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Physiology and Pathophysiology of Musculoskeletal Tissues

Dean Wang, Claire D. Eliasberg, Scott A. Rodeo

TENDON AND LIGAMENT

Structure

Tendons and ligaments are both dense, regularly arranged connective tissues. The surface of the tendon is enveloped in a white, glistening, synovial-like membrane, called the *epitenon*, which is continuous on its inner surface with the *endotenon*, a thin layer of connective tissue that binds collagen fibers and contains lymphatics, blood vessels, and nerves. In some tendons, the epitenon is surrounded by a loose areolar tissue called the *paratenon,* which functions as an elastic sheath through which the tendon can slide. In some tendons, the paratenon is replaced by a true synovial sheath or bursa consisting of two layers lined by synovial cells, called the *tenosynovium*, within which the mesotendon carries important blood vessels to the tendon.[1] In the absence of a synovial lining, the paratenon often is called a *tenovagina*. Together the epitenon and the paratenon compose the *peritenon* (Fig. 1.1). The blood supply to tendons has several sources, including the perimysium, periosteal attachments, and surrounding tissues. Blood supplied through the surrounding tissues reaches the tendon through the paratenon, mesotenon, or vincula. Vascular tendons are surrounded by a paratenon and receive vessels along their borders; these vessels then coalesce within the tendon. The relatively avascular tendons are contained within tendinous sheaths, and the mesotenons within these sheaths function as vascularized conduits called *vincula*. The muscle-tendon and tendon-bone junctions, along with the mesotenon, are the three types of vascular supply to the tendon inside the sheath. Other sources of nutrition[2] include diffusional pathways from the synovial fluid, which provide an important supply of nutrients for the flexor tendons of the hand, for example. The nervous supply to a tendon involves mechanoreceptors located near the musculotendinous junction, which provide proprioceptive feedback to the central nervous system.

Ligaments grossly appear as firm, white fibrous bands, sheets, or thickened strips of joint capsule securely anchored to bone. They consist of a proximal bone insertion, the substance of the ligament or the capsule, and a distal bone insertion. Because most insertions are no more than 1 mm thick, they contribute only a small amount to the volume and the length of the ligament. Bundles of collagen fibrils form the bulk of the ligament substance.[3–5] Some ligaments consist of more than one band of collagen fibril bundles. For example, the anterior cruciate ligament (ACL) has a continuum of fiber lengths; different fibers become taut throughout the range of motion.[6] The alignment of collagen fiber bundles within the ligament substance generally follows the lines of tension applied to the ligament. This is in contrast to the alignment of collagen fiber bundles within the tendon, which is generally parallel to its longitudinal axis. In addition, thinner collagen fibrils extend the entire length of the tendon. Light microscopic examination has shown that the collagen bundles have a wave or crimp pattern. The crimp pattern of matrix organization may allow slight elongation of the ligament without incurring damage to the tissue.[6] In some regions, the ligament cells align themselves in rows between collagen fiber bundles, but in other regions, the cells lack apparent orientation relative to the alignment of the matrix collagen fibers. Scattered blood vessels penetrate the ligament substance, forming small-diameter, longitudinal vascular channels that lie parallel to the collagen bundles. Nerve fibers lie next to some vessels, and, like tendon, nerve endings with the structure of mechanoreceptors have been found in some ligaments.[4,7,8]

Tendon and ligament insertions vary in size, strength, angle of the ligament collagen fiber bundles relative to the bone, and proportion of ligament collagen fibers that penetrate directly into bone.[4,5,9] Based on the angle between the collagen fibrils and the bone and the proportion of the collagen fibers that penetrate directly into bone, investigators group tendon and ligament insertions into two types: direct and indirect. Direction insertions typically occur at the apophysis or epiphysis of bone, often within or around a synovial joint, and consist of sharply defined regions where the collagen fibers appear to pass directly into the cortex of the bone.[9,10] Although the thin layer of superficial collagen fibers of direct insertions joins the fibrous layer of the periosteum, most of the tendon or ligament insertions consist of deeper fibers that directly penetrate the cortex, often at a right angle to the bone surface. The deeper collagen fibers pass through four zones with increasing stiffness: ligament substance, fibrocartilage, mineralized fibrocartilage, and bone.[9,10] This four-zone interface is known as the fibrocartilaginous enthesis.[11] Dissipation of force is achieved effectively through this gradual transition from tendon to fibrocartilage to bone. A larger area of fibrocartilage can be found on one side of the insertion, which is thought to be an adaptation to the compressive forces experienced by the tendon or ligament on that side.[12] Conversely, indirect or oblique insertions, such as the tibial insertion of the medial collateral ligament of the knee or the femoral insertion of the lateral collateral ligament, typically occur at the metaphysis

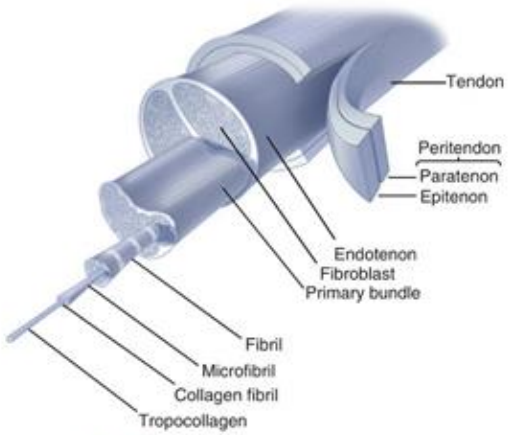

Fig. 1.1 Structural organization of tendon.

or diaphysis of bone without an intervening fibrocartilage zone. They usually cover more bone surface area than do direct insertions, and their boundaries cannot be easily defined because the collagen fibers pass obliquely along the bone surface rather than directly into the cortex.

Extracellular Matrix

Tendons and ligaments consist of relatively few cells and an abundant extracellular matrix primarily containing collagen, proteoglycans, and water. Tenocytes (tendon-specialized fibroblasts) are the dominant cell of tendons, whereas fibroblasts are the dominant cells of ligaments. Tenocytes and fibroblasts form and maintain the extracellular matrix. Within ligaments, fibroblasts vary in shape, activity, and density among regions of the same tissue and with the age of the tissue.[4,5,9,13] Both tenocytes and fibroblasts are spindle shaped, with fibroblasts being rounder, and extend between the collagen fibrils.[14] Endothelial cells of small vessels and nerve cell processes are also present.[4,5,9,13] Studies have shown that tendon and ligament contain a small population of resident stem cells which function to maintain tissue homeostasis during growth and repair.[15–17]

Type I collagen, which is the major component of the molecular framework, composes more than 90% of the collagen content of ligaments. Type III collagen constitutes approximately 10% of the collagen, and small amounts of other collagen types also may be present. Ligaments have a higher content of type III collagen than do tendons.[18] All types of collagen have in common a triple helical domain, which is combined differently with globular and nonhelical structural elements. The triple helix conformation of collagen is stabilized mainly by hydrogen bonds between glycine residues and between hydroxyl groups of hydroxyproline. This helical conformation is reinforced by hydroxyproline-forming and proline-forming hydrogen bonds to the other two chains. The physical properties of collagen and its resistance to enzymatic and chemical breakdown rely on covalent cross-links within and between the molecules.

Elastin is a protein that allows connective tissues to undergo large changes in geometry while expending little energy in the process. Tendons of the extremities possess small amounts of this structural protein, whereas most ligaments have little elastin (usually less than 5%), although a few, such as the nuchal ligament and the ligamentum flavum, have high concentrations (up to 75%). In most tendons, elastin is found primarily at the fascicle surface,[19] comprising less than 1% of the tendon by dry weight, and it is responsible for the crimp pattern of the tendon when viewed by a light microscope. Elastin forms protein fibrils or sheets, but elastin fibrils lack the cross-banding pattern of fibrillar collagen and differ in amino acid composition, including two amino acids not found in collagen (desmosine and isodesmosine). In addition, unlike collagen, elastin amino acid chains form random coils when the molecules are unloaded. This conformation of the amino acid chains makes it possible for elastin to undergo some deformation without rupturing or tearing and then, when the load is removed, to return to its original size and shape.

Approximately 1% of the total dry weight of tendon and ligament is composed of ground substance, which consists of proteoglycans, glycosaminoglycans, structural glycoproteins, plasma proteins, and a variety of small molecules. Most ligaments have a higher concentration of glycosaminoglycans than do tendons, due to the functional need for more rapid adaptation.[18] Proteoglycans and glycosaminoglycans both have important roles in organizing the extracellular matrix and control the water content of the tissue.[4,20–23] Tendon and ligaments contain two known classes of proteoglycans. Larger proteoglycans contain *long* negatively charged chains of chondroitin and keratan sulfate. Smaller proteoglycans contain dermatan sulfate. Because of their long chains of negative charges, the large articular cartilage-type proteoglycans tend to expand to their maximal domain in solution until restrained by the collagen fibril network. As a result, they maintain water within the tissue and exert a swelling pressure, thereby contributing to the mechanical properties of the tissue and filling the regions between the collagen fibrils. The small leucine-rich proteoglycans usually lie directly on the surface of collagen fibrils and appear to affect formation, organization, and stability of the extracellular matrix, including collagen fibril formation and diameter. They may also control the activity of growth factors by direct association.[21,24]

Although noncollagenous proteins contribute only a small percentage of the dry weight of dense fibrous tissues, they appear to help organize and maintain the macromolecular framework of the collagen matrix, aid in the adherence of cells to the framework, and possibly influence cell function. One noncollagenous protein, fibronectin, has been identified in the extracellular matrix of ligaments and may be associated with several matrix component molecules and with blood vessels. Other noncollagenous proteins undoubtedly exist within the matrix, but their identity and their functions have not yet been defined. Many of the noncollagenous proteins also contain a few monosaccharides and oligosaccharides.[4,5]

Injury

Acute strains and tears to tendons and ligaments disrupt the matrix, damage blood vessels, and injure or kill cells. Damage to cells, matrices, and blood vessels and the resulting hemorrhage

start a response that leads to a sequential process of inflammation, repair, and remodeling.[25,26] These events form a continuous sequence of cell, matrix, and vascular changes that begins with the release of inflammatory mediators and ends when remodeling ceases.[25] As with any injury to biologic tissue, acute inflammation lasts 48 to 72 hours after the injury and then gradually resolves as repair progresses. Some of the events that occur during inflammation, including the release of cytokines or growth factors, may help to stimulate tissue repair.[25] These mediators promote vascular dilation and increase vascular permeability, leading to exudation of fluid from vessels in the injured region, which causes tissue edema. Blood escaping from the damaged vessels forms a hematoma that temporarily fills the injured site. Fibrin accumulates within the hematoma, and platelets bind to fibrillar collagen, thereby achieving hemostasis and forming a clot consisting of fibrin, platelets, red cells, and cell and matrix debris. The clot provides a framework for vascular and fibroblast cell invasion. As they participate in clot formation, platelets release vasoactive mediators and various cytokines or growth factors (e.g., transforming growth factor-β [TGF-β] and platelet-derived growth factor). Polymorphonuclear leukocytes appear in the damaged tissue and the clot. Shortly thereafter, monocytes arrive and increase in number until they become the predominant cell type. Enzymes released from the inflammatory cells help to digest necrotic tissue, and monocytes phagocytose small particles of necrotic tissue and cell debris. Endothelial cells near the injury site begin to proliferate, creating new capillaries that grow toward the region of tissue damage. Release of chemotactic factors and cytokines from endothelial cells, monocytes, and other inflammatory cells helps to stimulate migration and proliferation of the fibroblasts that begin the repair process.[25]

Overuse tendon injury is one of the more common forms of musculoskeletal injury and clinical causes of pain, although controversy exists in the literature about a universal classification and the responsible pathologic entities. A classification of Achilles tendon disorders[27] provides a guide to the structural manifestations of overuse injury as follows: (1) peritendinitis, or inflammation of the peritenon; (2) tendinosis with peritendinitis; (3) tendinosis without peritendinitis; (4) partial rupture; and (5) total rupture. Other classifiers have added a sixth category, tendinitis, in which the primary site of injury is the tendon, with an associated reactive peritendinitis.[28] The classification is not universal because some tendons lack a paratenon and instead have synovial sheaths; furthermore, it is unclear if certain histopathologic conditions are actually separate entities. For instance, human biopsy studies have been unable to show histologic evidence of acute inflammation within the tendon substance.[29] Because of uncertainty regarding the histologic features of these conditions, several authors have suggested use of the term *tendinopathy* rather than *tendinitis*.[30,31]

Studies have shown that in cases of chronic tendinosis, the pathologic lesion is typical of a degenerative process rather than an inflammatory one and that this degeneration occurs in areas of diminished blood flow. Several authors have documented the existence of areas of marked degeneration without acute or chronic inflammatory cell accumulation in most of these cases.[32–34] These changes are separate and distinct from the site of rupture. A review of patients with chronic tendinitis syndrome revealed similar findings of tendon degeneration.[27,35] Nirschl[35] described the pathology of chronic tendinitis as "angiofibroblastic hyperplasia." A characteristic pattern of fibroblasts and vascular, atypical, granulation-like tissue can be seen microscopically.[35,36] Cells characteristic of acute inflammation are virtually absent. These observations suggest that factors other than mechanical overuse play an important role in the pathogenesis of these tendon lesions.

In several studies, a correlation between age and the incidence of chronic tendinopathy has been identified.[37,38] In vitro studies have shown decreased proliferative and metabolic responses of aging tendon tissue.[39] Other causative factors include the lack of blood flow in certain areas (e.g., supraspinatus and Achilles tendon) that may predispose a tendon to rupture or may result in chronic tendinopathy.[40] Biopsy specimens of young patients with symptoms of chronic tendinopathy have revealed a change in the morphology of tenocytes adjacent to areas of collagen degeneration.[28]

Repair

Tendons and ligaments may possess both intrinsic and extrinsic capabilities for healing, and the contribution of each of these two mechanisms probably depends on the location, extent, and mechanism of injury and the rehabilitation program used after the injury. Several studies[2,41–46] have suggested that the inflammatory response is not essential to the healing process and that these tissues possess an intrinsic capacity for repair. Recent research has isolated intrinsic stem cells within tendon and ligament, although their in vivo identities, niche, and role in healing remain controversial.[17,47] Lindsay and Thomson[43] were the first to show that an experimental tendon suture zone can be isolated from the perisheath tissues and that healing progressed at the same rate as when the perisheath tissues were intact. Later, in isolated segments of profundus tendon in rabbits, these researchers found anabolic and catabolic enzymes, which showed that an active metabolic process existed in the isolated tendon segments.[44]

As in other areas in the body, tendon healing proceeds in three phases: (1) an inflammatory stage, (2) a reparative or collagen-producing stage, and (3) a remodeling phase.

Inflammatory Phase

Tendon and ligament healing begins with hematoma formation and an inflammatory reaction that includes an accumulation of fibrin and inflammatory cells. A clot forms between the two ends and is invaded by cells resembling fibroblasts and migratory capillary buds. Within 2 to 3 days of the injury, fibroblasts within the wound begin to proliferate rapidly and synthesize new matrix. They replace the clot and the necrotic tissue with a soft, loose fibrous matrix containing high concentrations of water, glycosaminoglycans, and type III collagen. Inflammatory cells and fibroblasts fill this initial repair tissue. Within 3 to 4 days, vascular buds from the surrounding tissue grow into the repair tissue and then canalize to allow blood flow to the injured tissue and across small tissue defects. This vascular granulation tissue fills the tissue defect and extends for a short distance into the surrounding tissue but has little tensile strength. The inflammatory phase is evident until the 8th to 10th day after injury.

Reparative Phase

As the repair progresses during the next several weeks, proliferating fibroblasts continue to produce fibrous tissue containing a high proportion of type III collagen. Collagen synthesis reaches its maximal level after approximately 4 weeks, and at 3 months, collagen synthesis continues at a rate 3 to 4 times that of normal tissue. Over time, water, glycosaminoglycan, and type III collagen concentrations decline, the inflammatory cells disappear, and the concentration of type I collagen increases. Newly synthesized collagen fibrils increase in size and begin to form tightly packed bundles, and the density of fibroblasts decreases. Matrix organization increases[48–51] as the fibrils begin to align along the lines of stress, the number of blood vessels decreases, and small amounts of elastin may appear within the site of injury. The tensile strength of the repair tissue increases as the collagen concentration increases.

Remodeling Phase

Repair of many tendon and ligament injuries results in an excessive volume of highly cellular tissue with limited mechanical properties and a poorly organized matrix. Remodeling reshapes and strengthens this tissue by removing, reorganizing, and replacing cells and matrix.[25] In most tendon and ligament injuries, evidence of remodeling appears within several weeks of injury as fibroblasts and macrophages decrease, fibroblast synthetic activity decreases, and fibroblasts and collagen fibrils assume a more organized appearance. As these changes occur in the repair tissue, collagen fibrils grow in diameter, the concentration of collagen and the ratio of type I to type III collagen increase, and the water and proteoglycan concentrations decline. During the months after the injury occurs, the matrix continues to align, presumably in response to loads applied to the repair tissue. The most apparent signs of remodeling disappear within 4 to 6 months of injury. However, removal, replacement, and reorganization of repair tissue continue to some extent for years.[50,52,53] The mechanical strength of the healing tendon and ligament increases as the collagen becomes stabilized by cross-links and the fibrils assemble into fibers.

Factors Affecting Healing

Among the most important variables that affect healing of tendon and ligament are the type of tendon or ligament, the size of the tissue defect, and the amount of load applied to the repair tissue. For example, injuries to capsular and extra-articular ligaments stimulate production of repair tissue that will fill most defects, but injuries to intra-articular ligaments, such as the ACL, often fail to produce a successful repair response. Treatments that achieve or maintain apposition of torn tissue and that stabilize the injury site decrease the volume of repair tissue necessary to heal the injury, which can benefit the healing process. Such treatments may also minimize scarring and help to provide near-normal tissue length. For these reasons, avoidance of wide separation of ruptured tendon or ligament ends and selection of treatments that maintain some stability at the injured site during the initial stages of repair are generally desirable.

Early excessive loading in the immediate postoperative period may have a deleterious effect on tendon and ligament healing by disrupting the repair tissue, leading to gap formation and ischemia, adverse changes in tendon matrix, and possible rupture.[4,25,54–56] However, controlled loading of tendon and ligament repair tissue can promote healing and enhance the mechanical and biologic characteristics of tendon-to-bone healing.[57] The optimal amount of tension necessary to promote an acceptable clinical response is currently not well understood and depends on the type of tissue and healing environment, but it is clear that remodeling of collagen scar tissue into mature tendon tissue depends on the presence of tensile forces.[58,59] The concept of immediate passive mobilization after flexor tendon repair in the hand was introduced by Kleinert and coworkers,[60] who showed that, during limited active extension, reciprocal relaxation of the flexor tendons occurs, allowing passive extension of the repaired tendon. This controlled passive motion was found to be effective experimentally and clinically in decreasing the tethering effect of adhesions and in improving the rates of tendon repair, gliding function, and strength of the tendon.

Methods for Augmentation of Tendon and Ligament Healing

A large body of research has demonstrated the potential for growth factors to improve tendon and ligament tissue healing by stimulation of cell proliferation, chemotaxis, matrix synthesis, and cell differentiation (summarized in Table 1.1). In addition to multifunctional cytokines such as TGF-β and platelet-derived growth factor, work has focused on recapitulating the cellular and molecular signals that are expressed during embryonic tendon development, such as scleraxis and TGF-β3.[61] However, challenges in the delivery of these growth factors, specifically regarding the optimal carrier vehicles and proper dosing regimen, to the desired site still remain.

Platelet-rich plasma (PRP), an autologous blood concentrate, can be used to locally deliver a high concentration "cocktail" of cytokines and has gained popularity as a treatment modality for tendon and ligament injuries. Recent studies have reported potentially promising results with the use of PRP to augment healing of rotator cuff repair[62–64] and patellar tendinopathy.[65] However, the results of PRP for augmentation of tendon and ligament healing have been variable, which can partially be attributed to the lack of understanding of the optimal PRP formulation for different tissues and pathologies, as well as the tremendous variability in the methods of PRP production among commercial systems.[66,67] To complicate matters further, within a given separation technique, there is a high degree of intersubject and intrasubject variability in the composition of PRP produced.[68]

Cell-based approaches appear promising for tendon and ligament tissue engineering and improvement of healing. Therapies using mesenchymal stem cells (MSCs) derived from adipose and bone marrow to augment tendon and ligament healing have garnered the most attention due to their multipotent potential and ability to exert a paracrine effect to modulate and control inflammation, stimulate endogenous cell repair and proliferation, inhibit apoptosis, and improve blood flow.[14,69] However, like PRP augmentation therapy, continued research is needed to identify the optimal cell source and the ideal treatment protocol needed to drive differentiation of these or neighboring

TABLE 1.1 Growth Factors in Soft Tissue Repair

Biologic Factor	Functions	Reference
TGF-β	Influx of mononuclear cells and fibroblasts	Lee J et al: *Iowa Orthop J* 1998
	Enhanced collagen deposition	Spindler KP et al: *J Orthop Res* 2002
		Spindler KP et al: *J Orthop Res* 2003
		Kashiwagi K et al: *Scand J Plast Reconstr Surg Hand Surg* 2004
		Kim HJ et al: *Connect Tissue Res* 2007
		Kim HM et al: *Connect Tissue Res* 2011
		Manning CN et al: *J Orthop Res* 2011
		Kovacevic D et al: *Am J Sports Med* 2011
GDF 5/6/7	Influx of mononuclear cells and fibroblasts	Wolfman NM et al: *J Clin Invest* 1997
	Enhanced collagen deposition	Aspenberg P et al: *Acta Orthop Scand* 1999
		Rickert M et al: *Growth Factors* 2001
		Forslund C et al: *J Orthop Res* 2003
		Virchenko O et al: *Scand J Med Sci Sports* 2005
		Fealy S et al: *Am J Sports Med* 2006
		Dines JS et al: *J Shoulder Elbow Surg* 2007
		Saiga K et al: *Biochem Biophys Res Commun* 2010
		Date H et al: *J Orthop Res* 2010
IGF-1	Proliferation of fibroblasts	Abrahamsson SO et al: *J Orthop Res* 1991
	Enhanced collagen deposition	Abrahamsson SO et al: *J Orthop Res* 1996
		Kurtz CA et al: *Am J Sports Med* 1999
		Dahlgren LA et al: *J Orthop Res* 2002
		Dahlgren LA et al: *J Orthop Res* 2005
		Provenzano PP et al: *BMC Physiol* 2007
PDGF-B	Influx of mononuclear cells and fibroblasts	Lee J et al: *Iowa Orthop J* 1998
	Enhanced angiogenesis	Hildebrand KA et al: *Am J Sports Med* 1998
	Enhanced collagen deposition	Nakamura N et al: *Gene Ther* 1998
		Kobayashi M et al: *J Shoulder Elbow Surg* 2006
		Uggen C et al: *Arthroscopy* 2010
		Hee CK et al: *Am J Sports Med* 2011
bFGF	Proliferation of fibroblasts	Lee J et al: *Iowa Orthop J* 1998
	Enhanced collagen deposition	Cool SM et al: *Knee Surg Sports Traumatol Arthrosc* 2004
		Saiga K et al: *Biochem Biophys Res Commun* 2010
		Date H et al: *J Orthop Res* 2010
HGF	Enhanced angiogenesis	Ueshima K et al: *J Orthop Sci* 2011
	Enhanced collagen deposition	
PRP	Enhanced angiogenesis	Murray MM et al: *J Orthop Res* 2006
	Enhanced collagen deposition	Murray MM et al: *J Orthop Res* 2007
		Joshi SM et al: *Am J Sports Med* 2009
VEGF	Enhanced angiogenesis	Boyer MI et al: *J Orthop Res* 2001
	Enhanced collagen deposition	Petersen W et al: *Arch Orthop Trauma Surg* 2003
BMP-12	Enhanced ossification	Aspenberg P et al: *Scand J Med Sci Sports* 2000
	Enhanced angiogenesis	Lou J et al: *J Orthop Res* 2001
	Enhanced collagen deposition	Seeherman HJ et al: *J Bone Joint Surg Am* 2008

bFGF, Basic fibroblast growth factor; *BMP-12*, bone morphogenetic protein-12; *GDF*, growth/differentiation factor; *HGF*, human growth factor; *IGF-1*, insulin-like growth factor-1; *PDGF-β*, platelet-derived growth factor-β; *PRP*, plasma-rich protein; *TGF-β*, transforming growth factor-β; *VEGF*, vascular endothelial growth factor.

cells into mature tenocytes and fibroblasts. Recent studies have identified resident tissue-specific stem cells in the perivascular regions of native tendon and ligament that detach from vessels in response to injury, migrate into the interstitial space, and deposit extracellular matrix,[70,71] although their precise potential for use in augmenting tendon and ligament healing remains to be elucidated.

Research has also investigated scaffold materials to augment tendon repair and ligament reconstruction. Porcine-derived small intestine submucosa has been used as a collagen scaffold to augment Achilles tendon and rotator cuff tendon repair. However, negative clinical results have been reported, including inflammatory/immunologic response to the small intestine submucosa material believed to be due to residual porcine DNA in the implant.[72,73] Various other allografts and xenografts, such as collagen allograft matrices and porcine dermal xenografts, are commercially available and differ from porcine small intestine submucosa in both biologic and mechanical composition.[74,75] Nanomaterials are promising for tendon and ligament tissue engineering because the microstructure of the material mimics

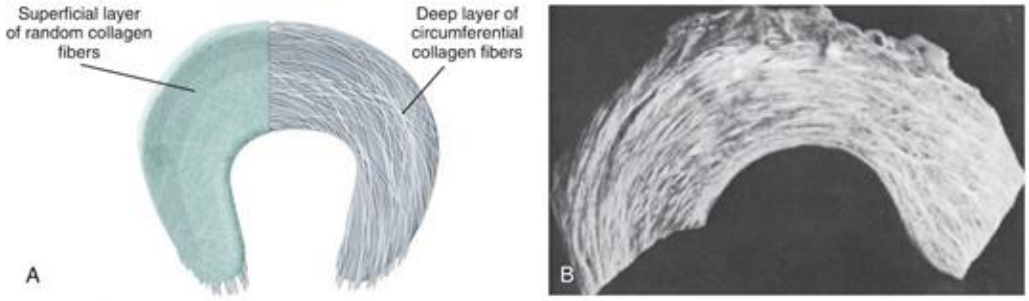

Fig. 1.2 (A) Diagram of collagen fiber architecture throughout the meniscus. Collagen fibers of the thin superficial sheet are randomly distributed in the plane of the surface and are predominantly arranged in a circumferential fashion deep in the substance of the tissue. (B) Macrophotograph of bovine medial meniscus with the surface layer removed, showing the large circumferentially arranged collagen bundles of the deep zone. ([A] Modified from Bullough PG, Munuera L, Murphy J, et al. The strength of the menisci of the knee as it relates to their fine structure. *J Bone Joint Surg Br.* 1970;52:564–570. [B] From Proctor CS, Schmidt MB, Whipple RR, et al. Material properties of the normal medial bovine meniscus. *J Orthop Res.* 1989;7:771–782.)

native extracellular matrix. Multiphasic scaffolds are being used to create bone-ligament composites.[76] In addition to various scaffold materials and cell types, it has become clear that mechanical stimulation of the neotissue is also critical to optimize the structure and composition of the tissue.[77] The specific scaffold can be modified in vitro by seeding marrow stromal cells on the scaffold and applying cyclic stretching to increase the alignment of cells, as well as to improve the production and orientation of collagen. When applied in vivo, such a tissue-engineered scaffold could serve to accelerate the healing process, ultimately helping to make a better neoligament or tendon.

MENISCUS

Structure

Human menisci are semilunar in shape[78] and consist of a sparse distribution of cells surrounded by an abundant extracellular matrix.[79–81] The meniscus functions to optimize force transmission and provide stability to the knee. The medial meniscus is the dominant secondary stabilizer in an ACL-deficient knee during the Lachman maneuver,[82] whereas the lateral meniscus is the dominant secondary stabilizer in an ACL-deficient knee during the pivot shift maneuver.[83] Within the meniscus lies an anisotropic, inhomogeneous, and highly ordered arrangement of collagen fibrils. The meniscal surface is composed of a randomly woven mesh of fine collagen type II fibrils that lie parallel to the surface. Below this surface layer, large, circumferentially arranged collagen fiber bundles (mostly type I) spread through the body of the tissue (Fig. 1.2).[84,85] These circumferential collagen bundles give menisci great tensile stiffness and strength parallel to their orientation.[85] The collagen bundles insert into the anterior and the posterior meniscal attachment sites on the tibial plateau, providing for rigid and strong attachment sites. Fig. 1.2A illustrates these large fiber bundles and the thin superficial surface layer. Fig. 1.2B is a photograph of a bovine medial meniscus with the surface layer removed, showing the large collagen bundles of the deep zone.

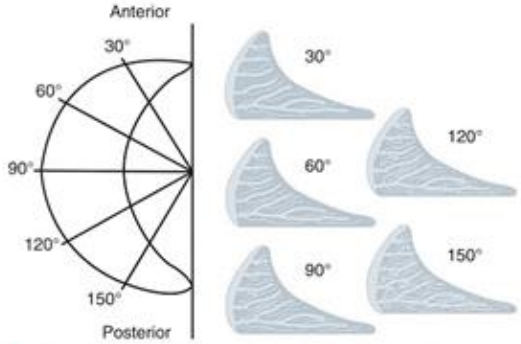

Fig. 1.3 Radial collagen fiber bundles of the meniscus. Radial tie fibers consisting of branching bundles of collagen fibrils extend from the periphery of the meniscus to the inner rim in every radial section throughout the meniscus. They are more abundant in the posterior sections and gradually diminish in number as the sections progress toward the anterior region of the meniscus. (Modified from Kelly MA, Fithian DC, Chern KY, et al. Structure and function of meniscus: basic and clinical implications. In: Mow VC, Ratcliffe A, Woo SL, eds. *Biomechanics of Diarthrodial Joints.* Vol 1. New York: Springer-Verlag; 1990.)

Radial sections of meniscus (Fig. 1.3) show radially oriented bundles of collagen fibrils, or "radial tie fibers," among the circumferential collagen fibril bundles, weaving from the periphery of the meniscus to the inner region.[85,86] These tie fibers help to increase the stiffness and the strength of the tissue in a radial direction, thereby resisting longitudinal splitting of the collagen framework. In cross section, these radial tie fibers appear to be more abundant in the posterior sections than in the anterior sections of the meniscus.[87]

Unlike articular cartilage, the peripheral 25% to 30% of the lateral meniscus and the peripheral 30% of the medial meniscus[78,88–90] have a blood supply, and the peripheral regions of the meniscus, especially the meniscal horns,[91,92] have a nerve supply as well. Branches from the geniculate arteries form a capillary