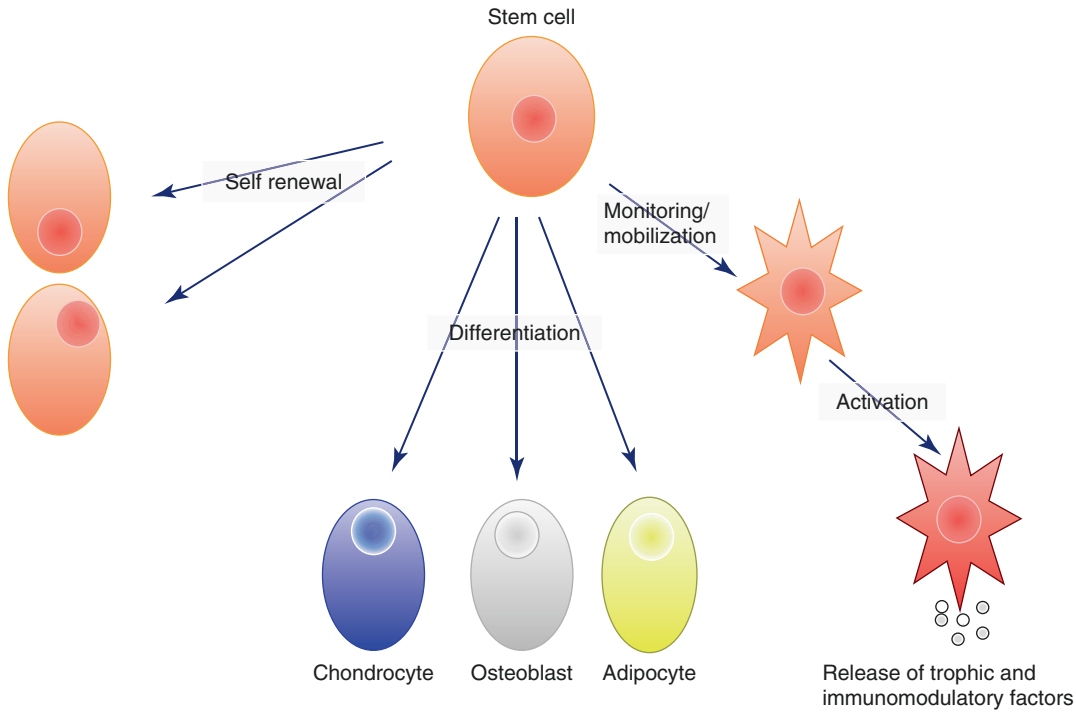

Fig. 13.3 The four cardinal properties of stem cells: proliferation, multipotentiality, monitoring/mobilization, and paracrine function

based upon which environment they reside is not fully understood.

Cells with stem properties are present in many environmental niches, including the bone marrow, adipose tissue, synovial tissue, muscle tissue, and tendon tissue. Two stem cell types, the hematopoietic stem cell (HSC) and perivascular stromal cell (PSC), can be aspirated from bone marrow. The interplay, interaction, and superiority between these two cell types are complex and incompletely understood, and it is unclear which of these cells is the parent cell upon culture [56–59]. Both of these cells have stem properties and have been shown to differentiate to tissues of orthopedic interest [60]. To utilize these cell types, the orthopedic community primarily utilizes point-of-care bone marrow aspiration and concentration, while the hematology-oncology community mobilizes these cells from the bone marrow to the blood stream with pharmaceutical agents and harvests via apheresis. Bone marrow aspiration produces variable numbers of stem cells, with studies ranging from 1 stem cell per mL of tissue collected to 300 thousand stem cells per mL of tissue collected [61]. Mobilization and apheresis can produce large volumes of peripheral blood-derived cells with 600 thousand HSC per mL and 2.32 million PSC per mL of tissue collected [62]. These cells can be stored for serial injections.

In adipose tissue, cells adherent to the abluminal side of blood vessels, known as pericytes, also carry stem qualities. Aspiration and processing of adipose tissue can access these stem cells, producing a product often referred to as stromal vascular fraction (SVF). Processing of lipoaspirate to create stromal vascular fraction requires mechanical or enzymatic processing. This produces variable numbers of stem cells, with quantitative studies ranging from 5 thousand to 1.5 million stem cells per mL of tissue collected [61]. Similar to adipose-derived stem cells, synovial-derived and muscle-derived stem cells also require mechanical or enzymatic processing. For applications involving large numbers of cells, investigators often utilize culturing techniques for all sources with the exception of mobilization and apheresis harvest. As clinicians, three challenges have proven more important than which cell type to utilize: (1) patient-care logistics regarding collection and application, (2) the undefined dose-response curve regarding stem cells, and (3) government/community regulation.

Stem cell studies and the meniscus are currently limited to preclinical animal study and should be divided into studies investigating tissue regeneration and studies investigating methods to improve meniscal repair. Meniscus regeneration studies have evaluated autologous bone marrow-derived cultured mesenchymal stem cells (bMSCs) and synovial-derived cultured mesenchymal stem cells (sMSCs), determining that stem cells carry substantial regeneration potential [63, 64]. The application of meniscus regeneration study to clinical practice requires further development, and review of these studies helps us preview where cell therapy is heading.

One of the earliest studies evaluated the implantation of bMSCs in a hyaluronan/gelatin scaffold into a segmental meniscal defect in rabbits, with integration and meniscus-like fibrocartilage in 8 of 11 rabbits treated with bMSCs and 2 of 11 rabbits treated with a scaffolds alone [63]. This group investigated further whether culture was necessary and whether differentiation of cells was necessary in a similar follow-up study using hyaluronan-collagen matrices and bone marrow aspirate in one group, undifferentiated bMSCs in another group, and bMSCs that had been cultured in a chondrogenic medium to differentiated them toward the fibrochondrocyte lineage [64]. Marrow aspirate did not improve healing. The non-differentiated cultured bMSCs produced the best results with meniscus-like tissue that was fully integrated into the surrounding tissue, while the differentiated bMSCs produced a moderate improvement in healing [64]. This

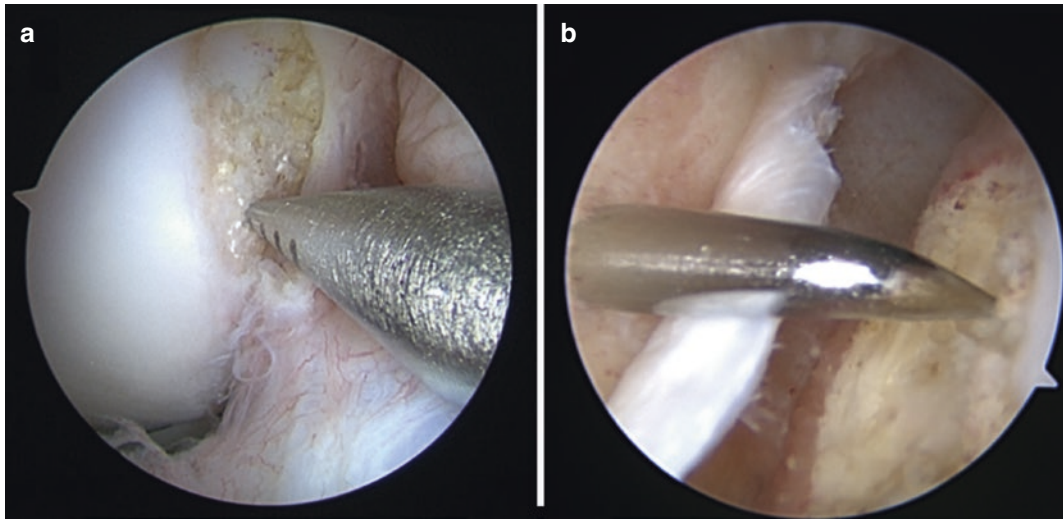

Fig. 13.4 Marrow stimulation is performed at the intercondylar notch (**a**) and outer side of the femoral condyle (**b**) to augment meniscal repair

study leads the authors to theorize that preimplantation differentiation of stem cells may not be necessary. Studies involving sMSCs have involved cultured synovial stem cells injected intra-articularly as opposed to implanted in a scaffold [65–68]. An initial study in rabbits found that labeled sMSCs injected intra-articularly after creation of a cylindrical meniscal defect adhered to the site of the defect, differentiated into cells resembling fibrochondrocytes, and enhanced the quality of meniscal regeneration [65]. This was followed by a massive meniscal defect study illustrating improved regeneration of tissue after one injection of sMSCs compared to a control [66] and a similar massive defect study with three serial injections in a porcine model [67]. An additional group has applied these concepts to a primate model providing histologic evidence of improvement with stem cells in a model more closely resembling humans [68].

There have been two studies regarding cell therapies and the augmentation of meniscal repair. One study evaluated the use of marrow stimulation to improve meniscal healing after the creation of a cylindrical defect (Fig. 13.4). Marrow stimulation of the intercondylar notch improved the quality and quantity of the healing tissue in a rabbit model [69]. Another study which evaluated the use of adipose-derived cultured mesenchymal stem cells (aMSCs) to improve healing rates of longitudinal meniscus tears treated with suture repair in a rabbit model illustrated increased healing rates in the groups treated with aMSCs [70].

Conclusion

The primary challenges of meniscal repair are the limited blood supply, the harsh nature of the biochemical and mechanical nature of the joint, and instances where injury destroys meniscal tissue. As knowledge of the anatomy and biochemistry of the meniscus have improved, biologic options to augment repair have progressed. Synovial abrasion and marrow stimulation are mechanical methods with clear support (Fig. 13.5). Scaffolds have a clearly defined role, while blood- and cell-based products require further refinement before wholehearted, evidence-based use is advocated.

Fig. 13.5 Apheresis allows for the mobilization, harvest (**a**), and storage of a large quantity of stem cells (**b**) which allows serial injection throughout the healing phase of the meniscus. This process is currently under development with an FDA observed trial

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