Anatomical Review of the Anterior Cruciate Ligament

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The anterior cruciate ligament (ACL) is one of the two cruciate ligament structures in the center of the knee, the other being the posterior cruciate ligament. The cruciate ligaments consist of regularly oriented dense connective tissue surrounded by a vascular synovial envelope. They are composed of collagen fibrils which combine to form larger fibers, larger subfasicular units, & finally fascicles. The ligaments are surrounded by a paratenon, the fascicles by an epitenon, & the fibers by an endotenon.

Although the cruciate ligaments are intra-articular (within the capsule of the knee), because of their surrounding synovial membrane, they are extrasynovial. The synovium of the knee covers the two cruciate ligaments, isolating them from synovial fluid. A simple break in the synovial covering may lead to destruction of the ligament's integrity by exposing it to the fluid environment & also by compromising the vascular supply, which appears to extend from the covering to the internal ligament.

Embryology

Streeter[13-18] proposed a widely accepted developmental staging system and outlined the criteria of each horizon or stage. This classification system is based on external form and structural organization of the embryo and it is useful for understanding the first four weeks of development. The system comprises of 23 stages or horizons based on morphological events and it ranges from a single-cell stage to the end of the embryonic stage which has been arbitrarily defined as occurring when the nutrient vessel has penetrated to the humerus, forming the primitive bone marrow cavity. In this system, the first stage occurs with the single-cell egg and progresses to stage 23, in which the chief aspects of differentiation are complete. The remainder of gestation, the fetal period, is concerned primarily with growth. The leg bud first appears in horizon 13 which is one stage later than the arm bud as the development of the embryo takes place in a cephalocaudal direction. As the limbs develop in a proximodistal direction, the limb buds arise as a localized differentiation at the extremes of the lateral plate mesoderm.

During horizon 18, a mass of blastemal cells form the interzone between the femur and tibia. They differ from the chondogenic cells as they do not formate matrix, however, they are identical to undifferentiated mesenchyme. This interzone comprises of three distinct layers, namely the central, intermediate and dense, which develop during horizons 20 and 21. The central layer is composed of loosely randomly arranged cells between the two denser or chondrogenic layers, which will form the future articular cartilage. The cells are aligned parallel with the adjacent epiphyseal region in these two layers. The intermediate zone merges laterally with the joint capsule mesenchyme and is well vascularised. The synovium and other intracapsular structures such as tendons, ligaments and menisci will arise from this layer. The denser zones, being avascular, will form the parallel bundles of collagen and are continous with the perichondrium.

The intermediate zone undergoes autolysis and cavitation as development continues. A vertical septum in the central portion of the knee separates the medial and lateral condylar joints. Its lower border is attached to the intercondylar area of the tibial plateu while the posterior half of its upper border is attached to intercondylar notch of the femur. It will extend anteriorly from the intercondylar notch of the patellar to just below the patellar articular surface. A proliferation appears within this central septum and extends backwards to the anterior cruciate ligament as the inner zone undergoes cavitation. This will separate the septum into the anterior portion, the infrapatellar synovial fold, and the posterior part which the anterior and the posterior cruciate ligament will derive from. [19]

By the end of horizon 22, at approximately 45 days, the femoral and tibial condyles would have formed discrete cartilaginous forms and the patella tendon would have also been condrified within the patellar ligament.[20] Both the anterior and posterior cruciate ligaments develop in the posterior aspect of the central septum and the collateral ligaments will appear as well.

The ACL itself appears as a condensation of vascular synovial mesenchyme in the blastoma at about 6.5 weeks.[2] It begins as a ventral ligament & gradually invaginates with the formation of the intercondylar space. It appears well before joint cavitation & remains extrasynovial at all times. Although it changes very little to achieve its final form, it does migrate posteriorly. The fact that the cruciate ligaments & semilunar cartilages are derived from the same blastoma tends to corroborate the thesis that these structures function in concert.[3]

By 9 weeks, the cruciate ligaments are composed of numerous immature fibroblasts having scanty cytoplasm and fusiform nuclei, the long axes of which are parallel to the course of the ligaments. At 10 weeks, the ACL and PCL are separate from each other and are easily distinguished from one another by the direction of their parallel fibers. While

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no blood vessels are seen in the cruciate ligaments at this time, capillaries are noted in the blastema adjacent to the ligaments. Over the next 4 weeks, the cruciate ligaments become better differentiated from the adjacent tissues and the attachment sites appear to become more specialized. Blood vessels are also seen in the loose tissue surrounding the cruciate ligaments at this time. By 18 weeks, the cruciate ligaments stand almost alone, and a few vascular elements are to be found within their substance. During the following weeks the chief changes, in addition to growth, are the increase in vascularity and the appearance of efinite fat cells in the mass of connective tissue anterior to the cruciate ligaments and inferior to the patella; thus the infrapatellar fat pad comes into being at this time. By 20 weeks, the cruciate ligaments resemble those of the adult, and their remaining development consists of marked growth with little change in form.

Blood Supply

The blood supply to the cruciates stems primarily from the femoral side through the middle geniculate artery, which branches from the popliteal artery at the level of the joint line. There are also contributions from the superior & inferior medial & lateral geniculate arteries. Because the blood supply is so dependent on one side, midsubstance ligament disruptions commonly lead to death of the ligament via vascular compromise and loss of the structural integrity of the collagen fibers.

Ligamentous branches of the middle geniculate artery & terminal branches of the inferior geniculate arteries supply the synovial plexus overlying the ligaments. According to Arnoczky, the synovial vessels contribute to a network of periligamentous vessels which surround the ligament. The periligamentous vessels give rise to smaller connecting branches which penetrate the ligament transversely, communicating with a plexus of endoligamentous vessels which run longitudinally parallel to the collagen fibers in the ligament.[6]

Nerve Supply

The nerve supply to the cruciate ligaments originates from the posterior articular branch of the posterior tibial nerve. Most of the nerve fibers are associated with endoligamentous vessels & are found in the subsynovial layer or near insertions of the ACL[1], but some lie alone within the ligament and appear to function in proprioception. Monoclonal antibody stains have demonstrated a maximum of 17 mechanoreceptors in the ACL of a 3-year old child.[4] These numbers decrease with age & disease. The receptors found are primarily Ruffini receptors & free nerve-endings that are thought to function as stretch receptors & nociceptors respectively.[5] This is in agreement with animal studies which have demonstrated that mechanoreceptors with myelinated axons are present in the ACL & electromyographic studies demonstrated that they are mainly responding in extension. In addition to their function as nociceptors, free nerve-endings may serve as local effectors by releasing neuropeptides with vasoactive function. Thus, they may have a modulatory effect in normal tissue homeostasis or in remodeling of grafts.[6]

Attachments and In-depth Anatomy

The ACL has a femoral attachment in the form of a segment of a circle on the medial surface of the lateral femoral condyle in the intercondylar notch.[6,10] The bony origin is 11 to 24 mm in diameter.[1] From here, the ACL passes anteriorly, medially, and distally to its insertion on the tibia. The ACL fibers fan out as they approach the tibial insertion.[12] Its tibial attachment is anterior & lateral to the anterior tibial spine, beneath the transverse meniscal ligament. It is somewhat wider and stronger than the femoral attachment, measuring approximately 11 mm (range 8-12 mm) in width & 17 mm (range 14-21 mm) in the anteroposterior direction.[1,6,10]

The ACL is composed of two major bundles, an anteromedial bundle & a posterolateral bundle. These names describe the anatomic position of each bundle from the femoral condyle to the attachment site on the tibial plateau surface. Each bundle, in turn, is composed of numerous fascicles.

The posterolateral bundle arises from the posterior aspect of the oval femoral origin & inserts into the lateral aspect of the tibial insertion area. This bundle is larger & significantly stronger than the anteromedial. The anteromedial bundle originates from the anterior femoral origin & inserts into the medial side of the tibial insertion.

The two bundles spiral round each other & permit tibiofemoral rotation throughout the range of motion of the knee.[6-11] When the knee is extended, the posterolateral bundle is tight & the anteromedial bundle is mildly lax. As the knee is flexed, the femoral attachment of the anterior cruciate ligament becomes more horizontal, loosening the posterolateral bundle & tightening the anteromedial bundle.[6-11] This corresponds with clinical findings. Injury to the anteromedial portion of the ACL demonstrates more anterior laxity at 90° (anterior drawer test).[6-11] Arnoczky, however, points out that the division into anteromedial & posterolateral bundles is an oversimplification. He states that the ACL is actually a continuum of fibers, a different portion of which is tight throughout the range of motion.[6]

No fibers of the ACL are truly isometric. The least amount of variation in length appears to occur in the anteromedial portion (1.5mm) during range of motion.

The ACL on average is 38 mm long, 11 mm wide and 5 mm thick. Its ultimate tensile strength in young individuals is usually quoted as 1700 to 2000N. The primary function of the ACL is to prevent anterior displacement of the tibia and hyperextension of the knee. Secondary functions include resistance of varus/valgus stresses and internal rotation of the tibia on the femur.

Histology

In the histological analysis of the anterior cruciate ligament, the factors which are being considered are collagen bundle width, cell morphology, size and "crimp". Crimp is a feature of the anterior cruciate ligament and it represents a regular sinusoidal pattern in the matrix. Its amplitude and periodicity which appear to be structure

specific features can be evaluated best under polarized light. This accordion-like pattern in the matrix can functionally provide a "buffer" where elongation in the longitudinal manner can take place without fibrous damage. Other functions will include acting as a "shock absorber" along the length of the tissue as well as providing a mechanism for controlling of tension. However, when its physiological mechanical limits are exceeded, an irreversible damage occurs and hence, the physical properties of the anterior cruciate ligament are changed.[21] Two patterns of crimping are noted in the canine anterior cruciate ligament [22]. The fascicles located more centrally in the ligament are found to be either undulated in a planar wave pattern or straight while a helical wave pattern is observed in those located at the periphery.

Histological assessment of the anterior cruciate ligament of rabbits reveals collagen bundles which are orientated longitudinally with a width of 20 μm. However, the crimp period in the anterior cruciate ligament is relatively shorter with a length ranging from 45μm to 60 μm and the amplitude is less than 5μm. Fibroblasts which are round to ovoid in shape are found on either side of the collagen bundles of the ligament. They measure approximately 12-15 μm in length and 5-8 μm in diameter. Cells are arranged in a longitudinal fashion along the margins of the fasicicles. It has been noted that groups of cells are concentrated in the areolar connective tissue. Hence, it is postulated that these may be the ligamentous that correlate to the peritendineum areas.

With the use of the transmission electron microscopy (TEM), it is noted that the fibrils of the ligament exhibit a wide range of diameters.[23] The ovoid fibroblasts lie in columns between layers of compact parallel bundles of collagen fibrils. These cells have abundant cellular organelles which imply the high level of cellular activity. Moreover, they also have numerous microvilli, which are small cellular processes that project into a surrounding area of amorphous ground substance with reticular fibers but not extending into the compact parallel collagen fibers.

Biochemistry

Collagen

The collagen molecule which has measurements of 300nm in length and 1.5nm in diameter, appears rod-like and these rods are also named "tropocollagen". They are arranged in a three dimensional array in the extracellular environment and are affected by factors such as environmental stresses and other additional biological elements. Such extracellular factors have an impact on the orientation and the size of the fibrils that are formed from the tropocollagen units. With the use of transmission electron micrographs, it has been noted a small gap is present between the tropocollagen units when assembled linerly. This has been postulated to have a functional importance only in the bone.[24]

Each tropocollagen unit is made of three independently synthesized chains of amino acids with each chain being made up of 1000 amino acids. The amino acids in these chains are mainly praline, hydroxyproline and glycine with the latter being the smallest amino acid. The latter is present to allow for close packing of the three δ chains to form tropocollagen. The former two amino acids are cyclic imino acids and their structure is believed to provide rigidity to triple-helix structure of tropocollagen.[25-29] Following ribosomal assembly, collagen undergoes multiple modifications such as hydroxylation of proline or lysine and this involves either intracellular or extracellular enzymes. Most of the chains found in tropocollagen, otherwise known as δ helix chains are precisely oriented. Three such chains will associate to form tropocollagen molecule. Later, these units are packed together in the quarter-stagger manner which is viewed as 64nm subbonding on transmission electron micrographs to form the microfibrils that aggregate to form the ligament.[30]

The assembly of the three δ chains into tropocollagen is aided by a group of amino acids otherwise known as "registration peptides" which are located at the end of each such chain. The triple helix, together with its registration peptide, is called procollagen. Upon completion of the assembly of the triple helix, the registration peptides are redundant and hence are removed by an enzyme termed procollagen peptidase. This process occurs when the procollagen attempts to cross the cell membrane into the extracellular space.

Collagen Crosslinks

The quarter-staggered packing of tropocollagen units[31] and its propensity to form covalent intramolecular and intermolecular cross-links[32-38] contribute to the stability of collagen. The intramolecular cross-links are formed between δ chains of the same tropocollagen molecule while the intermolecular cross-links occur between adjacent tropocollagen molecules. Crosslinks are essential to provide resistance to breakdown by enzymes or chemicals and for tensile strength. Enzymatic reactions involving mainly lysine and hydroxylysine will result in the formation of cross-links. The initial reaction in this entire process involves the oxidative deamination of the terminal amine to an aldehyde by the action of the enzyme, lysyl oxidase and this confers stability to elastin. The allysyl residues condense with one another to form an aldol condensation product characteristic[39] of intramolecular cross-links. Intermolecular crosslinks occur in the reaction involving allysine with lysine or hydoxylysine to form a Schiff base (δ-semialdehyde). The double bonds which are from the products of aldol condensation and Schiff-base reaction are believed to undergo reduction to form more stable products *in vivo* with time.

Other more important bimolecular Schiff bases which are discovered in ligaments are hydroxylysinonorleucine (HLNL) and dihydroxylysinonorleucine (DHLNL). Although these hydroxylysine-containing cross-links are the most prevalent in native collagen, more complex forms have been noted such as histidinohydroxymerodesmosine (HHMD) which is a tetramolecular cross-link.

The anterior cruciate ligament is found to have the highest ratios {DHLNL/HLNL and (DHLNL + HLNL)/HHMD} of these crosslinks as compared to the other ligaments[40]. The functional purpose of the different types of crosslink that exist in the ligament is still not known. However,

DHLNL is found mainly in embryonic and healing tissue[41,42] while HLNL, in the healing tissue, will replace the former.[41] Hence, this indicates that a more mutable crosslink do exist in ligament to allow for reaction to a wide range and variety of forces.

Ground Substance

The term "Ground substance" refers to he portion of connective tissue which comprises of glycosaminoglycans (GAGs) and proteoglycans. On a dry weight basis, the ground substance constituents of tendon comprise less than 1% of the total tissue and slightly more in ligament. However, water makes up approximately 60 to 80% of the total wet weight and a significant part of this water is associated with the matrix. This water and material allows for lubrication and spacing which are important to the gliding purpose at the intercept points where fibers cross in the tissue matrices[43]. Gliding is an important physical property of the ligament and the ground substance as well as water also give rise to the tissues' viscoelastic properties. As water is entrapped between the large and highly charged molecules of the proteoglycans, its movement in the system is largely inhibited.

Proteoglycans are more or less chemically uniform in the different periarticular areas of the connective tissues. The proteoglycan subunit consists of a core protein with protein linked GAG side chains with hyaluronic acid, chondroitin 4-sulfate, chondroitin 6-sulfate as well as dermatan sulfate making up the majority of GAG that is present. Apart from hyaluronic acid, the remaining GAGs are bonded covalently to proteins so as to achieve a ggregates molecules which have massive molecular weight and are highly negatively charged. As they possess a large number of hydroxyl groups, they are able to form hydrogen bonds with water. Hence, this contributes important features to the collagen-fiber-ground-substance interaction. The anterior cruciate ligaments in the rabbits are found to have the highest proportion of GAGs as compared to the other tendons studied in the experiment such as the patellar tendon and the Achilles tendon[44]. It is noted that the higher the GAG content, the more water is associated with the complex. Hence, this will change the viscoelastic properties of the tissues and may aid in the "shock-absorbing" feature in the ligament. This is greatly optimized in the cruciate ligaments.

Glycoproteins

The important role of glycoproteins such as fibronectin[45] and actin in context of interaction with the cells of the tissues as well as their environment during processes such as healing, growing and remodeling has yet to be fully understood. However, it is noted that fibronectins which are high molecular weight extracellular proteins is essential in a vast range of cellular function especially those involving interaction between a cell and its extracellular matrix. Apart from being involved in intra- and extracellular matrix morphology, they also function to permit cell and cellular adhesion as well as cell migration. As they possess adhesive domain specific to fibrin, actin, hyaluronic acid, cell surface factors and collagen, they function to attract and couple key elements in normal healing and growing tissues. They are exceptionally important in soft connective tissue where the major components are collagen, cells and ground substance[45].

Fibronectin has been shown to be present in both tendons and ligaments of the rabbit including the anterior cruciate ligament.[46-49] The results concluded that ligaments are metabolically more active as compared to the tendons[50]. This was reflected by the higher level of proteoglycan, Type III collagen as well as cellularity and it is postulated that each component could have acted as an adherent factor for fibronectin. In fact, fibronectin has been demonstrated to aid wound healing[51] and may be required for normal collagen organization and deposition of fibroblasts in vitro[52]. Thus, fibronectin may be essential for the morphological as well as biochemical features of the anterior cruciate ligament following injury and during development.

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