Chapter 12
Tissue Engineering of Ligaments and Tendons

Patrick Vavken and Martha M. Murray

In the past, much of orthopedic surgery has been characterized by surgical repair of tissues that heal effectively and resection and replacement of tissues that do not. Replacement has been with metal, ceramic, or plastic (total joint replacement) or with grafts (ACL reconstruction, meniscal transplant). With the discovery of the cellular and molecular events preventing the tissues within joints to heal, new approaches to specifically address the problems of intra-articular tissue healing have been developed to assist with the move from tissue resection and replacement towards tissue repair and regeneration.

In the late 1990s, a paradigm shift from replacement to regeneration was initiated in general surgery, a trend that quickly spread to orthopedic research and more slowly to orthopedic clinical practice. This new paradigm underscores the enhancement of intrinsic healing. One of the most effective tools in this endeavor is tissue engineering. In a landmark publication, tissue engineering was defined as "interdisciplinary field in which the principles of engineering and the life sciences are applied towards the generation of biologic substitutes aimed at the creation, preservation or restoration of lost organ function" [1]. Briefly, these biological substitutes are made from a combination of three constituents: (1) cells, (2) biomaterial, and (3) signals. Cells can be of any type, including fully differentiated cells, such as cartilage cells (chondrocytes), tendon cells (tenocytes), ligament cells (fibroblasts) or the more flexible progenitor (stem) cells that can become one of many different

P. Vavken, MD, MSc (✉)
Department of Orthopedic Surgery, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA
e-mail: patrick.vavken@childrens.harvard.edu

M.M. Murray, MD
Department of Orthopedic Surgery, Division of Sports Medicine, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA
e-mail: martha.murray@childrens.harvard.edu

M.M. Murray et al. (eds.), *The ACL Handbook: Knee Biology, Mechanics, and Treatment*, DOI 10.1007/978-1-4614-0760-7_12,

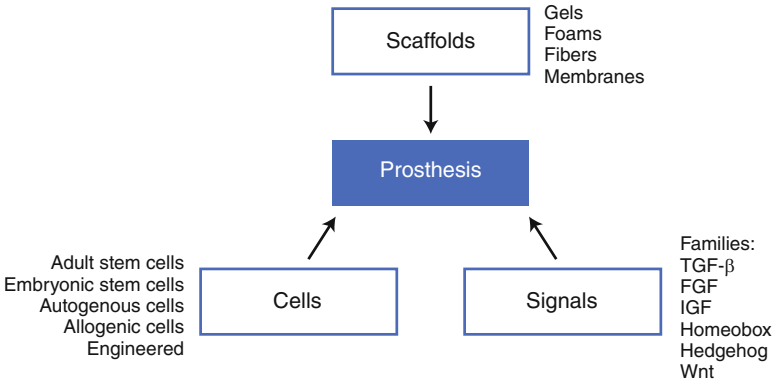

Fig. 12.1 *The triad of tissue engineering*. Tissue engineering rests in three pillars: cells, signals, and biomaterials. Combinations of these three pillars are used to enhance tissue healing, support tissue function, or substitute lost tissues. It is important to remember that constituents from each pillar can have more than one function. Collagen, for example, is a biomaterial but also a signal for platelets to release growth factors. Cells can lump together and form their own biomaterials, or the condensation of cells can act as a signal initiating differentiation

cell types. These cells are usually seeded into a biomaterial (scaffold) that supports cell growth and gives structural stability. Lastly, signals such as growth factors or hormones are used to channel cell differentiation and regulate their biosynthetic activity (Fig. 12.1).

Do We Need Tissue Engineering in ACL Treatment?

Earlier chapters in this book have described the epidemiology of ACL injuries and the problems associated with ACL healing; thus, this content will only be repeated very briefly here. The ACL is quintessential for stability and thus the function of the knee. Tears of the anterior cruciate ligament cause pain and instability and predispose patients to osteoarthritis in long term.

As discussed in Chap. 2, direct repair for the ACL was proposed as a treatment early as 1895, and this technique was further developed well into the 1970s and 1980s [2]. However, a number of studies showed poor outcome after primary repair, and this technique was subsequently abandoned [3, 4]. The current gold standard in ACL treatment is removal of the torn ACL tissue and then replacement with either autologous (patient's own) patellar, hamstring, or quadriceps tendon. Allografts from cadavers, as well as synthetic grafts, are available, but their use is limited by availability and the potential of disease transmission in the former and inflammatory reactions of the foreign body type and medium term failures in the latter. Modern techniques in ACL reconstruction have consistently produced satisfactory results in

joint stability, range of motion, and pain. However, recent studies have presented evidence of relatively high rates of premature osteoarthritis despite ACL reconstruction, even after controlling for other intra-articular damage caused by the initial trauma [5–8].

Given this need for highly effective therapies for these increasingly common diseases, ligament and tendon tissue engineering might very well become a valuable addition to the armamentarium of regenerative medicine in this field.

What Can We Learn from Healthy Ligaments?

When developing a new ACL treatment, be it tissue engineering based or not, it is crucial to familiarize oneself with how a healthy ACL functions. With this as a guide, one can establish targets and directions for a new treatment. The purpose of the ACL is to withstand tensile forces. The healthy ACL supports loads of about 450N during normal activities [9] and will withstand up to 2000N before failing [9]. These mechanical properties are a direct result of the strong tensile characteristics of the aligned collagen protein that makes up the majority of the ligament and resist the tensile loads. Frank and Amiel described dense type I collagen bundles, with additional smaller amounts of type III collagen and glycosaminoglycans in ligaments [9, 10]. On the structural level, both cells and fibers exhibit an undulating pattern, called crimp, which allows for the ligament to stretch up to 6 % before permanent damage starts to happen (Fig. 12.2).

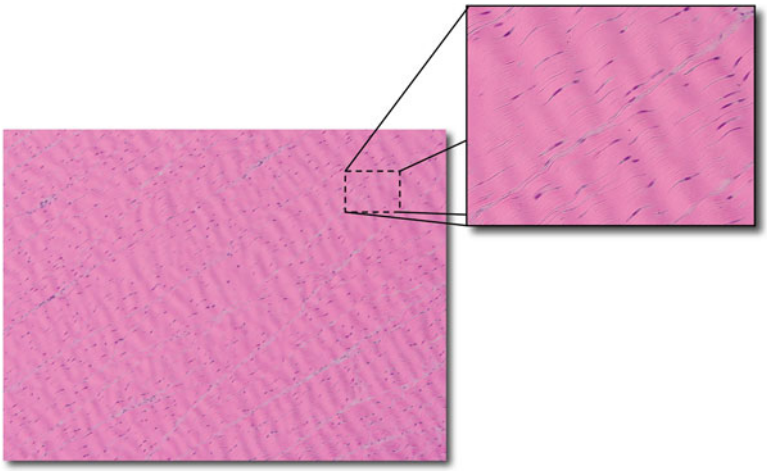

Fig. 12.2 *Crimp*. A healthy ligament exhibits a crimp or a wavy structure that can be seen in light microscopy. This crimp has a major implication in the biomechanics of the tissue. At higher magnification (smaller panel), one can observe that the cells in the tissue follow the crimp closely. Reestablishing crimp is a critical parameter in tissue engineering of ligaments

Healing of ligaments depends on a number of factors. It is commonly accepted that tears of the anterior cruciate ligament will not heal, while tears of the medial collateral ligament heal spontaneously. Rotator cuff tendon tears do not heal while Achilles tendon tears do. Both the ACL and torn rotator cuff tendon are inside the joint (intrasynovial) in humans, and it is thought that they fail to heal due to factors of the intra-articular environment.

A blood clot that forms in the wound site for tissues outside the joint (extrasynovial) serves as a provisional scaffold for inflammatory cell attachment and as a source of stimulatory cytokines from platelet activation. Within this clot, the damaged tissue is absorbed and new tissue is produced. In intrasynovial tissues, the formation of such a blood clot does not occur [11], a fact that is attributed to mechanical factors of the fluid environment as well as biochemical factors such as the presence of activated plasmin in the injured joint. Without a provisional scaffold, the wound site remains empty and the injured ends of the tissue are covered by proliferating synovial cells and retract due to the production of smooth muscle actin-alpha (a contractile protein) in the ligament itself. Bridging the wound site of an intra-articular ligament with a material that could encourage local cell ingrowth and stimulate collagen production in the wound site may be a critical step in healing of tissues within joints.

Tissue engineering is a logical solution for the lack of a scaffold within the ACL wound site. The success of such treatment in vivo should be evaluated by the mechanical strength of the implanted construct over time, which is a function of both the quantitative and qualitative reproduction of cell-matrix interactions. Its clinical success has to be judged in the light of long-term effectiveness at limiting further joint deterioration including cartilage damage, since this is the area of weakness in current treatments.

The composition of the tissue engineering construct, in terms of cells, biomaterials, and signals, should be carefully chosen for any application. Thus, before discussing more complicated tissue engineering-based ACL treatments, a look at the three variables of cells, biomaterials, and signals will be presented.

Cell Sources

Various kinds of cells have been studied for their potential in ACL tissue engineering. An ideal cell source would provide cells with a high proliferation rate and a high biosynthetic activity to build and remodel the ligament as fast and accurately as possible. Fibroblasts of different origins have been extensively studied, following the logic that highly differentiated cells possess all the phenotypic properties necessary to produce and maintain an adequately composed extracellular matrix.

Like currently employed cartilage repair procedures involving scaffolds seeded with chondrocytes, fibroblasts could potentially be obtained for seeding in a ligament scaffold in an initial arthroscopic procedure. Like articular cartilage procedures, this arthroscopy could be performed weeks before the repair procedure. The cells obtained during the initial arthroscopy could be taken to the lab and cultured and stimulated to proliferate until enough cells were present for reimplantation into the injured knee.

Another option would be a one-step technique in which fibroblasts would be isolated in the operating room and directly reimplanted, although low cell numbers might limit such a method. It has been shown by Murray et al. that the fibroblasts from the human ACL are viable long after the initial ACL trauma, and that they are able to migrate into a biomaterial used for tissue engineering-augmented ACL repair [12, 13].

The major problems associated with using differentiated adult fibroblasts are their fairly low proliferation rates and relative scarcity. This has led investigators to consider another cell source: undifferentiated mesenchymal progenitor cells (MPC). These cells can be obtained in relatively high numbers from the bone marrow or other adult tissues. They have a high proliferation rate and the potential to differentiate into multiple different cell types.

However, there is a small but persisting risk of faulty differentiation of MPC that might lead to problems in a clinical application. For example, pluripotential cells implanted to stimulate ligament healing might instead head down the osteogenesis pathway and form spicules of bone within the ligament. This could cause stress risers within the ligamentous tissue and make it easier for the tissue to fail. In addition, the classic way to obtain MPC is a bone marrow biopsy, which is a technically straightforward, yet considerably painful procedure.

Biomaterials

After choosing a cell source, an appropriate scaffolding or biomaterial that satisfies a number of stipulations has to be selected. A suitable scaffold should foster tissue remodeling by providing an environment that stimulates cellular attachment, growth, and biosynthetic activity. Biocompatibility and degradation rates that match tissue remodeling are also likely to be important. Additionally, safety is an important issue, since some biomaterials might provoke inflammatory responses, cause arthrofibrosis, and lead to loss of joint function or systematic adverse reactions. Finally, the biomaterial has to be chosen according to the planned procedure. Tensile strength is less important than enhancement of cellular behavior in primary repair, where the suture repair carries the load, while it is pivotal for scaffolds chosen as an ACL graft.

Natural polymers have a long and successful history in tissue engineering, and collagen is an obvious choice for a tissue-engineered ligament. Collagen, a natural polymer, is and has been in clinical use for decades in suture materials and clotting agents. Its safety profile is well established. Collagen is also used as biomaterial in clinically available tissue engineering methods such as autologous chondrocyte implantation and has been shown to enhance cellular phenotypes in this application [14] (Fig. 12.3). Bovine collagen has been used in multiple studies to establish and sustain fibroblast cultures, yet with somewhat inconsistent results [16, 17]. However, the effect of collagen on cellular behavior depends not only on its mere presence but also on material characteristics such as pore size, cross-linking, and fiber diameter [14, 15]. Other natural polymers that have been studied include hyaluronic acid, fibrin, and chitosan-alginate. Hyaluronic acid is a well-known biomaterial in tissue engineering and has been shown to beneficially influence cellular behavior. Wiig and

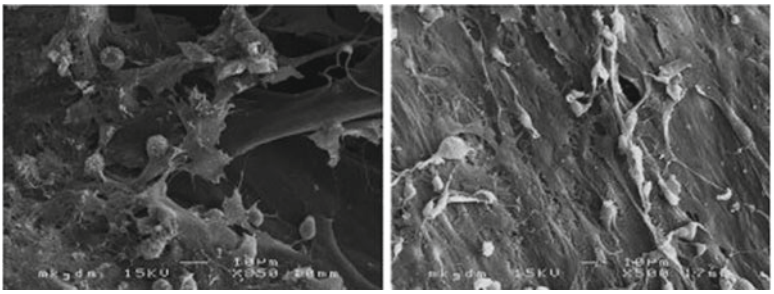

Fig. 12.3 *Collagen biomaterial*. This figure shows an electron microscopy picture of chondrocytes on a collagen matrix. The cells adhere to the surface of the biomaterial and express the same morphology that we have seen in earlier cell culture pictures (cf. Fig. 10.1) (Used with permission from Dorotka et al. [15])

coworkers reported improved healing of a central ACL defect after injection of hyaluronic acid in a rabbit model [18]. Cristino et al. showed mesenchymal progenitor cell growth and differentiation in a modified hyaluronic-acid-based scaffold [19]. Hyaluronic acid has also been shown to have a beneficial effect in the prevention of osteoarthritis in anterior cruciate deficient knees [20, 21]. Fibrin has the advantage of producing a biodegradable scaffold when mixed with thrombin.

Biomaterials like poly(lactic acid), poly(glycolic acid), and other synthetic polymers have been used as suture materials with much success and minimal adverse events. The advantage of these polymers is that their composition can be controlled and adjusted for specific purposes. With modern processing techniques, these polymers can be spun into microfibers, which have been proven to enhance cell attachment by a high area to volume ratio and beneficial properties in mass transport of nutrients [22]. Additionally, these polymers have convincing mechanical properties. Of special interest is silk, which holds a position at the intersection between naturally occurring and synthetically modified materials. Silk in its native form is coated with sericin – a glue-like protein which can cause an immune reaction in humans. Modification of silk by removing the sericin yields an inert, biocompatible material with excellent mechanical properties, similar to the native ACL. Silk has also been used successfully as a scaffold for fibroblasts and shown to enhance fibroblastic differentiation of mesenchymal progenitor cells [23].

Growth Factors and Signaling Molecules

Signaling is the third factor in the triad of tissue engineering. Signaling can be used to direct cellular activity to achieve the desired outcome in terms of cell growth or matrix production. Growth factors that have been associated with cell growth and differentiation were studied initially in an effort to identify factors that would be beneficial in wound repair. Transforming growth factor beta (TGF-β), insulin-like growth factor (IGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) have been shown to improve growth and bioactivity

of fibroblasts [24]. On the other hand, various growth factors, such as TGF and vascular endothelial growth factor (VEGF), have been shown to be produced by fibroblasts themselves and thus have also been investigated for their use in tissue engineering of ligaments and tendons [25, 26]. However, the effects of many growth factors are still not completely understood and how to combine these and optimize their function is difficult to say the least. In one elegant study, the investigators used a carefully chosen growth factor cocktail in tendon repair and were able to get the desired high increase in cell growth. However, this was associated with a mechanically inferior scar [27]. Thus, even careful and thoughtful planning and design may not translate into the desired effect in vivo.

Another very important source of cell stimuli is the physical and mechanical environment of the cells. The structure of the biomaterial selected as the scaffold, in terms of both chemical composition and structural properties, has been shown to stimulate cell attachment, growth, differentiation, and biosynthesis. Mechanical stimuli such as tensile and torsional stress also affect cellular behavior. However, little is known about the details of these effects and the interactions between them. Hence, the directed use of these stimuli in tissue engineering, beyond a general beneficial effect, is not yet possible.

Approaches to Clinical ACL Tissue Engineering

Generally, two philosophies exist in the management of the torn ACL: replacement using a graft or primary repair. Either of these techniques may potentially be enhanced using tissue engineering. For a replacement (also called an "ACL reconstruction"), a graft or synthetic material is used to replace the entire ACL. In this case, cells and scaffolds could be used to enhance the healing of a tendon graft or synthetic ligament to the bone. Advantages of the reconstructive approach are immediate mechanical function and a minimal change from currently used techniques, thus avoiding a steep learning curve. However, the immediate mechanical strength also introduces the potential problem of stress shielding. Stress shielding, where the load is taken by the implanted scaffold rather than the tissue developing within it, can deprive cells of important mechanical stimuli to drive their bioactivity. A bio-artificial ACL has been presented by Goulet et al. [28]. Briefly, this group suggested a complete substitute consisting of two bone plugs connected with a surgical thread. During culture cells attach to this thread and deposit a matrix rich in type I collagen thus building a ligament-like structure (Fig. 12.4). This graft healed well in a goat model and showed tissue ingrowth and vascularization in histology. After 13 months it showed 36 % of the mechanical strength of a normal goat ligament. In a similar approach, Ma et al. from the University of Michigan generated a multiphasic (bone-ligament-bone) ACL construct from bone marrow stem cells (BMSC). Briefly, BMSC were cultured in vitro from either bone or ligament and then combined to a functional graft of approx 80 mm length and 3 mm diameter. These constructs were implanted into sheep after ACL excision and the animals were followed for up to 6 months. At this time, histological and biomechanical

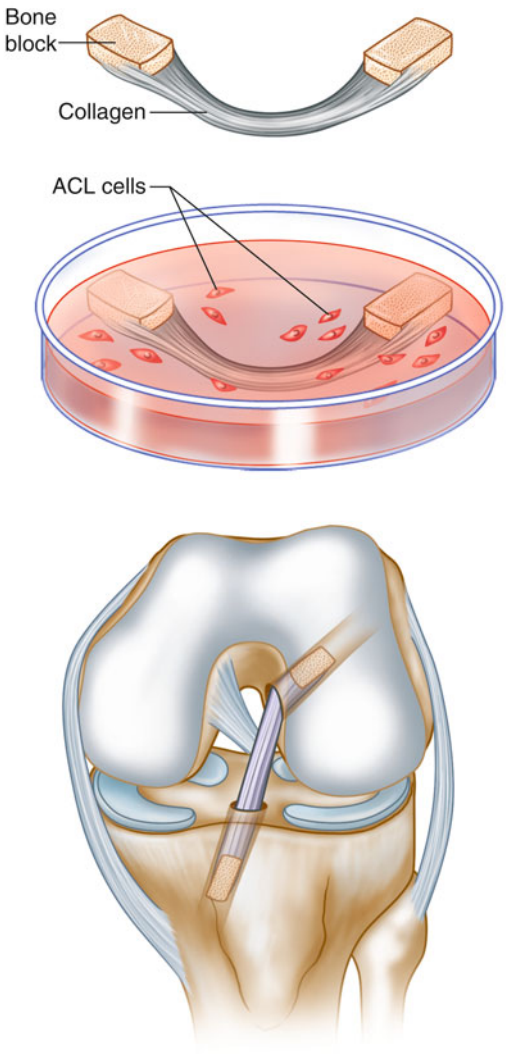

Fig. 12.4 *An artificial ACL.* The *top panel* shows an artificial ACL, that is, collagen fibers attached to bone blocks. In the *middle panel*, this construct is kept in cell culture and ligament cells are cultured on the collagen fibers. Finally, the cell-laden graft is implanted into a goat knee (*lower panel*). Goulet et al. [28]

assessment showed vascularization and innervation of the graft, as well as good bone integration and biomechanics very close to the contralateral, normal knees.

Another approach aims at using tissue engineering to enhance primary repair. The rationale of this approach is that the intricate nature of the ligament insertion, proprioceptive nerves and the complex architecture of the ligament are preserved. Furthermore, the ACL remnants can serve as reservoirs of fibroblasts. Murray and coworkers have described the specifics of such an approach in much detail. In summary, they demonstrated that human fibroblasts remain viable in the ACL stump and are able to migrate into a collagen scaffold as could be used in a bio-enhanced primary repair procedure [12, 13]. Addition of platelet-rich plasma to this scaffold was shown to promote cellular migration and proliferation in a central defect model, thus stimulating healing [29]. Further examination revealed good defect filling in

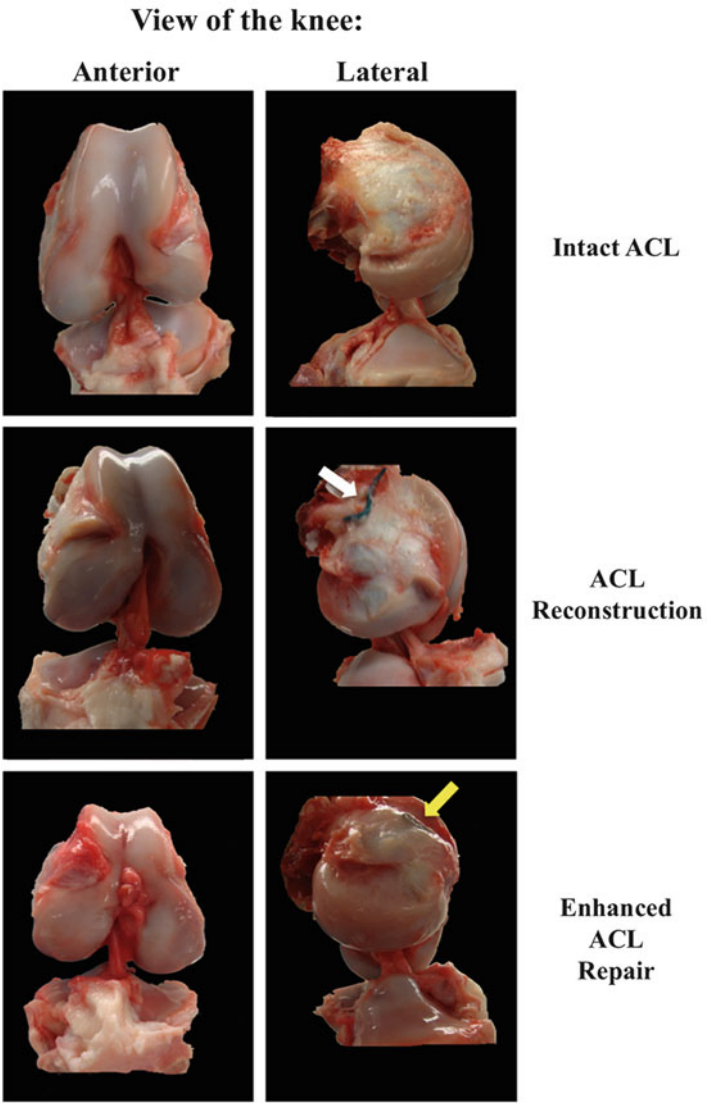

Fig. 12.5 *Tissue engineering enhanced ACL repair*. An alternative to ACL replacement, with a tissue graft or an artificial ACL, is tissue engineering-enhanced ACL repair. Briefly, the torn ends are sutured together and a biomaterial-signal composite is used to enhance healing. In the figure, we can see a normal ACL, an ACL reconstruction (15 weeks after the procedure), and an enhanced ACL repair (15 weeks after the procedure), all from a pig model. The *arrows* show the fixation devices for the surgical procedures. Biomechanical comparison at 15 weeks showed no difference in the strength of an ACL reconstruction or ACL repair (Reprinted from *Arthroscopy*, vol 28, Patrick Vavken et al. [32], with permission from Elsevier)

histology [30]. In a more challenging animal model, complete transections of the ACL in pigs were repaired using the same technique, and significant improvement in mechanics was shown [31] (Fig. 12.5).

Conclusions

Tissue engineering uses combinations of cells, scaffolds, and growth factors to form a biomaterial that can be used to replace or regenerate injured tissues. Cell choices include those found in the mature tissue of interest (i.e., fibroblasts for ligament engineering) or cells that are found in the developing tissue (e.g., mesenchymal stem cells) that can be coerced into turning into the desired cell type. Cells can also be implanted with a scaffold or encouraged to migrate into a scaffold from their residence in the local environment of the wound. Scaffolds can be mechanically strong, particularly for replacing load-bearing structures, or they can be purely biologic in function, as in supplementing a suture repair where the sutures will carry the load and the scaffold provides the biology. The desired signaling molecules may be multiple and complex as presented in the prior chapter on wound healing, thus autologous cells capable of releasing these factors over days to weeks might be useful as sustained delivery systems. The possible combinations of these three elements provide enormous flexibility and potential for regenerating musculoskeletal tissues.

Acknowledgement Research reported in this chapter was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Numbers RO1-AR054099 and RO1-AR056834. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Langer R, Vacanti JP. Tissue engineering. Science. 1993;260(5110):920–6.
2. Mayo Robson A. Ruptured cruciate ligaments and their repair by operation. Ann Surg. 1903;37:716–8.
3. Sandberg R, Balkfors B, Nilsson B, Westlin N. Operative versus non-operative treatment of recent injuries to the ligaments of the knee. A prospective randomized study. J Bone Joint Surg Am. 1987;69(8):1120–6.
4. Feagin Jr JA, Curl WW. Isolated tear of the anterior cruciate ligament: 5-year follow-up study. Am J Sports Med. 1976;4(3):95–100.
5. Ferretti A, Conteduca F, De Carli A, Fontana M, Mariani PP. Osteoarthritis of the knee after ACL reconstruction. Int Orthop. 1991;15(4):367–71.
6. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004;50(10):3145–52.
7. Spindler KP, Warren TA, Callison Jr JC, Secic M, Fleisch SB, Wright RW. Clinical outcome at a minimum of five years after reconstruction of the anterior cruciate ligament. J Bone Joint Surg Am. 2005;87(8):1673–9.
8. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. Ann Rheum Dis. 2004;63(3):269–73.
9. Frank C, Amiel D, Woo SL, Akeson W. Normal ligament properties and ligament healing. Clin Orthop Relat Res. 1985;(196):15–25.
10. Amiel D, Frank C, Harwood F, Fronek J, Akeson W. Tendons and ligaments: a morphological and biochemical comparison. J Orthop Res. 1984;1(3):257–65.

11. Murray MM, Martin SD, Martin TL, Spector M. Histological changes in the human anterior cruciate ligament after rupture. J Bone Joint Surg Am. 2000;82(10):1387–97.
12. Murray MM, Bennett R, Zhang X, Spector M. Cell outgrowth from the human ACL in vitro: regional variation and response to TGF-beta1. J Orthop Res. 2002;20(4):875–80.
13. Murray MM, Spector M. The migration of cells from the ruptured human anterior cruciate ligament into collagen-glycosaminoglycan regeneration templates in vitro. Biomaterials. 2001;22(17):2393–402.
14. Nehrer S, Breinan HA, Ramappa A, et al. Canine chondrocytes seeded in type I and type II collagen implants investigated in vitro. J Biomed Mater Res. 1997;38(2):95–104.
15. Dorotka R, Toma CD, Bindreiter U, Zehetmayer S, Nehrer S. Characteristics of ovine articular chondrocytes in a three-dimensional matrix consisting of different crosslinked collagen. J Biomed Mater Res B Appl Biomater. 2005;72(1):27–36.
16. Bellincampi LD, Closkey RF, Prasad R, Zawadsky JP, Dunn MG. Viability of fibroblast-seeded ligament analogs after autogenous implantation. J Orthop Res. 1998;16(4):414–20.
17. Dunn MG, Liesch JB, Tiku ML, Zawadsky JP. Development of fibroblast-seeded ligament analogs for ACL reconstruction. J Biomed Mater Res. 1995;29(11):1363–71.
18. Wiig ME, Amiel D, VandeBerg J, Kitabayashi L, Harwood FL, Arfors KE. The early effect of high molecular weight hyaluronan (hyaluronic acid) on anterior cruciate ligament healing: an experimental study in rabbits. J Orthop Res. 1990;8(3):425–34.
19. Cristino S, Grassi F, Toneguzzi S, et al. Analysis of mesenchymal stem cells grown on a three-dimensional HYAFF 11-based prototype ligament scaffold. J Biomed Mater Res A. 2005;73(3): 275–83.
20. Smith Jr GN, Mickler EA, Myers SL, Brandt KD. Effect of intraarticular hyaluronan injection on synovial fluid hyaluronan in the early stage of canine post-traumatic osteoarthritis. J Rheumatol. 2001;28(6):1341–6.
21. Sonoda M, Harwood FL, Amiel ME, Moriya H, Amiel D. The effects of hyaluronan on the meniscus in the anterior cruciate ligament-deficient knee. J Orthop Sci. 2000;5(2):157–64.
22. Lee CH, Shin HJ, Cho IH, et al. Nanofiber alignment and direction of mechanical strain affect the ECM production of human ACL fibroblast. Biomaterials. 2005;26(11):1261–70.
23. Chen J, Altman GH, Karageorgiou V, et al. Human bone marrow stromal cell and ligament fibroblast responses on RGD-modified silk fibers. J Biomed Mater Res A. 2003;67(2): 559–70.
24. Deuel T, Chang Y. Growth factors. 3rd ed. Academic Press; Waltham, MA. 2007.
25. Vavken P, Saad FA, Fleming BC, Murray MM. VEGF receptor mRNA expression by ACL fibroblasts is associated with functional healing of the ACL. Knee Surg Sports Traumatol Arthrosc. 2011;19(10):1675–82.
26. Vavken P, Saad FA, Murray MM. Age dependence of expression of growth factor receptors in porcine ACL fibroblasts. J Orthop Res. 2010;28(8):1107–12.
27. Rodeo SA, Potter HG, Kawamura S, Turner AS, Kim HJ, Atkinson BL. Biologic augmentation of rotator cuff tendon-healing with use of a mixture of osteoinductive growth factors. J Bone Joint Surg Am. 2007;89(11):2485–97.
28. Goulet F, Germaine L, Rancourt D, Caron C, Nromand A, Aufer F. Tendons and ligaments. 3rd ed. Elsevier; Amsterdam, Netherlands. 2007.
29. Murray MM, Spindler KP, Devin C, et al. Use of a collagen-platelet rich plasma scaffold to stimulate healing of a central defect in the canine ACL. J Orthop Res. 2006;24(4):820–30.
30. Murray MM, Spindler KP, Ballard P, Welch TP, Zurakowski D, Nanney LB. Enhanced histologic repair in a central wound in the anterior cruciate ligament with a collagen-platelet-rich plasma scaffold. J Orthop Res. 2007;25(8):1007–17.
31. Murray MM, Spindler KP, Abreu E, et al. Collagen-platelet rich plasma hydrogel enhances primary repair of the porcine anterior cruciate ligament. J Orthop Res. 2007;25(1):81–91.
32. Vavken P et al. Biomechanical outcomes after bioenhanced anterior cruciate ligament repair and anterior cruciate ligament reconstruction are equal in a porcine model. Arthroscopy. 2012;28(5):672–80.