Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(10): 53120
https://doi.org/10.31083/FBL53120

Review

Collagen Ultrastructural Properties and Mechanosensing in the Mammalian Extracellular Matrix: A Theoretical Model From Epidermis to Bone Marrow

Marco Franchi[1,*], Leonardo Franchi[2], Sylvia Mangani[3], Konstantinos Spanopoulos[3], Zoi Piperigkou[3], Nikos K. Karamanos[3,*]

[1]Department for Life Quality Study, University of Bologna, 47921 Rimini, Italy
[2]Department of Medicine, University of Bologna, 40100 Bologna, Italy
[3]Biochemistry, Biochemical Analysis & Matrix Pathobiology Research Group, Laboratory of Biochemistry, Department of Chemistry, University of Patras, 26504 Patras, Greece
*Correspondence: marco.franchi3@unibo.it (Marco Franchi); n.k.karamanos@upatras.gr (Nikos K. Karamanos)
Academic Editor: Katarzyna Anna Cieslik
Submitted: 20 April 2026 Revised: 19 June 2026 Accepted: 29 July 2026 Published: 14 October 2026

Abstract

Extracellular matrix (ECM) components that transmit mechanical loads are ubiquitous in the mammalian body. Collagen, the primary structural component of most ECMs, is present throughout connective tissues (CTs) and forms a continuous fibrous scaffold that joins ECMs and extends from the epidermis to the bone marrow. Within each ECM, both fibrillar collagen and the interposed glycosaminoglycans (GAGs) and proteoglycans (PGs), which bind and retain water, dynamically adapt to functional requirements. In this review, we describe how type I and III fibrillar collagens, which are the predominant collagens found in the body, form fibrils of different sizes, structures, and orientations that allow them to resist and transmit tensile forces from the environment to the deeper bone marrow, and, in some tissues, to resist compressive loads. These collagen types are embedded within a viscous matrix of GAGs and PGs that mainly oppose compressive loads and further contribute to the mechanical and functional properties of the continuous collagen network. These factors are consistent with a theoretical model emphasizing a broad role for ECM systems in sensing, adapting, and transmitting external mechanical stimuli from the epidermis to the bone marrow, allowing these signals to act across the basement membrane, dermis, hypodermis, fascia superficialis, subcutaneous tissue, deep fascia, muscle sheaths, tendon, ligament, periosteum, bone, and endosteum.

Keywords: extracellular matrix; collagen; collagen fibrils; sensing networks; skin; bone marrow

1. Introduction

The anatomical and functional features of all mammals depend on the ability of their tissues to adapt to various mechanical forces [1,2,3]. Connective tissue (CT) separates and integrates various tissue types in the mammalian body, and is sensitive to mechanical loading. The blood- and lymphatic vessel-rich extracellular matrix (ECM) is a key component of the CT that also harbors nerves and specialized neuroreceptors responsible for transmitting information from the environment to the central nervous system [4]. Environmental mechanical stimuli can be converted into chemical signals that induce changes in the organization and biomechanical properties of the ECM to modulate tissue development, growth, remodeling, repair, and regeneration, in addition to influencing the pathogenesis of many diseases, as well as the invasion, drug resistance, and immunotherapeutic sensitivity of cancers [5,6,7,8].

Mammals interact with the external environment primarily through the skin, which consists in large part of the epidermis, a thin (31.2–596.6 µm) stratified squamous epithelial layer [9]. All epithelia, including those in the digestive tract, act as barriers to permeability that protect underlying tissues. In addition to these barrier functions, epithelial tissues can sense and respond to mechanical stress, as the physical deformation of the epithelial cytoskeleton in the epidermis can be transduced into electrical or chemical signals capable of influencing the organization and remodeling of the underlying ECM [10]. As this process of mechanotransduction can induce the production and activity of proteolytic enzymes, which are crucial for tissue adaptation, ECM layers are highly responsive to components within the CT [6,7]. The ECM layers found within every organ or system are physically connected, providing paths for vessels and nerves to access distant tissues. In light of their unique properties, these ECM networks offer a uniquely dynamic scaffold that also contributes to the transmission of external mechanical loads from the surface of the body to deeper tissues.

The human body contains a range of CT types distributed throughout the skin and bones. In the skin, the superficial epidermis is strongly connected to an underlying specialized ECM known as the basement membrane (BM). Beneath the BM is a second ECM layer known as the dermis, which includes two different fibrous sublayers: the papillary dermis and the reticular dermis. The hypo-

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

dermis, located beneath the dermis, is generally regarded as the deepest layer of the skin. Based on its structural organization and biomechanical characteristics, the hypodermis forms part of the fascial system of the skin, often referred to as the "third ECM layer", encompassing the hypodermis, superficial fascia, subcutaneous tissue, and deep fascia. The deep fascia is tightly associated with the superficial muscle sheaths, known as the epimysium, as well as the sheaths associated with certain tendons and ligaments. The epimysium gives rise to the perimysium, which wraps around groups of myofibers to form the endomysium. The perimysium directly merges into tendons, which attach to the bone by perforating Sharpey's fibers [11]. The muscle epimysium is also continuous with the outer tendon sheath known as the paratenon, which is connected through the mesotenon with the other tendon sheaths, including the epitenon and the endotenon. The paratenon merges with the periosteum, which is a connective membrane covering the bone that is strongly attached to the bone surface to support bone vascularization and nutrient delivery.

External mechanical forces applied to cells and ECM components generate different types of stress, including tensional, compressive, torsional, and shear stress [5]. Tissues and cells may be stretched uniaxially or multiaxially by tensile strain. Tendons and ligaments, along with the cells that comprise them, primarily undergo uniaxial stretching and thus align along the principal force direction. In contrast, the dermis and skin fibroblasts are subjected to multidirectional tensile and compressive forces. Moreover, bone tissue and osteocytes can be subjected to compression and tension, while cartilage and chondrocytes are primarily exposed to hydrostatic pressure that generates shear stresses [5,12]. Forms of skin massage are widely used to relax or stimulate skeletal muscles, while mechanical loading generated by muscle activity is known to regulate bone development and maintain skeletal homeostasis. In this article, we describe the continuous collagen-based ECM network and propose a theoretical model in which the collagen network enables mechanosensing and the transmission of mechanical forces from the environment to the deep bone marrow, across the skin, fascia, muscle, tendons, ligaments, and bone. This model may help elucidate a range of physiological processes and provide insights into the underlying mechanisms of clinical and experimental therapies that intentionally modify or remodel the ECM to promote healthy tissue repair.

2. Major ECM Components Involved in Sensing Networks

In fresh CTs, water is the main component of the ECM, while collagen is the main structural component in dehydrated tissues. Collagen is also the most abundant protein in all mammals, comprising approximately 30% of total body protein. The collagen superfamily includes 28 collagen types (I-XXVIII). However, only a few collagen types form fibrils (including types I, II, III, V, XI, XIV, XVII) and fewer aggregate into fibers (including types I, II, III, V) [13]. All collagen types are characterized by a common triple-helical domain, known as tropocollagen, which constitutes between 96% (collagen I) and 10% (collagen XII) of their molecular structure. In fibrillar collagens, tropocollagen consists of three left-handed polypeptide α-chains assembled into a right-handed triple helix resembling a rod of 300 nm in length and 1.5 nm in diameter. Tropocollagen molecules form microfibrils that further organize into fibrils. These fibrillar collagens, in turn, form three-dimensional (3D) scaffolds for the epithelia, and through interactions with multiple cell-surface receptor families and other ECM components, they provide the structural and mechanical strength of CTs [14]. In skin, tendons, ligaments, and bone, collagen fibrils and fibers generally resist tension. However, under certain physiological or pathological conditions, they may contribute to resistance against pressure or limit cell invasion, while still being subject to stretching resulting from lateral compression [15,16,17,18]. As collagen fibrils and fibers tend to align with the direction of force, analysis of their orientation can provide insight into the direction of applied forces and the functional mechanical role of the tissue [19]. Tendon is a prototypical example of a tissue type in which collagen fibrils form fibers running in straight lines parallel to one another that are optimized for uniaxial loading and efficient transmission of muscle-generated forces to bone, thereby generating joint movement.

Although many nonfibrillar collagen types, including types IV, VI, and VII, contribute to the biomechanical properties of CTs, fibrillar collagens are primarily responsible for the transmission of mechanical forces. Among these fibrillar collagens, types I–III are the dominant components of the fibrillar network in the dermis, bone, cartilage, tendons, ligaments, and interstitial matrices [6,20]. Types I and III collagen make up 90% of all collagen in the body, with type I making up approximately 70%, and type III comprising 5–20% [21]. Both type I and III fibrils exhibit rope-like structures that resist the transmission of tensional forces, although only type I collagen fibrils oppose unidirectional tensional loads, as is observed in tendons and ligaments. Type I fibrils exhibit a larger diameter (150–300 nm), a 5° microfibrillar helical array, and are stiffer than the thinner (25–100 nm) and more flexible type III collagen fibrils, which exhibit a 17° microfibrillar array and can better resist multidirectional forces such as those encountered in the skin [22,23,24]. In general, type I collagen fibrils form straight fibers that align along the dominant direction of mechanical stress, whereas type III fibrils are more responsive to multidirectional loading and typically aggregate into undulating or reticular fibers with less uniform orientation [23].

Elastin is a less abundant fibrillar component of the ECM that plays an essential role in the formation of fibers containing a fibrillin–rich microfibrillar scaffold [24]. In

skin, elastic fibers account for approximately 2–4% of the fat-free dry weight of the dermis and are critical for tissue flexibility, elastic recoil, and the physiological extensibility of the organs [25]. Elastin is a major structural component of highly compliant tissues and is therefore particularly abundant in organs and tissues like the aorta and major blood vessels (28–32% dry mass), lungs (3–7%), elastic ligaments (50%), tendons (4%), and skin (2–3%) [26,27]. Elastic fibers absorb tensional loads by efficiently storing elastic strain energy when stretched. Moreover, they can elongate to more than twice their resting length before failure, and once tension is released, they return to their original length without hysteresis [28,29]. The elastic properties of elastin are dependent on tissue hydration, and its recoil properties are largely driven by hydrophobic interactions within the protein network [30,31].

In all ECMs, fibrils and fibers are held together by a hydrophilic molecular complex that consists of hydrophilic glycosaminoglycans (GAGs), proteoglycans (PGs), and large amounts of water attracted by the strong negative charge of GAGs. This allows the ECM to absorb compressive forces and protect tissues from friction. One example of a tissue rich in GAGs/PGs is the articular cartilage, where these molecules contribute to resistance against compressive loading, reduce friction, and facilitate smooth joint movement. In the skin, GAGs include heparan sulfate (HS), heparin (Hep), chondroitin sulfate (CS), keratan sulfate (KS), dermatan sulfate (DS), and hyaluronan (HA) [32,33]. HA is the only non-sulfated GAG produced on the cell membrane and secreted into the pericellular space, without any covalent protein linkage. HA is present at high levels in many ECMs and plays defined biomechanical functions by forming hydrated aggrecan-HA aggregates that contribute to water retention in CTs [34,35]. In addition, several extracellular PGs play key roles in regulating and maintaining collagen fibrillogenesis [32,33,36,37].

Fibronectin is another fibrillar ECM component that can form insoluble fibrils [38]. Fibronectin binds to collagen, and fibronectin-collagen fibril interactions regulate de novo fibrillogenesis, thus contributing significantly to the mechanical properties of the ECM [39]. Mechanical stretching of fibronectin fibrils can activate a mechanical response pathway in fibroblasts [40], as fibronectin can bind to cell surface receptors known as integrins, as well as components of the BM [41]. Mechanical forces regulate the interactions between fibronectin and type I collagen, which forms a denser and stiffer microenvironment to limit cancer cell invasion in the tumor stroma [42].

All major ECM macromolecules contribute to tissue biomechanics. However, collagen fibrils, which primarily resist and transmit tensile forces, and the PG/GAG-water complex, which mainly withstands compressive loading, are the principal structural elements responsible for mechanical function. The fibrillar type I and type III collagens that predominate most ECM structures respond differently to various loads. The ratio of type I: type III collagen ranges from 2:1 to 3:1 in pliable tissues like the skin, intestines, blood vessels, and lungs, whereas rigid tissues (bone, tendon) almost exclusively contain type I collagen [43]. Heterotrimeric type I collagen, which consists of two α1 chains and one α2 chain, supplies high tensile strength and rigidity to tissues and is specialized for resisting and transmitting tensile loads. Homotrimeric type III collagen, which consists of three α1 chains, exhibits greater flexibility and plays critical roles in wound repair, skeletal muscle integrity, vascular stability, and the structural support of blood vessels, lymphatic vessels, and nerves [44]. These two different types of fibrillar collagen can also co-assemble to form hybrid fibrils in which type III collagen influences fibril diameter and modulates type I collagen stiffness [45]. Both the size and functional/mechanical properties of type I and type III collagen fibrils differ substantially, with the stiffer and thicker type I fibrils, which measure up to 500 nm in diameter, being suited for resisting and transmitting tensile forces. In contrast, the more flexible and thinner type III fibrils (30–60 nm) are more compliant and less adapted for transmitting unidirectional loads, but they contribute substantially to tissue elasticity. When type I collagen fibrils are laterally compressed, they resist the applied pressure while simultaneously experiencing tensile loading along their longitudinal axis [16,45,46].

3. Skin Layers: Structural Organization, Tissue Integrity, and Functional Roles

The skin consists of three distinct tissue layers: the superficial epidermis, the dermis, which consists of the papillary dermis and reticular dermis, and the underlying hypodermis [47]. Given the structural organization and biomechanical functions of the hypodermis, we discuss this layer as part of the deeper CT that includes the fascia superficialis, subcutaneous adipose tissue, and deep fascia.

3.1 Epidermis and the First ECM Layer of the Skin: The Basement Membrane

The skin provides mechanical resistance against moderate injury. The stratified squamous epithelium that forms the human epidermis is continuously subject to physical stresses and friction, which are sensed and transmitted to the underlying ECM [48,49,50]. Epidermal tissue integrity is supported by intercellular adhesions, including adherens junctions, tight junctions, and desmosomes [51,52]. These structures are primarily involved in sensing and transmitting tensile forces between and within cells by modulating plasma membrane tension and actomyosin cytoskeletal dynamics, thereby activating intracellular signaling pathways [51,53]. Changes in plasma membrane tension induce the opening of transmembrane mechanosensitive ion channels and specific ions that initiate diverse cellular responses [54]. Through the transmission of mechanical and biochemical signals, epithelial cells can adapt their metabolism

and morphological phenotype to changing environmental and mechanical conditions by reorganizing the cytoskeletal system [55,56,57,58,59]. To facilitate both nutrient exchange and mechanical integration, the interface between the epidermis and dermis is amplified by epidermal papillae that intertwine with the underlying dermal papillae, which form the papillary dermis.

The BM separates the epidermis from the underlying dermis. Though thin, the BM is stiffer than the overlying cells and serves as an important intermediary for the transmission of mechanical signals, as mechanical forces acting on epidermal cells are conveyed through the cytoskeleton to the BM and subsequently transmitted to the underlying ECM through a combination of mechanotransductive and biochemical signal transduction [60,61,62]. In addition to the epithelia, BM layers also surround muscle fibers, adipocytes, and Schwann cells [63].

The BM is a dynamic ECM structure that undergoes continuous turnover, thereby modifying its thickness and mechanical properties [64]. At the ultrastructural level, the BM consists of distinct layers, including the basal lamina—composed of the lamina lucida and lamina densa—as well as the lamina reticularis. The basal lamina contains glycoproteins such as laminin and nidogen (entactin), as well as the HS-containing PG perlecan. The primary component of the BM is type IV collagen, which forms a mechanical collagen network that provides tensile strength to the underlying ECM components [65,66,67]. Hemidesmosomes anchor basal keratinocytes to the lamina densa through laminin-mediated attachments. In addition to type IV collagen, type XV and XVIII collagens, which are major components of the endothelial BM, and cell-associated type XIII collagen transmit mechanical signals from cells to fibrillar collagens within the ECM [68,69]. BM stiffness is closely associated with the extent of type IV collagen crosslinking, with the disruption of this collagen network being linked to mechanical disruption of the BM [70]. The lamina reticularis consists of type I, III, and V collagens that form heterogeneous fibers, with type V collagen fibrils regulating the formation of type I and III fibrils [71]. Furthermore, anchoring fibrils containing type VII collagen form loop-like structures that connect laminin to the lamina reticularis [71,72,73,74,75,76,77]. Together, these epithelial filaments form a continuous mechanical linkage between epithelial cytoskeletal elements and the type I and III collagen fibrils of the underlying papillary dermis that allows for the transmission of external mechanical forces (Fig. 1).

Mechanical signals and biochemical cues can regulate cellular behavior and tissue patterning. Mechanosensing is mediated by transmembrane integrins consisting of two α and β subunits. These integrins are key components of two major adhesion systems: focal adhesions, which are mechanosensing complexes that connect integrins to the actin cytoskeleton, and hemidesmosomes, which anchor epithelial cells to the ECM through laminin and the keratin intermediate filament network [52]. Integrins physically link the intracellular F-actin network of epithelial cells to ECM proteins, including fibronectin, vitronectin, type I and III collagens, and laminins [78,79]. Because integrins bind directly to fibrillar collagens and other ECM components, they form as key adhesion receptors that serve as bidirectional allosteric mechanical and chemical signaling relays [78]. In addition to integrins, the cell surface PG syndecan-1 links squamous epithelial cells to ECM components, such as fibronectin [80]. Epidermal cells exist in continuous mechanical and biochemical communication with the underlying connective tissues, which adapt their ECM composition and structural organization in response to changing environmental conditions [7]. Type I and III fibrillar collagens sense, adapt to, and transmit/oppose tensional loads in distinct manners when subjected to mechanical stretching. Interfibrillar GAGs, including decorin and biglycan in tendons, further modulate collagen organization and contribute to tissue adaptation under mechanical loading.

3.2 The Second ECM Layer of the Skin: The Papillary and Reticular Dermis

The dermis forms the second major tissue layer of the skin and provides the skin with the majority of its mechanical strength. The ECM composition of the dermis is distinct, with superficial type I and III collagen fibrils of the papillary dermis being linked to the BM through type VII collagen or anchoring fibrils that also interweave with deeper collagen networks extending throughout the papillary and reticular dermis. This ECM is a form of loose CT and forms the dermal papillae that interdigitate with epidermal rete ridge projections [47]. Dermal papillae contain blood vessels and nerves surrounded and protected by collagen fibers embedded within a microfibrillar network of oxytalan, elaunin, and elastic fibers arranged in a spiral structure that enables them to withstand compressive, tensile, and shear forces [81,82]. The helical collagen fibers in dermal papillae act as shock absorbers, absorbing, storing, and releasing elastic energy in addition to transmitting pressure or tension to the underlying reticular dermis layer [83]. The ultrastructural organization of collagen fibrils and fibers within decellularized rat dermis as viewed by scanning electron microscopy (SEM) is shown in Fig. 2A,B.

The underlying reticular dermis is denser and more irregular than the papillary dermis, containing thicker collagen fibrils and fibers. Barton and Marks reported that fibril diameters in normal skin exhibit a unimodal distribution and increase from the papillary to the reticular dermis (56.2 nm vs. 62.8 nm) [84]. The papillary dermis contains type I and III collagen fibrils that are randomly oriented and interspersed with elastic fibers. In contrast, the underlying reticular dermis includes larger fibrils (mean 80 nm), with type I collagen accounting for 80–90% of the fibrillar population and type III collagen comprising the remaining 10–20%. This mixture of type I and III collagen exhibits

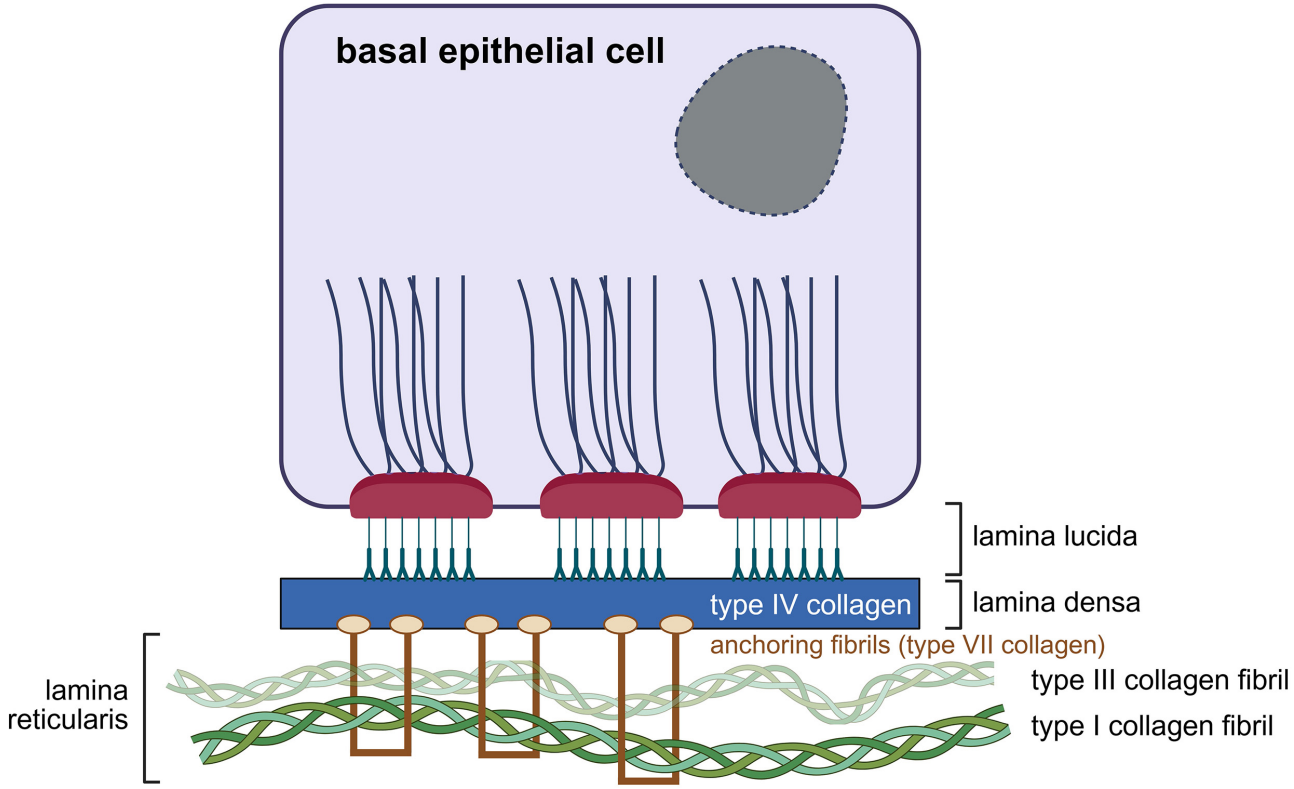


Fig. 1. Composition and anchoring of the basement membrane. The basement membrane consists of two layers: the basal lamina (formed by the lamina lucida and lamina densa) and the reticular lamina (formed mostly of type III collagen). Basal epithelial cells are tightly anchored to the basement membrane by hemidesmosomes (red), and the basement membrane is connected to type I and type III collagens in the dermis ECM by anchoring fibrils (type VII collagen; dark orange). Type III collagen fibrils (light green) are thinner and more pliable than the thicker and stiffer type I collagen fibrils (dark green). Created in BioRender. Piperigkou, Z. (2026) https://core.local.biorender.dev/api/short-link/rro2f2t.

greater elasticity than a matrix composed purely of type I collagen [35,44,85,86]. The dermis also contains specialized collagenous structures known as skin ligaments or retinacula cutis superficialis, which consist of vertically and obliquely oriented collagen bundles extending through the tissue. These structures contribute to the transmission of tensile forces while also helping the skin resist shear stress. The mechanical transmission of forces through the dermis to deeper CTs is mediated through the intervening hypodermis, discussed in the following section.

In the dermal ECM, the hydrophobic collagen fibrils and fibers are bound together with hydrophilic GAG chains, including HA, DS, and CS. These connections form a dynamic hydrated meshwork with elastic strings that transmit tensile, compressive, and shear forces from the superficial ECM networks to the deeper layers [2]. HA in the skin and joints forms aggregates with extracellular versican, thereby contributing to skin hydration and viscoelasticity. In the dermis, HA-associated water supports lubrication, cell migration, pressure absorption, and force transmission [87,88]. When dermal collagen fibers are subjected to tensile loading, they align along the direction of loading, as PGs and GAGs facilitate collagen fibril sliding [35,89,90].

3.3 The Third ECM Layer: Fasciae and Adipose Tissue

The hypodermis lies beneath the reticular dermis and primarily consists of loose CT rich in GAGs and PGs that cover the body and contains adipose lobules that provide thermal insulation and mechanical protection for the overlying skin [47,91]. The hypodermis, also known as the areolar adipose tissue, exhibits a honeycomb-like architecture in which adipocytes are organized within a fibrous collagenous framework [47]. Microscopic examination of the hypodermis reveals flattened lobules consisting of large, compacted adipocytes approximately 80 µm in diameter that are separated by many mostly vertically oriented type I collagenous septa known as retinacula cutis superficialis, which are generally oriented vertically and connect the ECM of the reticular dermis to the underlying superficial fascia. In addition to collagen, they contain elastic fibers and contribute to the transmission and resistance of tensile forces between the epidermis and the superficial fascia [91,92,93,94].

Adipogenesis is highly sensitive to internal and external mechanical loads that induce cytoskeletal changes in the adipose-derived stem cells and/or modulate ECM–associated signaling pathways. The adipose tissue is rou-

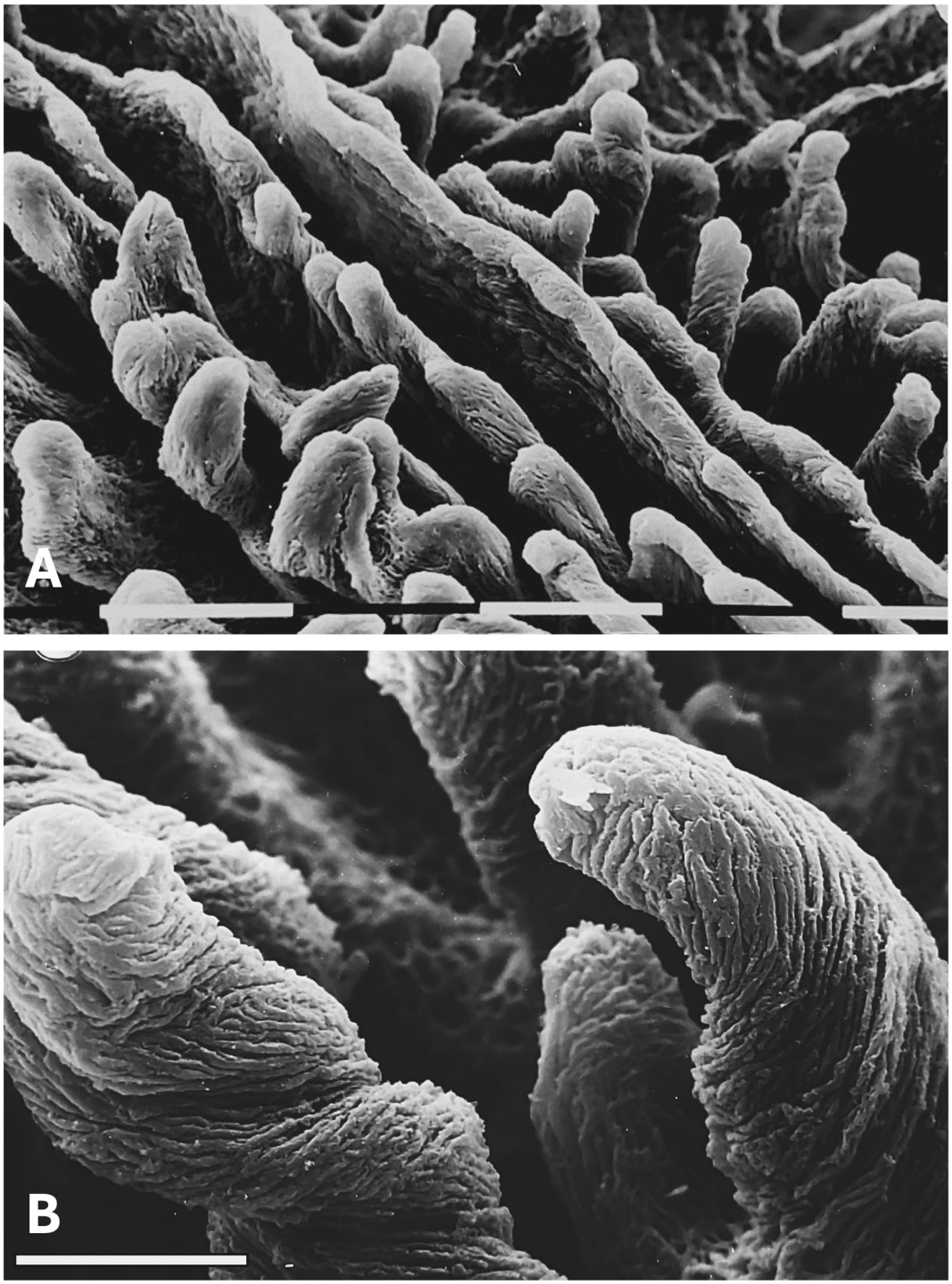


Fig. 2. Scanning electron microscopy images of the structural organization of collagen fibrils and fibers in decellularized rat dermis. (A) The papillary dermis ECM exhibits parallel ridges, including regularly distributed dermal papillae that mainly consist of collagen fibrils and fibers. Scale bar, 100 µm. (B) At higher magnification, the dermal papillae exhibit a regular helical array of collagen fibrils that form thin and flexible fibers. Scale bar, 10 µm.

tinely subjected to a mix of tensile, compressive, and shear forces. Tensile loads and shear stresses are likely conveyed through the collagen scaffold and the retinacula cutis superficialis, whereas adipocytes primarily resist compressive loading. Individual adipocytes possess mechanosensitive and mechanoresponsive properties [95]. When the hypodermis is subjected to static stretching, fibroblasts respond by expanding and remodeling their cytoskeleton within minutes, influencing the viscoelastic properties of the stretched hypodermis. The fibrillar collagen network

is vital for adipocyte integrity, functioning as a supportive framework that protects against mechanical disruption [96,97,98].

The microvacuolar structure of the hypodermis also enables it to serve as an important reservoir for interstitial fluid, thereby influencing tissue stiffness. Hydrophilic HA, together with other GAGs or PGs, forms aggregates that function as shock–absorber complexes and sponges capable of absorbing interstitial fluid when an increase in tissue pressure occurs, as in the context of inflammation [47]. Water plays an essential role in regulating the mechanical properties of the skin, with dehydrated skin samples being up to 60 times stiffer than the wet ones [99,100,101].

In the hypodermis, adipocytes are encapsulated by a BM containing type IV collagen that is surrounded by a network of type I collagen fibrils produced largely by the adipocytes themselves, which constitute the principal ECM component of this tissue [102,103]. The transmission of tensional forces in the hypodermis may be mediated by the BM network that surrounds adipocytes, which withstand compressive loads, but can also contribute to force transmission through deformation of their cytoplasm [96,104]. Adipocytes store energy, secrete adipokines to regulate inflammation, and control metabolism and systemic homeostasis, in addition to playing a critical role in cellular communication and mechanosensing [105,106,107,108]. Adipocytes also stiffen as they differentiate due to lipid droplet accumulation [109]. Overall, adipocytes embedded within a collagen-rich matrix respond to both compressive and tensile stimuli, which can influence lipid storage, while alterations in the surrounding ECM can, in turn, modulate adipocyte function [110].

Two distinct membranous soft CT layers lie beneath the hypodermis: the superficial fascia and the deep fascia [111]. The collagen content of the deep fascia is higher than that of the superficial fascia [112]. The superficial fascia is a thin layer of CT (approximately 500–700 μm thick), with region-specific variations in both thickness and density [113]. This layer provides a conduit for nerves, lymphatic vessels, and blood vessels [114]. Structurally, the superficial fascia is composed of loosely organized, interwoven collagen fibers with a largely random orientation, together with abundant elastic fibers arranged into membranous sheets. It is also connected to the collagen fibers of the reticular dermis by the superficial retinacula cutis, and to the deep fascia by the deep retinacula cutis [47,115]. The superficial fascia plays a key structural role in maintaining the integrity and stability of the dermis, hypodermis, and subcutaneous tissues through the mechanical actions of the retinacula dermis. Its collagen and elastic components suggest that the superficial fascia plays an essential role in regulating tissue biomechanics, permitting movement between the skin and deeper anatomical structures [113]. In the superficial fascia, type I and type III collagens exhibit regional variability, although both are generally present at comparable levels in the superficial fascia [112]. The superficial fascial layer is present throughout the human body with regional variability such that it is thickest in the leg and thinnest over the dorsum of the hand. It provides structural support to the hypodermis, as well as subcutaneous structures such as veins, contributing to their patency. Anatomical investigations have also demonstrated a close interaction between the dorsal fascia superficialis and the adipose lobules of the subcutaneous tissue in Asian women [113].

3.4 Deep Adipose Tissue and Deep Fascia

Under the superficial fascia lies a deep lamellar adipose layer known as the subcutaneous tissue or adipofascia [116]. The subcutaneous tissue is confined between the fascia superficialis and the deep fascia, which are structurally connected by the retinacula cutis profunda [117]. These retinacula are similar to the retinacula cutis superficialis in terms of composition and form an extensive network throughout the adipose layers present over most of the body, with anatomical region-specific variations in length and density. They function as an endoskeletal framework that contributes to a reduction in the elasticity of the subcutaneous tissue [91] while permitting constant changes in tissue length through adaptation to stretching and compression [118]. The subcutaneous tissue layer is predominantly found in the abdomen, flanks, trochanteric region, knees, back of the arms, and the upper third of the inner face of the thighs, though its distribution varies with gender and age. For instance, approximately 51% of subcutaneous tissue in women is located in the abdominal region, compared with 66% in men. The thickness of the subcutaneous tissue layer is also related to the body contour and localized tissue changes evident in obesity [94]. About 80% of all body fat is subcutaneous fat that, like other forms of adipose tissue, plays key mechanical roles, including the protective buffering of external forces to protect the body [119]. This loose CT also functions as an endocrine organ capable of releasing estrogens and other endocrine mediators, such as adipokines or lipokines. It is the main site of adipocyte storage, allowing for the accumulation of lipids and the release of accumulated energy.

The subcutaneous adipose layer functions as a cushion, can insulate the body from heat and cold, and comprises the deepest layer of the cutaneous immune barrier [120,121]. Subcutaneous tissue is similar to the hypodermis, albeit with larger, flattened, less defined adipocyte lobules, and with collagenous septa that are less prominent and tend to follow predominantly oblique trajectories. These ligaments are connected to the underlying deep fascia and facilitate the sliding of the subcutaneous tissue over the underlying deep fascia [119]. In addition, lipid mobilization from the larger adipocytes of the subcutaneous tissue occurs more slowly during weight loss than from adipocytes within the hypodermis [94]. The common ECM components in subcutaneous tissue form a network that provides cell sig-

naling cues and mechanical support, regulating adipocyte morphology and functionality. Adipocytes secrete SPARC, an acidic glycoprotein rich in cysteine that is also known as osteonectin or BM-40, which stimulates metalloproteinase production and is associated with hyperplasia and adipogenesis. Osteonectin also binds to type I collagen fibrils, which are particularly structured to play a specific role in the transmission of tensile loads [122].

The deep fascia is located between the subcutaneous adipose tissue and the underlying skeletal muscle epimysium, although continuity between the superficialis and deep fascia has been noted in some regions [123]. The thickness of this CT layer varies regionally, with a mean thickness of 1 mm. The deep fascia surrounds the superficial skeletal muscles, nerves, and blood vessels throughout the body [124]. In some areas, it also exists in direct contact with the periosteum covering bones. It appears as a dense, glossy, fibrous lamina primarily composed of type I collagen and reinforced by the retinacula cutis profunda [125]. Dense, closely packed collagen fibers are organized in two to three layers of thick bundles with sparse elastic fibers separated by a loose CT layer [115]. Although some collagen fibers display irregular orientations, the larger bundles are often arranged perpendicular to the underlying epimysium, suggesting a potential role in transmitting tensile forces between the deep fascia and the epimysium [126]. However, in human deep fascia, type III collagen is typically more abundant than type I collagen [112]. The elasticity of type III collagen allows for sliding between different tissues. The deep fascia is also rich in HA, blood vessels, lymphatic channels, nociceptors, proprioceptors, mechanoreceptors, thermoreceptors, and chemoreceptors [127]. Pathological changes in the fascia are associated with increased tissue stiffness, altered myofibroblast activity, changes in collagen and matrix metalloproteinase expression, and increased density of nociceptive nerve fibers accompanied by inflammatory and immune cell infiltration [124]. The deep fascia is tightly joined to the connective sheaths of the superficial skeletal muscles, as well as the tendons and ligament sheaths. Close connections have been described between the deep fascia and the paratenon of the gracilis, semitendinosus, semimembranosus, and sartorius tendons around the knee joint [128]. The deep fascia plays an exoskeletal mechanical role, providing sites for muscular attachment and forming osteofascial compartments through the presence of intermuscular septa. It coordinates muscle contraction, facilitates venous return, dissipates stress concentrated at entheses, protects underlying structures, and serves as a body-wide proprioceptive organ [111]. The deep fascia also contributes to lubrication by facilitating tissue gliding [129]. Cells of the deep fascia, known as fasciacytes, produce HA that is present both between the deep fascia and epimysium, as well as within the deep fascia between adjacent layers containing densely packed collagen fibers and elastic fibers arranged in different orientations, forming angles of approximately 78° [114,115,130]. The biomechanical functions of HA, which are structurally identical across bacteria and vertebrate CTs [131], stem primarily from its ability to bind water molecules, forming a viscous tissue environment that supports lubrication and water homeostasis while controlling molecular filtration and diffusion [115,132].

4. Extracellular Matrices in Skeletal Muscle: The Epimysium, Perimysium, and Endomysium

Skeletal muscle is composed of contractile muscle fibers, as well as ECM sheaths that account for 1–10% of total muscle mass and are structurally continuous with the tendon [133]. Muscle ECM networks are composed of an external epimysium layer surrounding the entire muscle, an intermediate perimysium layer extending from the epimysium to surround groups of muscle cells, and the inner endomysium layer extending from the perimysium and surrounding individual myofibers [134] (Fig. 3, Ref. [11]). While these three forms of intramuscular CT differ in composition and structure depending on muscle composition, topographic location, and function, the following discussion focuses on their general structural characteristics [135,136]. The skeletal muscle ECM primarily consists of type I and III collagen, with type I predominating in the epimysium and perimysium, whereas type III is the dominant type found in the endomysium. Types IV, V, VI, XI, XII, XIV, XV, and XVIII collagens are also present in smaller amounts within these networks [137]. The structural characteristics of collagens within the muscular fasciae suggest their importance in the transmission and distribution of mechanical forces during normal musculoskeletal function [138]. The skeletal muscle ECM also contains PGs, with the most abundant being decorin and biglycan, both of which exhibit CS and DS chains. Heparan sulfate proteoglycans (HSPGs), including collagen XVIII, perlecan, and agrin, account for approximately 30% of the total PG content in rat skeletal muscle ECM [134]. HA is also present and distributed heterogeneously through connective tissue sheaths of skeletal muscle [139].

The epimysium is a superficial, thick connective sheath in close contact with the deep fascia that encases each individual muscle and defines muscle volume. Microscopic findings have prompted some researchers to regard the deep fascia and the underlying epimysium as a unique structural unit referred to as the deep/muscular fascia. Epimysium thickness varies with anatomical location, body mass index (BMI), age, and pathophysiological conditions [140]. The epimysium includes predominantly type I collagen fibers, with a smaller complement of type III fibers, and with 15% elastic fibers also being present in the water-rich PG matrix [141]. The orientation of collagen fibers in the epimysium differs across muscles and species. In bovine semitendinosus muscle, for example, epimysium

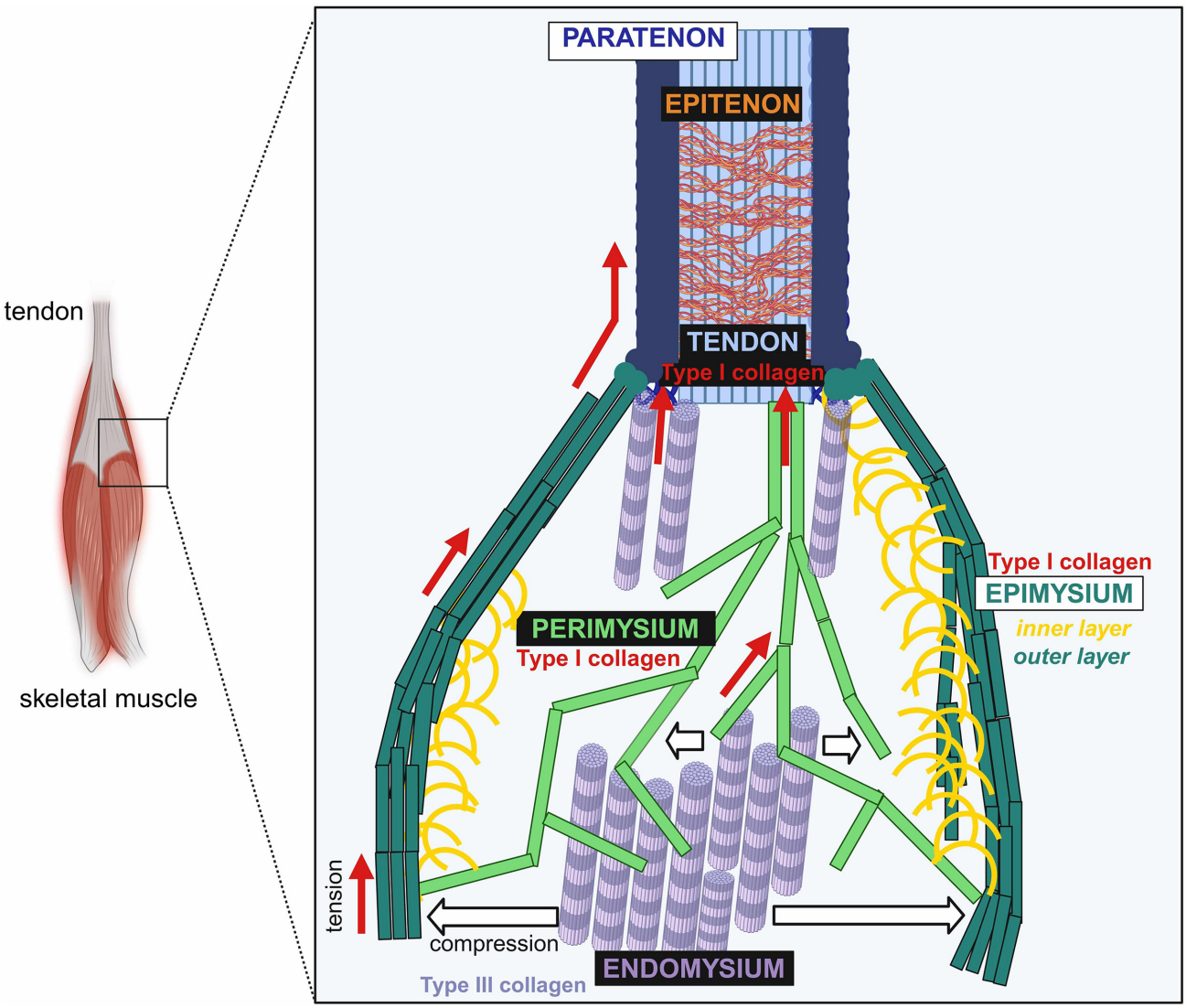


Fig. 3. Collagen fibers that form the muscle sheaths (epimysium, perimysium, endomysium) follow different courses but exhibit mutual continuity. Longitudinally oriented type I collagen fibers, which predominate in the epimysium (dark green) and perimysium (light green), are continuous with the collagen fibers of the tendon (light blue) and tendon sheaths (paratenon, dark blue; epitenon, red). The orientations of these fibers suggest the directions along which they can transmit lateral forces associated with skeletal muscle contraction. During contraction, each myofiber increases in circumference, which generates lateral pressure and a consequent stretching of the randomly oriented and parallel type III collagen reticular fibers of endomysium. During myofiber contraction, the stretched endomysial fibers compress the perimysial fibers (small white arrows), which are stretched to transmit tension (red arrows) along their course following a dominant oblique direction relative to the muscle axis. Direct myofiber-perimysium contacts at the perimysial junctional plates also enable direct transfer of force from muscle fibers to the perimysial collagen network [11]. Muscle contraction induces lateral compression of epimysial fibers (large white arrows), which are stretched and transmit tension (red arrows). Because the collagen fibers of the perimysium and epimysium are continuous with those of the tendon and tendon sheaths, respectively, they contribute to the lateral transmission of contractile forces. In addition, collagen fibrils and fibers of the endomysium are in continuity with those of the tendon and are involved in the direct mechanical transfer of muscle contraction-related forces. Created in BioRender. Piperigkou, Z. (2026) https://BioRender.com/6rf6l02.

includes two distinct layers, including one composed of collagen fibers lying in an extremely regular wavy pattern parallel to the axis of the muscle fiber, as well as an outer layer formed by several wavy sheets of collagen fibers running transverse to the long axis of the muscle fiber (Fig. 3; Fig. 4A). A 1 mm-thick sheath including fiber bundles measuring 200–300 microns in diameter coursing longitudinally and parallel to the main axis of muscle fiber has also been described [142]. In the thick epimysium of the semitendinosus muscle, collagen fibers are densely packed and run

parallel to the muscle's long axis [143]. In the tibialis anterior muscle of rats, Gao et al. [135] distinguished different layers of epimysium, including an inner layer with randomly oriented thinner fibril bundles as well as an outer layer containing thicker fibril bundles with a predominant fiber direction. In different species, the epimysium appears to consist of different layers of collagen fibers, with highly organized outer layers as well as disorganized middle and inner layers [135,144,145] (Fig. 4). Between these two layers, a middle collagen layer forms from sheets of very finely intertwined collagen fibrils. The architecture of collagen in muscle-associated ECM layers also changes through the increasing axial alignment of these fibers in response to muscle stretching. Collagen fibers found in the diaphragm epimysium and perimysium begin at different angles and can also undergo reorientation in the same direction in response to muscle elongation [145].

All fascial layers provide intermuscular connections that can transmit muscular force between adjacent muscles acting in concert with one another. Collagen fibers of the epimysium have been reported to merge into the paratenon, which is contiguous with the inner tendon sheath, or epitenon, covering tendon collagen fibers [146]. The epimysium is thought to be involved in transmitting tensional forces [147,148] (Fig. 4). Immobilization induces the thickening of muscle fascia associated with reduced muscular elasticity/stiffness [149].

The ultrastructural properties of collagen fibers in the perimysium have been studied in various animals in an effort to understand the mechanical function of this muscle sheath. Das et al. [136] were able to observe both thin and thick transversal fibers composing the perimysium. Similarly, two sets of wavy or crimped collagen fiber bundles enmeshed in a PG matrix were described as running parallel to the surface of muscle fibers, with their long axes at +55° and –55° relative to the direction of the muscle fiber [143] (Fig. 4).

In the perimysium, large fibers are primarily composed of type I collagen, with type III collagen as a minor component and even smaller amounts of type V collagen [145,150]. Collagen fibers have been shown to run in different directions in rat skeletal muscle without any dominant orientation [151]. SEM imaging of rat gastrocnemius muscle confirmed that perimysial collagen fibers differ in thickness, run in different directions with a predominantly oblique course, and closely adhere to the endomysium fibrils (Fig. 4A–D). In the bovine masseter muscle, the perimysium is composed of longitudinal, oblique, and circular collagen bundles interconnected by thin collagen fibers. It primarily consists of type I collagen, although type III, V, and VI collagens are also present [152]. In mice, longitudinally oriented fibers in the perimysium form a dense series of bands, with interconnections between transverse collagen fibers and muscle fibers. The collagen fibers of the perimysium can align after stretching, thereby contributing to the tensile mechanical properties of muscle [134,145]. The perimysium can achieve a high level of tensile stiffness, and its continuity with the epimysium, endomysium, and tendons can enable the transmission of high tensile loads [153]. Interestingly, the perimysium is composed of a highly ordered network of collagen fibers and binds tendon myofibers in a muscle-tendon unit, which may play a role in skeletal muscle lateral force transmission [154]. At the myotendinous junctions, collagen fibers of the perimysium appear more aligned and are continuous with tendon fibers [134,145,148,155] (Fig. 4A; Fig. 5A–C).

The endomysium is the inner connective sheath that completely covers each myofiber and consists of felt-like sheets of collagen fibrils [136]. It forms a continuous 3D network ranging from 0.2 to 1.0 μm in thickness and facilitates connections between adjacent muscle fibers, rather than keeping them physically separated [143]. The endomysial collagen fibers are reticular fibers that include thin fibrils running in a wave-like pattern parallel to the muscle cell surface in bovine skeletal muscle [142,154] (Fig. 4A–E). Their course has been reported to vary substantially, with angles ranging from 2.5° to 87.5°. The endomysium is particularly involved in the transmission of muscle contractile forces from adjacent muscle fibers within each fascicle [153]. In muscle sheaths, type IV collagen and laminin are only present in the endomysium [152,155]. Each skeletal muscle cell is covered by a 50 nm-thick BM containing type IV collagen associated with a network of laminin that can also bind to dystroglycan and integrins, mediating the anchorage of collagen IV to the sarcolemma. A microfibrillar network of type IV collagen also links to collagen fibrils composing the inner portion of the endomysium. As endomysial fibers adhere to the sarcolemma, every force generated by the myofibers is transmitted directly to the endomysium, which thus plays a role in lateral force transmission [153,156].

When the muscle is stretched, the fibers of the endomysium change their orientation along the long axis of the muscle, whereas these fibers align at ±90° relative to the long axis of the muscle on contraction [145]. The endomysium exhibits a honeycomb-like structure, with hexagonal myofiber cavities measuring 60–100 μm in diameter that include tightly arranged collagen fibrils from 30 to 70 nm in diameter [157]. The endomysium is primarily composed of thin type III collagen fibers, together with smaller amounts of type I collagen, and even smaller proportions of types IV and V collagen [158]. Ultrastructural SEM images confirm that the endomysium is directly connected to the tendon, in line with histological observations at the myotendinous junction in rats [159] (Fig. 5A–D).

The skeletal muscle transmits forces directly to the bone through tendons and via lateral transmission through the muscle sheaths (Fig. 3). The inner endomysium is mostly composed of very thin reticular fibers of type III collagen that are strongly connected to myofibers through

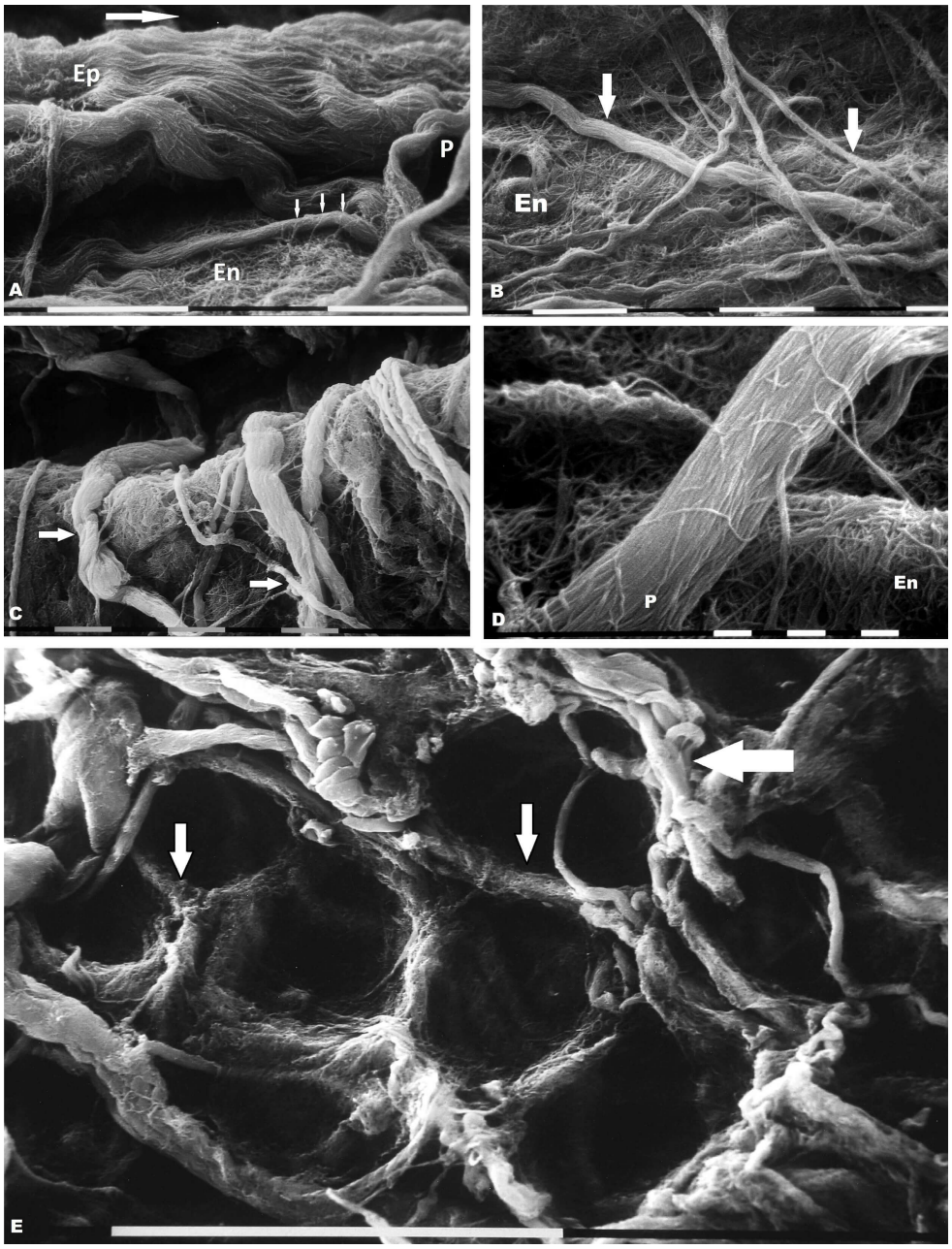


Fig. 4. Scanning electron microscopy images of the rat gastrocnemius muscle. (A) The thick epimysium (Ep) exhibits undulating fibrils that form fibers running longitudinally to the main muscle axis (large arrow). Helical fibers of the perimysium (P) run longitudinally or obliquely relative to the main axis of the muscle and closely enclose the underlying endomysium (En), which is formed from a network of small reticular fibers. Single collagen fibrils clearly anchor the perimysium to the endomysium (small arrows). Scale bar, 10 µm. (B) Perimysium collagen fibers of different sizes (arrows) adhering to the reticular fibers of endomysium (En) run in different directions. Scale bar, 10 µm. (C) In the deeper regions of the gastrocnemius muscle, a single muscle fiber is covered by endomysium reticular fibers, with perimysium fibers of different thicknesses (arrows) wrapping around muscle fibers, and larger fibers containing fibrils with a helical arrangement. Some fibers are oriented orthogonally to the main axis of the muscle fibers, whereas others run obliquely. Scale bar, 10 µm. (D) At higher magnification, the different sizes and courses of the individual fibrils that form straight fibers (likely corresponding to stretched helical fibrils) in the perimysium (P) and endomysium sheaths are more evident. Scale bar, 1 µm. (E) A transverse section of the rat gastrocnemius muscle after maceration. Muscle sheaths include the honeycomb endomysium composed of reticular fibers (small arrows) surrounding the digested muscle cells, and thicker perimysium fibers helically arranged (large arrow) in direct contact with the endomysial fibers. Scale bar, 100 µm.

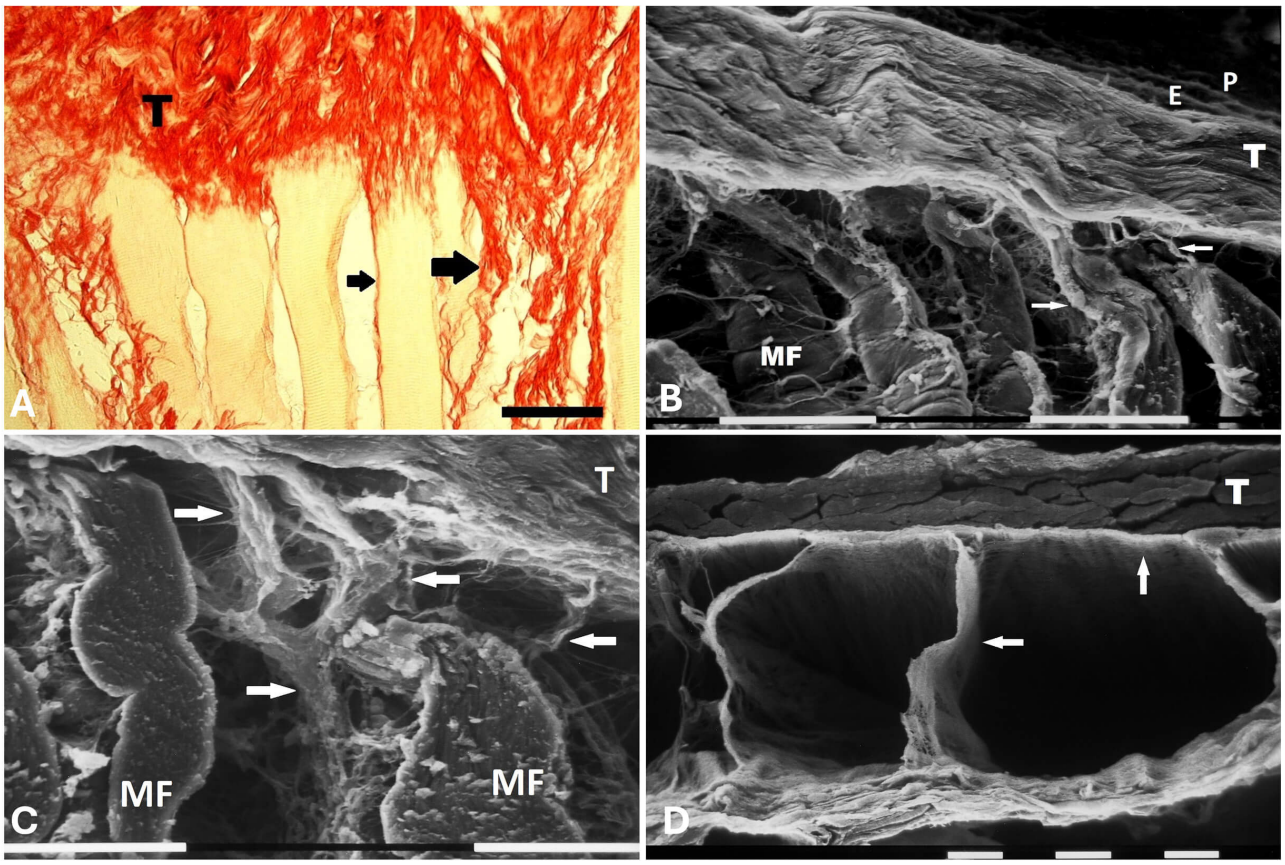


Fig. 5. Continuous collagen network connecting tendon, perimysium, and endomysium at the Achilles myotendinous junction. (A) Picrosirius red-stained histological section of rat triceps surae at the Achilles myotendinous junction. The red-stained collagen fibers of the tendon (T) run in continuity with the perimysium fibers (large arrow) that surround small groups of myofibers (light yellow). Collagen fibers of the tendon appear continuous with the thinner fibers of the endomysium (small arrow). Scale bar, 100 µm. (B) Scanning electron micrograph of triceps surae at the Achilles myotendinous junction. The tendon fibers and fibrils (T) are in tight contact with fibers of the perimysium (arrows), which surround the surface of intact muscle fibers (MF). Tendon sheaths covering the tendon are visible, including the inner epitenon (E) and the outer paratenon (P). White bar, 100 µm. (C) Scanning electron micrograph of rat triceps surae at the Achilles myotendinous junction. Densely packed fibrils forming collagen fibers in the tendon (T) are in tight contact with fibrils of the perimysium (arrows), which follow an oblique direction surrounding two sectioned muscle fibers (MF) exhibiting intracytoplasmatic myofibrils. Interfiber spaces appear empty after dehydration, but likely contain PGs and GAGs that bind water under physiological conditions. Black bar, 100 µm. (D) Rat triceps surae at the Achilles myotendinous junction after maceration. The collagen fibrils of the honeycomb endomysium wall (arrows) are in close contact with the tendon fibers (T). White bar, 10 µm.

a BM. The endomysial fibers wrap each myofiber and follow a course with a dominant circumferential orientation that suggests particular sensitivity to muscle cell changes. Endomysial fibers appear in close contact with those of the tendon at the myotendinous junction, both at the microscopic and ultrastructural levels. This may suggest that the endomysium can contribute to the direct transmission of contractile muscle forces to the tendon. However, when each myofiber contracts, its diameter increases and induces the stretching of the endomysial fibrils and fibers that can transmit tension to the perimysial fibers, enabling the further transmission of contractile muscle forces. The perimysial fibers appear larger than the endomysial ones, run obliquely with no particular orientation, cross and wrap around groups of muscle cells, and include predominantly type I collagen fibrils that are larger and stiffer than type III collagen-including fibrils. While hybrid fibrils formed of type I and III collagens are also present, type I collagen is the most abundant type within the perimysium and epimysium. Muscle sheaths were once thought to solely provide mechanical support to the passive elasticity of muscles. However, in most ECMs and skeletal muscle sheaths, the differences in the orientation, diameter, and supramolecular arrangement of collagen fibrils suggest that they may play a more specific role in which stiffer and straighter type I collagen fibrils oppose or transmit tensile loads, whereas the pliable type III fibrils primarily support passive muscle elasticity. It is therefore plausible that perimysial fibers

are structurally arranged to laterally transmit tensile forces that arise during muscle contraction to the tendon. The perimysium has also been reported to exhibit perimysial junctional plates in direct contact with myofibers, and perimysium fibers seem to directly merge into the tendon [11].

5. The Tendon and Peritendon Sheaths

Tendons generally connect muscles to bones, transmitting contractile muscle forces and generating joint movement. Tendons can vary in shape and size but have a common structure that is related to their biomechanical role. They are bands of dense, regular, fibrous CT primarily consisting of densely packed collagen fibers that run parallel to the direction of force, with interposed PGs. Tendons exhibit a well-organized, multihierarchical structure rich in collagen fibrils that further assemble to form fibers, which then group in fascicles and fiber bundles [160,161].

The ECM found within the human Achilles tendon primarily consists of collagen fibers formed from thick (30–130 nm), stiff fibrils formed predominantly of type I collagen (65–80%) with a straight course, albeit with some fibrils and fibers exhibiting crimping that functions as a biological hinge [162]. By allowing rigid fibrils to bend, these crimps act as shock absorbers when muscles contract and favor tendon elastic recoil [163,164]. Minor amounts of type III collagen and elastic fibers are also present. Tendons include relatively small amounts of PGs (2%) [133]. The major PGs found in tendon tissue are the small leucine-rich PGs (SLRPs) decorin and biglycan, which appear in the form of filaments regularly, orthogonally attached to fibrils to form interfibrillar bridges that regulate ECM assembly and collagen fibrillogenesis [165]. Decorin contains water-binding DS and CS, and provides appropriate spacing and lubrication within the tendon [133]. At myotendinous junctions, skeletal muscle cells transmit force across the cell membrane to ECM sheaths and then to tendons, such that force transmission occurs both along the surfaces of myofibers and at their ends [166].

The region where tendon fibers attach to bone is termed the enthesis. Both fibrous and fibrocartilaginous entheses have been described. In fibrous enthesis structures, as in the Achilles tendon, the collagen fibers and fibrils penetrate and thus physically merge into the ECM of bones [167]. This attachment is mediated by Sharpey's fibers, which are partially mineralized collagen bundles embedded within a GAG-rich matrix [168]. At these entheses, where tendons and ligaments attach to bone, fascial expansions are also present that link these structures with others nearby, including the deep fascia [111]. Tendons may be surrounded by different anatomical structures in direct contact with the tendon fibers, including the following: (1) fibrous sheaths or retinacula; (2) reflection pulleys; (3) synovial sheaths; (4) peritendon sheaths (paratenon) in tendons lacking a synovial sheath; and (5) tendon bursae [160]. These loose CT structures provide support for the vascular, lymphatic, and nerve supply, while also reducing friction with adjacent anatomical structures through the secretion of HA. In the Achilles tendon, the principal covering is the peritenon, which consists of an external paratenon and an inner epitenon directly covering the tendon surface. The epitenon extends into the tendon to form the endotenon, which is a sheath that surrounds and separates individual collagen fascicles [169,170]. A delicate acellular mesotenon sheath, which connects epitenon to the paratenon, acts as a spacer between the two sheaths and contributes to the formation of wide peritendinous spaces containing GAGs and PGs that trap water. In humans, paratenon collagen fibers composed of type I and type III collagens and minor elastic fibers have been described as variably oriented fibers with diameters ranging from 20 nm to 200 nm [171], or as being predominantly aligned with the long axis of the tendon [172,173,174]. The deep fascia can be in direct contact with the outer collagen fibers of the paratenon, which stretch during tendon movement, making these structures difficult to separate anatomically in certain regions [111,175,176]. In addition, the collagen fibers of the paratenon may be covered by deep fascia and are continuous with the epimysium and the bone periosteum (Fig. 6B).

6. Ligaments

Ligaments are specialized fibrous bands that span a joint and connect bones to one another, passively stabilizing joints while also limiting their movement. Ligament ECM composition is similar to that of tendons, characterized by predominantly parallel, crimped type I collagen fibers (~70–75%), together with PGs and elastin present in proportionally greater amounts than compared to tendons. They often have a well-vascularized overlying sheath, or epiligament, that covers and adheres to their surface [177,178]. Most ligaments, much like tendons, have fibrocartilaginous entheses that allow them to adapt to compressive loads [179]. Superficial ligaments are covered by the deep fascia, which provides a structural connection for the dissemination of mechanical loads. There are also many deep fascial sheaths that connect tendons and ligaments, and many examples of tendons and ligaments developing fascial expansions linking them with neighboring structures, such as the deep fascia [111]. Interestingly, ligaments play a crucial role in joint proprioception and, when strained, they activate neurological feedback signals that promote muscular contraction [177].

7. Bone, Periosteum, and Endosteum

Bone is a specialized mineralized CT that consists of a mineralized ECM primarily composed of large fibrils of type I collagen, with a diameter of approximately 100 nm, which form more than 90% of the organic mass of bone [180]. Collagen facilitates elastic deformation through sliding and slippage, whereas hydroxyapatite min-

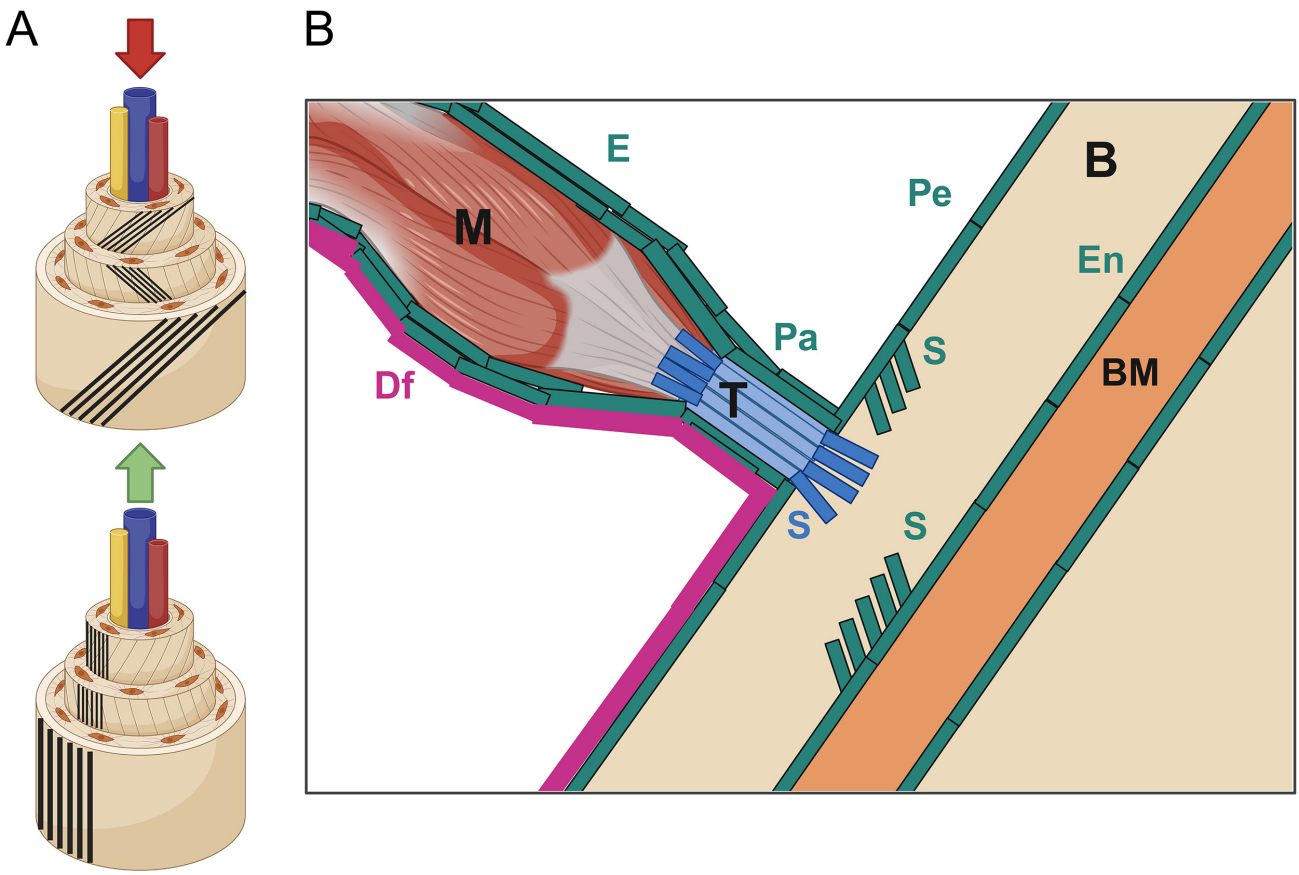


Fig. 6. Collagen fiber orientation and structural continuity at the muscle-tendon-bone interface. (A) Osteons in lamellar compact bone are formed of concentric lamellae helically arranged around the osteon axis and include type I collagen fibers that run parallel to one another inside each lamella, whereas adjacent lamellae exhibit alternating fiber orientations. Osteons subjected primarily to compressive loads (red arrow) exhibit transversely oriented collagen fibers, whereas those subjected primarily to tensile forces (green arrow) exhibit longitudinally oriented fibers. (B) The skeletal muscle (M), shown in red, and the collagen fibers of the tendon (T), shown in blue, are continuous with Sharpey's fibers (S, dark blue), penetrating the ECM of dense lamellar bone (B). The epimysium (E, light green) merges with the paratenon (Pa), which is continuous with the collagen fibers of the periosteum (Pe). The periosteum closely adheres and is anchored to the bone through perforating Sharpey's fibers (S) that penetrate the ECM of the bone. In long bones containing a medullary cavity, the endosteum (En) forms Sharpey's fibers (S) that are continuous with the sparse collagen network of the bone marrow (BM). The deep fascia (Df) is in contact and structurally continuous with the epimysium, paratenon, and periosteum. Created in BioRender. Piperigkou, Z. (2026) https://BioRender.com/qrnweox.

erals deposited within and on collagen fibrils ensure the strength and toughness of bone [181]. Polarized light microscopy studies of compact lamellar bone in long bones have identified three principal osteonal collagen architectures (transverse, alternating, and longitudinal), the organization of which is thought to optimize resistance to gravitational and mechanical loading [182].

Osteons are cylinder-like structures about 200–250 μm in diameter formed from concentric lamellae of mineralized collagen fibers. Osteons run roughly parallel to the long axis of the bone, with an inclination that is consistent across bones and varies between 5° and 15° [183]. Osteon lamellae, which are helically arranged around the main axis of the osteon, include type I collagen fibers running parallel to each other inside each lamella, but coursing orthogonally in adjacent lamellae to provide resistance against gravitational loading [184,185,186]. A similarly regular organization of orthogonal collagen fiber lamellae has also been described in the peritumoral microenvironment of the human breast, and such collagen arrays can provide resistance against cancer cell invasion *in vivo* [16].

In lamellar bone, collagen fibrils are able to adapt by aligning in response to local mechanical stresses and strains [187]. Longitudinally aligned fibrils primarily resist tensile forces, while transversely aligned fibrils resist compressive loading [181,188,189] (Fig. 6A). The extent of mineralization is closely associated with collagen fibril organization. Under polarized light microscopy, osteons with longitudinally oriented collagen fibers and a higher degree of mineralization appear stiffer and more structurally capable of

resisting tension and compression, whereas osteons that include oblique fibers exhibit greater ductility and efficiently dissipate energy [190]. Furthermore, more slowly deposited bone often contains a higher proportion of oblique and transverse collagen fibers [191]. Bone remodeling is regulated by osteoclasts that resorb bone and osteoblasts that form new bone. These cells are indirectly controlled by mechanical loading, which stimulates the osteocytes to produce factors capable of influencing osteoblast and osteoclast activity [192]. In addition, PGs and GAGs within the bone ECM regulate bone homeostasis and contribute to the mechanical properties of bone by retaining bound water. Biglycan and decorin are members of the SLRP family and are the major PGs found in bone [193,194].

The outer and inner surfaces of bone are covered by specialized CTs known as the periosteum and the endosteum. The periosteum is a membrane that covers and closely adheres to the outer surface of all bones at sites other than articular surfaces. The periosteum plays a role in bone matrix formation and mineralization through matrix vesicles, and is important for bone fracture healing [195,196]. It includes an outer fibrous layer and an inner layer with osteogenic potential. The outer fibrous layer is composed of two sublayers. The superficial sublayer contains small, densely packed type I collagen fibers, blood vessels, and many nerves [197], while the deeper sublayer contains many elastic fibers and collagen fibers primarily oriented along the femoral axis, with few cells and vessels in this region. The inner layer of the periosteum contains mesenchymal progenitor cells, differentiated osteogenic progenitor cells, osteoblasts in direct contact with the cortical bone surface, and fibroblasts present within a sparse collagenous matrix with a rich vascular and neural network [198,199]. The periosteum is strongly anchored to the bone surface through Sharpey's perforating collagen fibers, which run at 30° and cross the osteoblast layer to penetrate bone tissue (Fig. 6B). They form a net-like structure surrounded by the cytoplasmic processes of fibroblasts [200]. As Sharpey's fibers are rich in type III collagen, they may be particularly responsive to mechanical loading and could participate in the regulation of bone adaptation to physical activity [201].

Within the medullary cavity of long bones, there is a connective membrane known as the endosteum that lines the Haversian canal and all the internal cavities of the bone. The endosteum is thinner than the periosteum [202] and is classified into three topographic types: (1) the cortical endosteum lining the bone marrow cavity, (2) the osteon endosteum lining the Haversian canal and the Volkmann's canal, which primarily contains blood vessels and nerves, and (3) the trabecular endosteum covering the developing bone. Endosteum membranes are characterized primarily by osteogenic cells and, unlike the periosteum, do not exhibit a defined fibrillar structure. Some researchers have reported the presence of type III collagen fibers, also known as reticular fibers, in the endosteum [203,204], while others have described the presence of osteoblasts producing type I collagen [205]. Endosteum structures are strictly associated with bone metabolism, as they contribute to the growth, remodeling, and development of this mineralized tissue [206]. Sharpey's fiber system, described in the periosteum, has also been speculated to be present in the endosteum [201]. Within the long bones, the endosteum forms a mechanical connection between bone and bone marrow that includes both type I and type III collagens [207].

8. Conclusions and Clinical Considerations

In this review, we present a model of a continuous fibrillar collagen network formed by structurally and mechanically connected ECM networks spanning from the skin to the bone marrow. Within this network, the insoluble framework of collagen fibers and fibrils is held together by hydrophilic elastic linear GAGs and PGs, which are essential for supporting the biomechanical properties of the fibrillar collagen network and interact with other proteins like elastin and fibronectin. With the help of deformable BMs, integrin-mediated focal adhesions, and the mechanosensitive and mechanoresponsive adipocytes of the hypodermis and subcutaneous tissue, this fibrous collagen skeleton is able to adsorb and transmit information about environmental stimuli and skin structural conditions from the epidermis to bone marrow.

This model is based on the observation that different types of fibrillar collagen (mainly types I and III) and fiber orientation are primary determinants of ECM biomechanical properties. Type I and III collagens make up 90% of total collagen content in the body and form fibrils of varying diameters and microfibrillar arrangements in order to respond to mechanical stimuli in various ways. Fig. 7 provides a graphical summary of the distribution and interactions of type I and III fibrillar collagens, which form a continuous network among adjacent ECM networks.

Maintaining an appropriate ratio between the two fibrillar collagens necessitates a balance between strength and flexibility in CTs, and is crucial to reduce the risk of collagen-related disorders in many diseases [208]. Notably, changes in the type I/III collagen ratio have been reported in aging [209], in pathological conditions like osteoporosis, wound healing, diabetic complications, cardiac function, solid tumor invasion, periodontal diseases, hemorrhoids, hernia recurrence after the implantation of alloplastic prostheses, and pelvic organ prolapse [43,210,211,212].

The ultrastructural collagen interactions and mechanosensing functions that interlink different ECM networks from the epidermis to the bone marrow in this proposed theoretical model can offer insight into many biological processes critical for tissue adaptation and homeostasis, while also influencing disease pathogenesis and therapeutic outcomes. Notably, physical activity improves bone metabolism and reduces the risk of bone fractures by stimulating bone osteocytes. Osteocyte surface

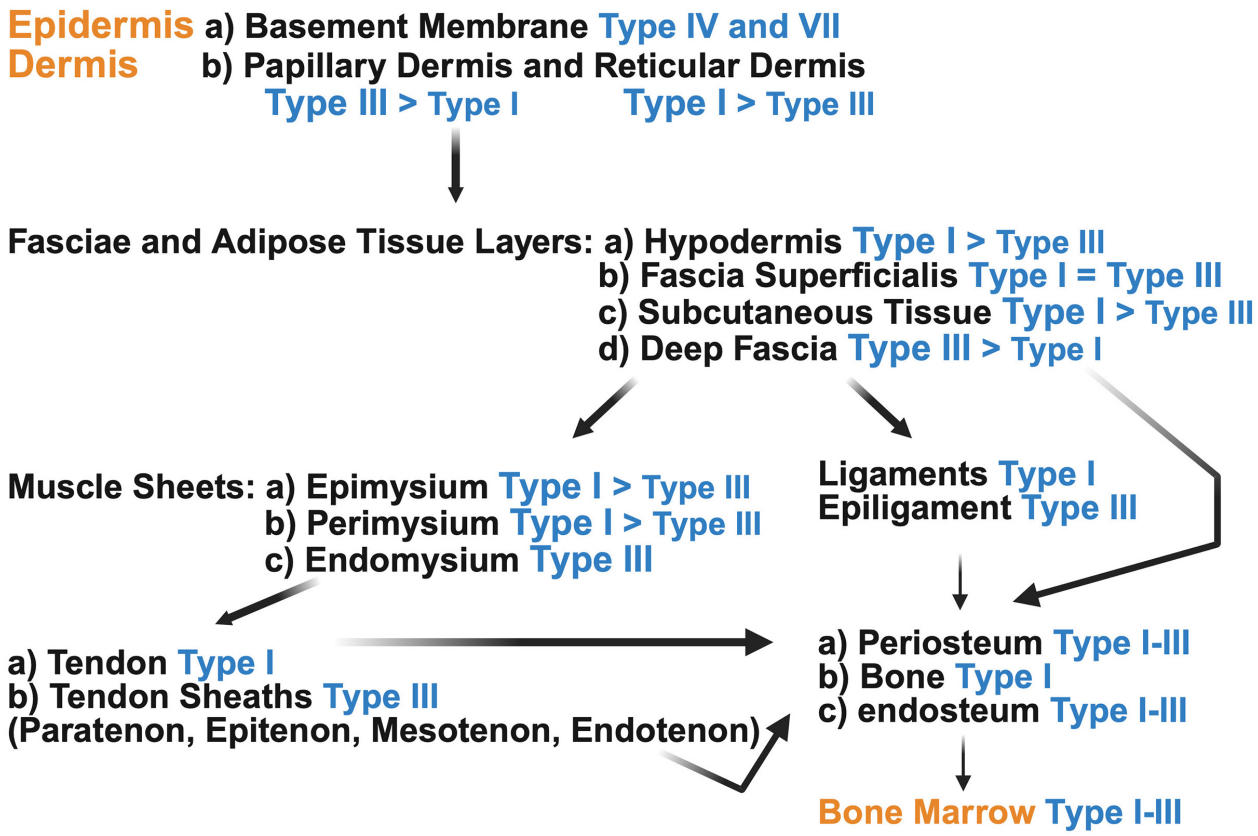


Fig. 7. Distribution and interactions of type I and III fibrillar collagens as components of a continuous ECM network from the epidermis to the bone marrow. Created in BioRender. Piperigkou, Z. (2026) https://BioRender.com/p6fd3p0.

deformation has been linked to changes in interstitial or peri-osteocyte fluid flow within the lacunar-canalicular network, which is rich in HA and perlecan/HSPG2. However, "collagen hillocks", also called "canalicular projections", directly connect the mineralized walls of osteocyte canaliculi to the plasma membrane of osteocyte dendrites, and the primary cilia of these mechanosensing cells are in contact with the pericellular matrix. Moreover, uncalcified collagen fibrils extending directly from the mineralized walls of the osteocyte canaliculi have been described as being in direct contact with the cell membrane through integrin-mediated focal adhesions [213,214]. Bone type I collagen fibrils that connect the mineralized bone matrix to the osteocyte dendrite may thus be able to adsorb and transmit some external loads from the superficial epidermis to the bone ECM, ultimately propagating the associated signals to the osteocytes.

Collagen-focused therapeutic strategies are an actively evolving field. Electrical stimulation, photobiomodulation, ultrasound-based approaches, and mechanical loading are all employed in clinical settings as adjunctive therapeutic interventions to induce tissue remodeling and favor collagen biosynthesis [215,216,217,218].

The clinical application of extracorporeal shock waves to the skin has been shown to stimulate rapid periosteal cell proliferation and migration and to thereby favor diabetic and chronic wound healing [219], bone fracture healing [220], and enhanced bone formation under osteoporotic conditions [221]. ECM components play an important role in normal wound healing, and their destruction impairs this healing process [222]. The potential skin-bone marrow mechanical interplay is further supported by the fact that normal skin serves as a target tissue for bone marrow-derived cells, highlighting the possibility of bidirectional communication between these tissues. In long bones, the endosteum forms the interface between the compact bone and bone marrow regions and is rich in type I and type III collagens. Interestingly, in the context of skin wound healing, the bone marrow provides both inflammatory (CD45+) and noninflammatory (CD45−) cell types, which are crucial for the process of skin repair. These cells produce both type I and III collagens, unlike skin-resident cells, which only produce type I collagen. Moreover, these cells migrate from bone marrow to skin through the blood, which is another essential CT system [223].

Overall, the persistent hierarchical and helical organization of collagen, from individual molecules to fibrils, fibers, and higher-order assemblies, is evident across the dermal papillae, tendons, ligaments, and bone osteons, confirming that fibrillar collagens (primarily type I and III) pro-

vide a structural framework while also playing a fundamental role in absorbing force and transmitting tensional and compressive loads from the skin to bone marrow, which serves as the main source of stem cells essential for development, tissue differentiation, tissue repair, and wound healing. The theoretical model is supported by different experimental data reported in this review. However, quantitative validation through further mechanical experiments would be necessary to test and confirm the force transmission, from epidermis to bone marrow, through different ECMs.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the corresponding authors on request. The authors declare that the images are unpublished archival material generated by Prof. Marco Franchi.

Author Contributions

MF, LF Conceptualization, Investigation, visualization; data curation; writing—review and editing; SM, KS, ZP, NKK: Investigation, Methodology, Project administration, Software, Resources, Supervision, Validation, Visualization; Writing—review and editing. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors have approved the final manuscript. The authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Ethics Approval and Consent to Participate

All surgical procedures were performed in accordance with the European and Italian Law on animal experimentation and the ethical principles stated in the "NIH Guide for the Care and Use of Laboratory Animals". The images of this manuscript are unpublished archival materials obtained from control groups of previous animal experiments started from 2010. The research protocol on animals was approved by the Ethical Committee of Rizzoli Orthopaedic Institute (Protocol: Tendine Rotuleo; Approved: December 15th, 2010). All pictures were generated from tissue samples collected from Sprague Dawley male rats aged about 5 months. We performed histological and SEM analysis on leg dermis, gastrocnemius muscle with the corresponding muscle sheaths, and Achilles tendon including relating tendon sheaths at the myotendinous junction. The animals were maintained under standard laboratory conditions at the Laboratory of Preclinical Surgical Studies of the Rizzoli Orthopedic Institute, Bologna, Italy.

Acknowledgment

The authors would like to thank Mr. Marios Vetoulas and Ms. Katerina Mineschou (Department of Chemistry, University of Patras, 26504, Greece) for reference formatting.

Funding

Z.P. and N.K.K. acknowledge funding by the European Union under the action HORIZON MSCA- 2022-SE-01 (CARES). Project ID: 101130985. Z.P. acknowledges FEBS as a funding contributor (FEBS Booster Fund 2024).

Conflicts of Interest

The authors declare no conflicts of interest. Nikos K. Karamanos is serving as one of the Editorial Board members of this journal. We declare that Nikos K. Karamanos had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Katarzyna Anna Cieslik.

References

[1] Weerdesteyn V, Hollands KL, Hollands MA. Gait adaptability. Handbook of Clinical Neurology. 2018; 159: 135–146. https://doi.org/10.1016/B978-0-444-63916-5.00008-2

[2] Franchi M, Piperigkou Z, Mastronikolis NS, Karamanos N. Extracellular matrix biomechanical roles and adaptation in health and disease. The FEBS Journal. 2024; 291: 430–440. https://doi.org/10.1111/febs.16938

[3] Núñez-Lisboa M, Echeverría K, Willems PA, Ivanenko Y, Lacquaniti F, Dewolf AH. Understanding gait alterations: trunk flexion and its effects on walking neuromechanics. The Journal of Experimental Biology. 2024; 227: jeb249307. https://doi.org/10.1242/jeb.249307

[4] Slater AM, Barclay SJ, Granfar RMS, Pratt RL. Fascia as a regulatory system in health and disease. Frontiers in Neurology. 2024; 15: 1458385. https://doi.org/10.3389/fneur.2024.1458385

[5] Wang JH, Li B. Mechanics rules cell biology. Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology: SMARTT. 2010; 2: 16. https://doi.org/10.1186/1758-2555-2-16

[6] Zeltz C, Orgel J, Gullberg D. Molecular composition and function of integrin-based collagen glues-introducing COLINBRIs. Biochimica et Biophysica Acta. 2014; 1840: 2533–2548. https://doi.org/10.1016/j.bbagen.2013.12.022

[7] Urbanczyk M, Layland SL, Schenke-Layland K. The role of extracellular matrix in biomechanics and its impact on bioengineering of cells and 3D tissues. Matrix Biology: Journal of the International Society for Matrix Biology. 2020; 85-86: 1–14. https://doi.org/10.1016/j.matbio.2019.11.005

[8] Di X, Gao X, Peng L, Ai J, Jin X, Qi S, et al. Cellular mechanotransduction in health and diseases: from molecular mechanism to therapeutic targets. Signal Transduction and Targeted Therapy. 2023; 8: 282. https://doi.org/10.1038/s41392-023-01501-9

[9] Lintzeri DA, Karimian N, Blume-Peytavi U, Kottner J. Epidermal thickness in healthy humans: a systematic review and meta-analysis. Journal of the European Academy of Dermatology and Venereology: JEADV. 2022; 36: 1191–1200. https://doi.org/10.1111/jdv.18123

[10] de Szalay S, Wertz PW. Protective Barriers Provided by the Epidermis. International Journal of Molecular Sciences. 2023; 24: 3145. https://doi.org/10.3390/ijms24043145

[11] Passerieux E, Rossignol R, Letellier T, Delage JP. Physical continuity of the perimysium from myofibers to tendons: involvement in lateral force transmission in skeletal muscle. Journal of Structural Biology. 2007; 159: 19–28. https://doi.org/10.1016/j.jsb.2007.01.022

[12] Du J, Sun X, Ao L, Zhou X, Shi H, Yong Q, et al. Impact of Abnormal Mechanical Stress on Chondrocyte Death in Osteoarthritis. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2025; 31: e948290. https://doi.org/10.12659/MSM.948290
[13] Szarek P, Ruberti JW. Collagen Mechanics. Sub-cellular Biochemistry. 2026; 113: 277–342. https://doi.org/10.1007/978-3-032-05273-5_10
[14] Bella J, Hulmes DJS. Fibrillar Collagens. In Parry DAD, Squire JM (eds.) Fibrous Proteins: Structures and Mechanisms (pp. 457–490). Springer International Publishing: Cham. 2017.
[15] Ruggeri A, Franchi M, Marini N, Trisi P, Piatelli A. Supracrestal circular collagen fiber network around osseointegrated non-submerged titanium implants. Clinical Oral Implants Research. 1992; 3: 169–175. https://doi.org/10.1034/j.1600-0501.1992.030403.x
[16] Franchi M, Masola V, Onisto M, Franchi L, Mangani S, Zolota V, et al. Ultrastructural Changes of the Peri-Tumoral Collagen Fibers and Fibrils Array in Different Stages of Mammary Cancer Progression. Cells. 2025; 14: 1037. https://doi.org/10.3390/cells14131037
[17] Nashchekina Y, Nashchekin A. Collagen Fibril Orientation In Vitro: From Formation to Advanced Biomaterial Development. Biomimetics (Basel, Switzerland). 2025; 10: 644. https://doi.org/10.3390/biomimetics10100644
[18] Heino J. The collagen family members as cell adhesion proteins. BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology. 2007; 29: 1001–1010. https://doi.org/10.1002/bies.20636
[19] Asgari M, Latifi N, Heris HK, Vali H, Mongeau L. In vitro fibrillogenesis of tropocollagen type III in collagen type I affects its relative fibrillar topology and mechanics. Scientific Reports. 2017; 7: 1392. https://doi.org/10.1038/s41598-017-01476-y
[20] Ruggeri A, Benazzo F, Reale E. Collagen fibrils with straight and helicoidal microfibrils: a freeze-fracture and thin-section study. Journal of Ultrastructure Research. 1979; 68: 101–108. https://doi.org/10.1016/s0022-5320(79)90146-1
[21] Reale E, Benazzo F, Ruggeri A. Differences in the microfibrillar arrangement of collagen fibrils. Distribution and possible significance. Journal of Submicroscopic Cytology. 1981; 13: 135–143.
[22] Ottani V, Martini D, Franchi M, Ruggeri A, Raspanti M. Hierarchical structures in fibrillar collagens. Micron (Oxford, England: 1993). 2002; 33: 587–596. https://doi.org/10.1016/s0968-4328(02)00033-1
[23] Franchi M, Raspanti M, Dell'Orbo C, Quaranta M, De Pasquale V, Ottani V, et al. Different crimp patterns in collagen fibrils relate to the subfibrillar arrangement. Connective Tissue Research. 2008; 49: 85–91. https://doi.org/10.1080/03008200801913635
[24] Depenveiller C, Baud S, Belloy N, Bochicchio B, Dandurand J, Dauchez M, et al. Structural and physical basis for the elasticity of elastin. Quarterly Reviews of Biophysics. 2024; 57: e3. https://doi.org/10.1017/S0033583524000040
[25] Halsey G, Sinha D, Dhital S, Wang X, Vyavahare N. Role of elastic fiber degradation in disease pathogenesis. Biochimica et Biophysica Acta. Molecular Basis of Disease. 2023; 1869: 166706. https://doi.org/10.1016/j.bbadis.2023.166706
[26] Uitto J. Biochemistry of the elastic fibers in normal connective tissues and its alterations in diseases. The Journal of Investigative Dermatology. 1979; 72: 1–10. https://doi.org/10.1111/1523-1747.ep12530093
[27] Wang K, Meng X, Guo Z. Elastin Structure, Synthesis, Regulatory Mechanism and Relationship With Cardiovascular Diseases. Frontiers in Cell and Developmental Biology. 2021; 9: 596702. https://doi.org/10.3389/fcell.2021.596702
[28] Gosline J, Lillie M, Carrington E, Guerette P, Ortlepp C, Savage K. Elastic proteins: biological roles and mechanical properties. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2002; 357: 121–132. https://doi.org/10.1098/rstb.2001.1022
[29] Trębacz H, Barzycka A. Mechanical Properties and Functions of Elastin: An Overview. Biomolecules. 2023; 13: 574. https://doi.org/10.3390/biom13030574
[30] Jamhawi NM, Koder RL, Wittebort RJ. Elastin recoil is driven by the hydrophobic effect. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2304009121. https://doi.org/10.1073/pnas.2304009121
[31] Asakura T, Naito A, Miyamoto K. Structural Analysis of Soluble Elastin in Dry and Hydrated States Using ^{13}C Solid-State NMR. Polymers. 2025; 17: 2638. https://doi.org/10.3390/polym17192638
[32] Karamanos NK, Piperigkou Z, Theocharis AD, Watanabe H, Franchi M, Baud S, et al. Proteoglycan Chemical Diversity Drives Multifunctional Cell Regulation and Therapeutics. Chemical Reviews. 2018; 118: 9152–9232. https://doi.org/10.1021/acs.chemrev.8b00354
[33] Karamanos NK, Theocharis AD, Piperigkou Z, Manou D, Passi A, Skandalis SS, et al. A guide to the composition and functions of the extracellular matrix. The FEBS Journal. 2021; 288: 6850–6912. https://doi.org/10.1111/febs.15776
[34] Lindahl U, Couchman J, Kimata K, Esko JD. Proteoglycans and Sulfated Glycosaminoglycans. In Varki A, Cummings RD, Esko JD, Stanley P, Hart GW, Aebi M, et al. (eds.) Essentials of Glycobiology (pp. 207-221). 3rd edn. Cold Spring Harbor Laboratory Press: Cold Spring Harbor (NY). 2015. https://doi.org/10.1101/glycobiology.3e.017
[35] Sharabi M. Structural Mechanisms in Soft Fibrous Tissues: A Review. Frontiers in Materials. 2022; 8: 793647. https://doi.org/10.3389/fmats.2021.793647
[36] Wang C, Kahle ER, Li Q, Han L. Nanomechanics of Aggrecan: A New Perspective on Cartilage Biomechanics, Disease and Regeneration. Advances in Experimental Medicine and Biology. 2023; 1402: 69–82. https://doi.org/10.1007/978-3-031-25588-5_5
[37] Chylińska N, Maciejczyk M. Hyaluronic Acid and Skin: Its Role in Aging and Wound-Healing Processes. Gels (Basel, Switzerland). 2025; 11: 281. https://doi.org/10.3390/gels11040281
[38] Sun Y, Hamlin AJ, Schwarzbauer JE. Fibronectin matrix assembly at a glance. Journal of Cell Science. 2025; 138: jcs263834. https://doi.org/10.1242/jcs.263834
[39] Dalton CJ, Lemmon CA. Fibronectin: Molecular Structure, Fibrillar Structure and Mechanochemical Signaling. Cells. 2021; 10: 2443. https://doi.org/10.3390/cells10092443
[40] Friedland JC, Lee MH, Boettiger D. Mechanically activated integrin switch controls alpha5beta1 function. Science (New York, N.Y.). 2009; 323: 642–644. https://doi.org/10.1126/science.1168441
[41] Kubow KE, Vukmirovic R, Zhe L, Klotzsch E, Smith ML, Gourdon D, et al. Mechanical forces regulate the interactions of fibronectin and collagen I in extracellular matrix. Nature Communications. 2015; 6: 8026. https://doi.org/10.1038/ncomms9026
[42] Hance AJ, Crystal RG. Rigid control of synthesis of collagen types I and III by cells in culture. Nature. 1977; 268: 152–154. https://doi.org/10.1038/268152a0
[43] Singh D, Rai V, Agrawal DK. Regulation of Collagen I and Collagen III in Tissue Injury and Regeneration. Cardiology and Cardiovascular Medicine. 2023; 7: 5–16. https://doi.org/10.26502/fccm.92920302
[44] Fleischmajer R, MacDonald ED, Perlish JS, Burgeson RE, Fisher LW. Dermal collagen fibrils are hybrids of type I and type III collagen molecules. Journal of Structural Biology. 1990; 105: 162–169. https://doi.org/10.1016/1047-8477(90)90110-x

[45] Franchi M, Masola V, Bellin G, Onisto M, Karamanos KA, Piperigkou Z. Collagen Fiber Array of Peritumoral Stroma Influences Epithelial-to-Mesenchymal Transition and Invasive Potential of Mammary Cancer Cells. Journal of Clinical Medicine. 2019; 8: 213. https://doi.org/10.3390/jcm8020213
[46] Sharabi M. Structural Motifs in Soft Fibrous Tissues: Revealing Structure-Mechanics Relationships in Deformation and Tear Resistance for Biomimetic Material Design. Advanced Healthcare Materials. 2025; 14: e2500153. https://doi.org/10.1002/adhm.202500153
[47] Wong R, Geyer S, Weninger W, Guimberteau JC, Wong JK. The dynamic anatomy and patterning of skin. Experimental Dermatology. 2016; 25: 92–98. https://doi.org/10.1111/exd.12832
[48] Sakaguchi S, Konyo M. Skin viscoelasticity effects on the periodic mechanical stimuli propagation between skin layers. Journal of the Mechanical Behavior of Biomedical Materials. 2024; 152: 106416. https://doi.org/10.1016/j.jmbbm.2024.106416
[49] Wong VW, Akaishi S, Longaker MT, Gurtner GC. Pushing back: wound mechanotransduction in repair and regeneration. The Journal of Investigative Dermatology. 2011; 131: 2186–2196. https://doi.org/10.1038/jid.2011.212
[50] Sonam S, Balasubramaniam L, Lin SZ, Ivan YMY, Jaumà IP, Jebane C, et al. Mechanical stress driven by rigidity sensing governs epithelial stability. Nature Physics. 2023; 19: 132–141. https://doi.org/10.1038/s41567-022-01826-2
[51] Chanet S, Martin AC. Mechanical force sensing in tissues. Progress in Molecular Biology and Translational Science. 2014; 126: 317–352. https://doi.org/10.1016/B978-0-12-394624-9.00013-0
[52] Kozyrina AN, Piskova T, Di Russo J. Mechanobiology of Epithelia From the Perspective of Extracellular Matrix Heterogeneity. Frontiers in Bioengineering and Biotechnology. 2020; 8: 596599. https://doi.org/10.3389/fbioe.2020.596599
[53] Diz-Muñoz A, Fletcher DA, Weiner OD. Use the force: membrane tension as an organizer of cell shape and motility. Trends in Cell Biology. 2013; 23: 47–53. https://doi.org/10.1016/j.tcb.2012.09.006
[54] Arnadóttir J, Chalfie M. Eukaryotic mechanosensitive channels. Annual Review of Biophysics. 2010; 39: 111–137. https://doi.org/10.1146/annurev.biophys.37.032807.125836
[55] Khalilgharibi N, Fouchard J, Asadipour N, Barrientos R, Duda M, Bonfanti A, et al. Stress relaxation in epithelial monolayers is controlled by the actomyosin cortex. Nature Physics. 2019; 15: 839–847. https://doi.org/10.1038/s41567-019-0516-6
[56] Dogterom M, Koenderink GH. Actin-microtubule crosstalk in cell biology. Nature Reviews. Molecular Cell Biology. 2019; 20: 38–54. https://doi.org/10.1038/s41580-018-0067-1
[57] Gillard G, Röper K. Control of cell shape during epithelial morphogenesis: recent advances. Current Opinion in Genetics & Development. 2020; 63: 1–8. https://doi.org/10.1016/j.gde.2020.01.003
[58] Smoler M, Coceano G, Testa I, Bruno L, Levi V. Apparent stiffness of vimentin intermediate filaments in living cells and its relation with other cytoskeletal polymers. Biochimica et Biophysica Acta. Molecular Cell Research. 2020; 1867: 118726. https://doi.org/10.1016/j.bbamcr.2020.118726
[59] Zha J, Zhang Y, Xia K, Gräter F, Xia F. Coarse-Grained Simulation of Mechanical Properties of Single Microtubules With Micrometer Length. Frontiers in Molecular Biosciences. 2021; 7: 632122. https://doi.org/10.3389/fmolb.2020.632122
[60] Kumar A, Placone JK, Engler AJ. Understanding the extracellular forces that determine cell fate and maintenance. Development (Cambridge, England). 2017; 144: 4261–4270. https://doi.org/10.1242/dev.158469
[61] Petridou NI, Spiró Z, Heisenberg CP. Multiscale force sensing in development. Nature Cell Biology. 2017; 19: 581–588. https://doi.org/10.1038/ncb3524
[62] Sekiguchi R, Yamada KM. Basement Membranes in Development and Disease. Current Topics in Developmental Biology. 2018; 130: 143–191. https://doi.org/10.1016/bs.ctdb.2018.02.005
[63] Page-McCaw A, Ferrell N. Basement membrane structure and function: Relating biology to mechanics. Matrix Biology: Journal of the International Society for Matrix Biology. 2025; 141: 16–31. https://doi.org/10.1016/j.matbio.2025.08.004
[64] Wuergezhen D, Gindroz E, Morita R, Hashimoto K, Abe T, Kiyonari H, et al. An eGFP-Col4a2 mouse model reveals basement membrane dynamics underlying hair follicle morphogenesis. The Journal of Cell Biology. 2025; 224: e202404003. https://doi.org/10.1083/jcb.202404003
[65] Salimbeigi G, Vrana NE, Ghaemmaghami AM, Huri PY, McGuinness GB. Basement membrane properties and their recapitulation in organ-on-chip applications. Materials Today. Bio. 2022; 15: 100301. https://doi.org/10.1016/j.mtbio.2022.100301
[66] Mak KM, Mei R. Basement Membrane Type IV Collagen and Laminin: An Overview of Their Biology and Value as Fibrosis Biomarkers of Liver Disease. Anatomical Record (Hoboken, N.J.: 2007). 2017; 300: 1371–1390. https://doi.org/10.1002/ar.23567
[67] Boudko SP, Danylevych N, Hudson BG, Pedchenko VK. Basement membrane collagen IV: Isolation of functional domains. Methods in Cell Biology. 2018; 143: 171–185. https://doi.org/10.1016/bs.mcb.2017.08.010
[68] Osidak MS, Osidak EO, Akhmanova MA, Domogatsky SP, Domogatskaya AS. Fibrillar, fibril-associated and basement membrane collagens of the arterial wall: architecture, elasticity and remodeling under stress. Current Pharmaceutical Design. 2015; 21: 1124–1133. https://doi.org/10.2174/1381612820666141013122906
[69] Gatseva A, Sin YY, Brezzo G, Van Agtmael T. Basement membrane collagens and disease mechanisms. Essays in Biochemistry. 2019; 63: 297–312. https://doi.org/10.1042/EBC20180071
[70] Leclech C, Natale CF, Barakat AI. The basement membrane as a structured surface - role in vascular health and disease. Journal of Cell Science. 2020; 133: jcs239889. https://doi.org/10.1242/jcs.239889
[71] Evans MJ, Fanucchi MV, Miller LA, Carlson MA, Nishio SJ, Hyde DM. Reduction of collagen VII anchoring fibrils in the airway basement membrane zone of infant rhesus monkeys exposed to house dust mite. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2010; 298: L543–L547. https://doi.org/10.1152/ajplung.00337.2009
[72] Sakai LY, Keene DR, Morris NP, Burgeson RE. Type VII collagen is a major structural component of anchoring fibrils. The Journal of Cell Biology. 1986; 103: 1577–1586. https://doi.org/10.1083/jcb.103.4.1577
[73] Keene DR, Sakai LY, Lunstrum GP, Morris NP, Burgeson RE. Type VII collagen forms an extended network of anchoring fibrils. The Journal of Cell Biology. 1987; 104: 611–621. https://doi.org/10.1083/jcb.104.3.611
[74] Burgeson RE. Type VII collagen, anchoring fibrils, and epidermolysis bullosa. The Journal of Investigative Dermatology. 1993; 101: 252–255. https://doi.org/10.1111/1523-1747.ep12365129
[75] Bruckner-Tuderman L, Höpfner B, Hammami-Hauasli N. Biology of anchoring fibrils: lessons from dystrophic epidermolysis bullosa. Matrix Biology: Journal of the International Society for Matrix Biology. 1999; 18: 43–54. https://doi.org/10.1016/s0945-053x(98)00007-9
[76] Villone D, Fritsch A, Koch M, Bruckner-Tuderman L, Hansen U, Bruckner P. Supramolecular interactions in the dermo-

epidermal junction zone: anchoring fibril-collagen VII tightly binds to banded collagen fibrils. The Journal of Biological Chemistry. 2008; 283: 24506–24513. https://doi.org/10.1074/jbc.M802415200

[77] Behrens DT, Villone D, Koch M, Brunner G, Sorokin L, Robenek H, et al. The epidermal basement membrane is a composite of separate laminin- or collagen IV-containing networks connected by aggregated perlecan, but not by nidogens. The Journal of Biological Chemistry. 2012; 287: 18700–18709. https://doi.org/10.1074/jbc.M111.336073

[78] Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002; 110: 673–687. https://doi.org/10.1016/s0092-8674(02)00971-6

[79] Ringer P, Colo G, Fässler R, Grashoff C. Sensing the mechanochemical properties of the extracellular matrix. Matrix Biology: Journal of the International Society for Matrix Biology. 2017; 64: 6–16. https://doi.org/10.1016/j.matbio.2017.03.004

[80] Sanderson RD, Hinkes MT, Bernfield M. Syndecan-1, a cell-surface proteoglycan, changes in size and abundance when keratinocytes stratify. The Journal of Investigative Dermatology. 1992; 99: 390–396. https://doi.org/10.1111/1523-1747.ep12616103

[81] Ottani V, Franchi M, De Pasquale V, Leonardi L, Morocutti M, Ruggeri A. Collagen fibril arrangement and size distribution in monkey oral mucosa. Journal of Anatomy. 1998; 192 (Pt 3): 321–328. https://doi.org/10.1046/j.1469-7580.1998.19230321.x

[82] Shirshin EA, Gurfinkel YI, Priezzhev AV, Fadeev VV, Lademann J, Darvin ME. Two-photon autofluorescence lifetime imaging of human skin papillary dermis in vivo: assessment of blood capillaries and structural proteins localization. Scientific Reports. 2017; 7: 1171. https://doi.org/10.1038/s41598-017-01238-w

[83] Roberts TJ, Azizi E. Flexible mechanisms: the diverse roles of biological springs in vertebrate movement. The Journal of Experimental Biology. 2011; 214: 353–361. https://doi.org/10.1242/jeb.038588

[84] Barton SP, Marks R. Measurement of collagen-fibre diameter in human skin. Journal of Cutaneous Pathology. 1984; 11: 18–26. https://doi.org/10.1111/j.1600-0560.1984.tb00345.x

[85] Limbert G. Mathematical and computational modelling of skin biophysics: a review. Proceedings. Mathematical, Physical, and Engineering Sciences. 2017; 473: 20170257. https://doi.org/10.1098/rspa.2017.0257

[86] Ohto-Fujita E, Shimizu M, Sano S, Kurimoto M, Yamazawa K, Atomi T, et al. Solubilized eggshell membrane supplies a type III collagen-rich elastic dermal papilla. Cell and Tissue Research. 2019; 376: 123–135. https://doi.org/10.1007/s00441-018-2954-3

[87] Wight TN. Provisional matrix: A role for versican and hyaluronan. Matrix Biology: Journal of the International Society for Matrix Biology. 2017; 60-61: 38–56. https://doi.org/10.1016/j.matbio.2016.12.001

[88] Lee DH, Oh JH, Chung JH. Glycosaminoglycan and proteoglycan in skin aging. Journal of Dermatological Science. 2016; 83: 174–181. https://doi.org/10.1016/j.jdermsci.2016.05.016

[89] Bancelin S, Lynch B, Bonod-Bidaud C, Ducourthial G, Psilodimitrakopoulos S, Dokládal P, et al. Ex vivo multiscale quantitation of skin biomechanics in wild-type and genetically-modified mice using multiphoton microscopy. Scientific Reports. 2015; 5: 17635. https://doi.org/10.1038/srep17635

[90] Lynch B, Bancelin S, Bonod-Bidaud C, Gueusquin JB, Ruggiero F, Schanne-Klein MC, et al. A novel microstructural interpretation for the biomechanics of mouse skin derived from multiscale characterization. Acta Biomaterialia. 2017; 50: 302–311. https://doi.org/10.1016/j.actbio.2016.12.051

[91] Sakata A, Abe K, Mizukoshi K, Gomi T, Okuda I. Relationship between the retinacula cutis and sagging facial skin. Skin Research and Technology: Official Journal of International Society for Bioengineering and the Skin (ISBS) [and] International Society for Digital Imaging of Skin (ISDIS) [and] International Society for Skin Imaging (ISSI). 2018; 24: 93–98. https://doi.org/10.1111/srt.12395

[92] Baptista LS, Côrtes I, Montenegro B, Claudio-da-Silva C, Bouschbacher M, Jobeili L, et al. A novel conjunctive microenvironment derived from human subcutaneous adipose tissue contributes to physiology of its superficial layer. Stem Cell Research & Therapy. 2021; 12: 480. https://doi.org/10.1186/s13287-021-02554-9

[93] Pirri C, Stecco C, Petrelli L, De Caro R, Özçakar L. Reappraisal on the Superficial Fascia in the Subcutaneous Tissue: Ultrasound and Histological Images Speaking Louder Than Words. Plastic and Reconstructive Surgery. 2022; 150: 244e–245e. https://doi.org/10.1097/PRS.0000000000009224

[94] Machado C, da Cunha MG, Rezende FC, Fonseca FLA, da Cunha ALG. Anatomical, Histological And Metabolic Differences Between Hypodermis And Subcutaneous Adipose Tissue. International Archives of Medicine. 2017; 10. https://doi.org/10.3823/2422

[95] Shoham N, Gefen A. Mechanotransduction in adipocytes. Journal of Biomechanics. 2012; 45: 1–8. https://doi.org/10.1016/j.jbiomech.2011.10.023

[96] Mariman ECM, Wang P. Adipocyte extracellular matrix composition, dynamics and role in obesity. Cellular and Molecular Life Sciences: CMLS. 2010; 67: 1277–1292. https://doi.org/10.1007/s00018-010-0263-4

[97] Langevin HM, Bouffard NA, Fox JR, Palmer BM, Wu J, Iatridis JC, et al. Fibroblast cytoskeletal remodeling contributes to connective tissue tension. Journal of Cellular Physiology. 2011; 226: 1166–1175. https://doi.org/10.1002/jcp.22442

[98] Langevin HM, Fujita T, Bouffard NA, Takano T, Koptiuch C, Badger GJ, et al. Fibroblast cytoskeletal remodeling induced by tissue stretch involves ATP signaling. Journal of Cellular Physiology. 2013; 228: 1922–1926. https://doi.org/10.1002/jcp.24356

[99] Limbert G, Kuhl E. On skin microrelief and the emergence of expression micro-wrinkles. Soft Matter. 2018; 14: 1292–1300. https://doi.org/10.1039/c7sm01969f

[100] Leyva-Mendivil MF, Page A, Bressloff NW, Limbert G. A mechanistic insight into the mechanical role of the stratum corneum during stretching and compression of the skin. Journal of the Mechanical Behavior of Biomedical Materials. 2015; 49: 197–219. https://doi.org/10.1016/j.jmbbm.2015.05.010

[101] Diosa JG, Moreno R, Chica EL, Villarraga JA, Tepole AB. Changes in the three-dimensional microscale topography of human skin with aging impact its mechanical and tribological behavior. PloS One. 2021; 16: e0241533. https://doi.org/10.1371/journal.pone.0241533

[102] Divoux A, Tordjman J, Lacasa D, Veyrie N, Hugol D, Aissat A, et al. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. Diabetes. 2010; 59: 2817–2825. https://doi.org/10.2337/db10-0585

[103] Jääskeläinen I, Petäistö T, Mirzarazi Dahagi E, Mahmoodi M, Pihlajaniemi T, Kaartinen MT, et al. Collagens Regulating Adipose Tissue Formation and Functions. Biomedicines. 2023; 11: 1412. https://doi.org/10.3390/biomedicines11051412

[104] Alkhouli N, Mansfield J, Green E, Bell J, Knight B, Liversedge N, et al. The mechanical properties of human adipose tissues and their relationships to the structure and composition of the extracellular matrix. American Journal of Physiology. Endocrinology and Metabolism. 2013; 305: E1427–E1435. https://doi.org/10.1152/ajpendo.00111.2013

[105] Crewe C, Funcke JB, Li S, Joffin N, Gliniak CM, Ghaben AL, et al. Extracellular vesicle-based interorgan transport of mitochondria from energetically stressed adipocytes. Cell Metabolism. 2021; 33: 1853–1868.e11. https://doi.org/10.1016/j.cmet.2021.08.002

[106] Kirichenko TV, Markina YV, Bogatyreva AI, Tolstik TV, Varaeva YR, Starodubova AV. The Role of Adipokines in Inflammatory Mechanisms of Obesity. International Journal of Molecular Sciences. 2022; 23: 14982. https://doi.org/10.3390/ijms232314982

[107] Kenmochi M, Kawarasaki S, Takizawa S, Okamura K, Goto T, Uchida K. Involvement of mechano-sensitive Piezo1 channel in the differentiation of brown adipocytes. The Journal of Physiological Sciences: JPS. 2022; 72: 13. https://doi.org/10.1186/s12576-022-00837-1

[108] Chaurasiya V, Pham DD, Harju J, Juuti A, Penttilä A, Emmagouni SKG, et al. Human visceral adipose tissue microvascular endothelial cell isolation and establishment of co-culture with white adipocytes to analyze cell-cell communication. Experimental Cell Research. 2023; 433: 113819. https://doi.org/10.1016/j.yexcr.2023.113819

[109] Shoham N, Girshovitz P, Katzengold R, Shaked NT, Benayahu D, Gefen A. Adipocyte stiffness increases with accumulation of lipid droplets. Biophysical Journal. 2014; 106: 1421–1431. https://doi.org/10.1016/j.bpj.2014.01.045

[110] Blade SP, Falkowski DJ, Bachand SN, Pagano SJ, Chin L. Mechanobiology of Adipocytes. Biology. 2024; 13: 434. https://doi.org/10.3390/biology13060434

[111] Benjamin M. The fascia of the limbs and back–a review. Journal of Anatomy. 2009; 214: 1–18. https://doi.org/10.1111/j.1469-7580.2008.01011.x

[112] Fede C, Clair C, Petrelli L, Sun Y, Biz C, Angelini A, et al. Redefining the Collagen Composition of Human Fasciae: Emerging Collagen Types and Structural Heterogeneity. International Journal of Molecular Sciences. 2026; 27: 1021. https://doi.org/10.3390/ijms27021021

[113] Si L, Li H, Li Z, Zhang M, Chen X, Yu L, et al. The Superficial Fascia System: Anatomical Guideline for Zoning in Liposuction-Assisted Back Contouring. Plastic and Reconstructive Surgery. 2023; 151: 989–998. https://doi.org/10.1097/PRS.0000000000010077

[114] Stecco C, Macchi V, Porzionato A, Duparc F, De Caro R. The fascia: the forgotten structure. Italian Journal of Anatomy and Embryology = Archivio Italiano Di Anatomia Ed Embriologia. 2011; 116: 127–138.

[115] Pratt RL. Hyaluronan and the Fascial Frontier. International Journal of Molecular Sciences. 2021; 22: 6845. https://doi.org/10.3390/ijms22136845

[116] Herbst KL. Subcutaneous Adipose Tissue Diseases: Dercum Disease, Lipedema, Familial Multiple Lipomatosis, and Madelung Disease. In Feingold KR, Ahmed SF, Anawalt B, Blackman MR, Boyce A, Chrousos G, et al. (eds.) Endotext. MDText.com, Inc.: South Dartmouth (MA). 2000.

[117] Herlin C, Chica-Rosa A, Subsol G, Gilles B, Macri F, Beregi JP, et al. Three-dimensional study of the skin/subcutaneous complex using in vivo whole body 3T MRI: review of the literature and confirmation of a generic pattern of organization. Surgical and Radiologic Anatomy: SRA. 2015; 37: 731–741. https://doi.org/10.1007/s00276-014-1409-0

[118] Tsukahara K, Tamatsu Y, Sugawara Y, Shimada K. Relationship between the depth of facial wrinkles and the density of the retinacula cutis. Archives of Dermatology. 2012; 148: 39–46. https://doi.org/10.1001/archdermatol.2011.727

[119] Yuan Y, Gao J, Ogawa R. Mechanobiology and Mechanotherapy of Adipose Tissue-Effect of Mechanical Force on Fat Tissue Engineering. Plastic and Reconstructive Surgery. Global Open. 2016; 3: e578. https://doi.org/10.1097/GOX.0000000000000564

[120] Mittal B. Subcutaneous adipose tissue & visceral adipose tissue. The Indian Journal of Medical Research. 2019; 149: 571–573. https://doi.org/10.4103/ijmr.IJMR_1910_18

[121] Brüggen MC, Stingl G. Subcutaneous white adipose tissue: The deepest layer of the cutaneous immune barrier. Journal Der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG. 2020; 18: 1225–1227. https://doi.org/10.1111/ddg.14335

[122] Chavey C, Boucher J, Monthouël-Kartmann MN, Sage EH, Castan-Laurell I, Valet P, et al. Regulation of secreted protein acidic and rich in cysteine during adipose conversion and adipose tissue hyperplasia. Obesity (Silver Spring, Md.). 2006; 14: 1890–1897. https://doi.org/10.1038/oby.2006.220

[123] Kirchgesner T, Demondion X, Stoenoiu M, Durez P, Nzeusseu Toukap A, Houssiau F, et al. Fasciae of the musculoskeletal system: normal anatomy and MR patterns of involvement in autoimmune diseases. Insights into Imaging. 2018; 9: 761–771. https://doi.org/10.1007/s13244-018-0650-1

[124] Kondrup F, Gaudreault N, Venne G. The deep fascia and its role in chronic pain and pathological conditions: A review. Clinical Anatomy (New York, N.Y.). 2022; 35: 649–659. https://doi.org/10.1002/ca.23882

[125] Wang HQ, Li XK, Wu ZX, Wei YY, Luo ZJ. The effect on the extracellular matrix of the deep fascia in response to leg lengthening. BMC Musculoskeletal Disorders. 2008; 9: 101. https://doi.org/10.1186/1471-2474-9-101

[126] Skalec A, Egerbacher M. The deep fascia and retinacula of the equine forelimb - structure and innervation. Journal of Anatomy. 2017; 231: 405–416. https://doi.org/10.1111/joa.12643

[127] Gatt A, Agarwal S, Zito PM. Anatomy, Fascia Layers. In StatPearls. StatPearls Publishing: Treasure Island (FL). 2023.

[128] Snoeck O, Beyer B, Rooze M, Feipel V. Anatomical study of paratenons and fascia lata connections in the posteromedial knee region. Surgical and Radiologic Anatomy: SRA. 2022; 44: 821–827. https://doi.org/10.1007/s00276-022-02927-6

[129] Bhattacharya S, Dubey DK. Effect of aggrecan degradation on the nanomechanics of hyaluronan in extra-fibrillar matrix of annulus fibrosus: A molecular dynamics investigation. Journal of the Mechanical Behavior of Biomedical Materials. 2020; 107: 103752. https://doi.org/10.1016/j.jmbbm.2020.103752

[130] McCombe D, Brown T, Slavin J, Morrison WA. The histochemical structure of the deep fascia and its structural response to surgery. Journal of Hand Surgery (Edinburgh, Scotland). 2001; 26: 89–97. https://doi.org/10.1054/jhsb.2000.0546

[131] Salwowska NM, Bebenek KA, Żądło DA, Wcisło-Dziadecka DL. Physiochemical properties and application of hyaluronic acid: a systematic review. Journal of Cosmetic Dermatology. 2016; 15: 520–526. https://doi.org/10.1111/jocd.12237

[132] Fakhari A, Berkland C. Applications and emerging trends of hyaluronic acid in tissue engineering, as a dermal filler and in osteoarthritis treatment. Acta Biomaterialia. 2013; 9: 7081–7092. https://doi.org/10.1016/j.actbio.2013.03.005

[133] Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiological Reviews. 2004; 84: 649–698. https://doi.org/10.1152/physrev.00031.2003

[134] Gillies AR, Lieber RL. Structure and function of the skeletal muscle extracellular matrix. Muscle & Nerve. 2011; 44: 318–331. https://doi.org/10.1002/mus.22094

[135] Gao Y, Kostrominova TY, Faulkner JA, Wineman AS. Age-related changes in the mechanical properties of the epimysium in skeletal muscles of rats. Journal of Biomechanics. 2008; 41: 465–469. https://doi.org/10.1016/j.jbiomech.2007.09.021

[136] Das C, Roy BC, Oshima I, Miyachi H, Nishimura S, Iwamoto

H, et al. Collagen content and architecture of the puboischiofemoralis muscle in male chicks and broilers with different growth rates on various nutritional planes. British Poultry Science. 2009; 50: 424–435. https://doi.org/10.1080/00071660903108061

[137] Nishimura T, Ojima K, Hattori A, Takahashi K. Developmental expression of extracellular matrix components in intramuscular connective tissue of bovine semitendinosus muscle. Histochemistry and Cell Biology. 1997; 107: 215–221. https://doi.org/10.1007/s004180050106

[138] Day JA, Copetti L, Rucli G. From clinical experience to a model for the human fascial system. Journal of Bodywork and Movement Therapies. 2012; 16: 372–380. https://doi.org/10.1016/j.jbmt.2012.01.003

[139] Laurent C, Johnson-Wells G, Hellström S, Engström-Laurent A, Wells AF. Localization of hyaluronan in various muscular tissues. A morphological study in the rat. Cell and Tissue Research. 1991; 263: 201–205. https://doi.org/10.1007/BF00318761

[140] Stecco A, Giordani F, Fede C, Pirri C, De Caro R, Stecco C. From Muscle to the Myofascial Unit: Current Evidence and Future Perspectives. International Journal of Molecular Sciences. 2023; 24: 4527. https://doi.org/10.3390/ijms24054527

[141] Stecco A, Macchi V, Stecco C, Porzionato A, Ann Day J, Delmas V, et al. Anatomical study of myofascial continuity in the anterior region of the upper limb. Journal of Bodywork and Movement Therapies. 2009; 13: 53–62. https://doi.org/10.1016/j.jbmt.2007.04.009

[142] Nishimura T, Hattori A, Takahashi K. Ultrastructure of the intramuscular connective tissue in bovine skeletal muscle. A demonstration using the cell-maceration/scanning electron microscope method. Acta Anatomica. 1994; 151: 250–257. https://doi.org/10.1159/000147671

[143] Purslow PP. The Structure and Role of Intramuscular Connective Tissue in Muscle Function. Frontiers in Physiology. 2020; 11: 495. https://doi.org/10.3389/fphys.2020.00495

[144] Sleboda DA, Stover KK, Roberts TJ. Diversity of extracellular matrix morphology in vertebrate skeletal muscle. Journal of Morphology. 2020; 281: 160–169. https://doi.org/10.1002/jmor.21088

[145] Wohlgemuth RP, Brashear SE, Smith LR. Alignment, cross linking, and beyond: a collagen architect's guide to the skeletal muscle extracellular matrix. American Journal of Physiology. Cell Physiology. 2023; 325: C1017–C1030. https://doi.org/10.1152/ajpcell.00287.2023

[146] Skalec A, Janeczek M, Czerski A. Anatomy and histology of the rabbit common calcanean tendon. Anatomia, Histologia, Embryologia. 2019; 48: 466–475. https://doi.org/10.1111/ahe.12468

[147] Turrina A, Martínez-González MA, Stecco C. The muscular force transmission system: role of the intramuscular connective tissue. Journal of Bodywork and Movement Therapies. 2013; 17: 95–102. https://doi.org/10.1016/j.jbmt.2012.06.001

[148] Scarr G. Fascial hierarchies and the relevance of crossed-helical arrangements of collagen to changes in shape; part II: The proposed effect of blood pressure (Traube-Hering-Mayer) waves on the fascia. Journal of Bodywork and Movement Therapies. 2016; 20: 629–638. https://doi.org/10.1016/j.jbmt.2015.10.008

[149] Slimani L, Micol D, Amat J, Delcros G, Meunier B, Taillandier D, et al. The worsening of tibialis anterior muscle atrophy during recovery post-immobilization correlates with enhanced connective tissue area, proteolysis, and apoptosis. American Journal of Physiology. Endocrinology and Metabolism. 2012; 303: E1335–E1347. https://doi.org/10.1152/ajpendo.00379.2012

[150] McLoon LK, Vicente A, Fitzpatrick KR, Lindström M, Pedrosa Domellöf F. Composition, Architecture, and Functional Implications of the Connective Tissue Network of the Extraocular Muscles. Investigative Ophthalmology & Visual Science. 2018; 59: 322–329. https://doi.org/10.1167/iovs.17-23003

[151] Järvinen TAH, Józsa L, Kannus P, Järvinen TLN, Järvinen M. Organization and distribution of intramuscular connective tissue in normal and immobilized skeletal muscles. An immunohistochemical, polarization and scanning electron microscopic study. Journal of Muscle Research and Cell Motility. 2002; 23: 245–254. https://doi.org/10.1023/a:1020904518336

[152] Nakamura YN, Iwamoto H, Etoh T, Shiotsuka Y, Yamaguchi T, Ono Y, et al. Three-dimensional observation of connective tissue of bovine masseter muscle under concentrate- and roughage-fed conditions by using immunohistochemical/confocal laser-scanning microscopic methods. Journal of Food Science. 2007; 72: E375–E381. https://doi.org/10.1111/j.1750-3841.2007.00413.x

[153] Purslow PP. Muscle fascia and force transmission. Journal of Bodywork and Movement Therapies. 2010; 14: 411–417. https://doi.org/10.1016/j.jbmt.2010.01.005

[154] Rowe RW. Morphology of perimysial and endomysial connective tissue in skeletal muscle. Tissue & Cell. 1981; 13: 681–690. https://doi.org/10.1016/s0040-8166(81)80005-5

[155] Campbell KP, Stull JT. Skeletal muscle basement membrane-sarcolemma-cytoskeleton interaction minireview series. The Journal of Biological Chemistry. 2003; 278: 12599–12600. https://doi.org/10.1074/jbc.R300005200

[156] Sharafi B, Blemker SS. A mathematical model of force transmission from intrafascicularly terminating muscle fibers. Journal of Biomechanics. 2011; 44: 2031–2039. https://doi.org/10.1016/j.jbiomech.2011.04.038

[157] Nishimura T, Hattori A, Takahashi K. Structural weakening of intramuscular connective tissue during conditioning of beef. Meat Science. 1995; 39: 127–133. https://doi.org/10.1016/0309-1740(95)80014-x

[158] Purslow PP, Trotter JA. The morphology and mechanical properties of endomysium in series-fibred muscles: variations with muscle length. Journal of Muscle Research and Cell Motility. 1994; 15: 299–308. https://doi.org/10.1007/BF00123482

[159] Czyrny Z. On Tendinous Systems of Muscles - A Histology-US Correlation. Journal of Surgery. 2021; 6: 1395. https://doi.org/10.29011/2575-9760.001395

[160] Franchi M, Trirè A, Quaranta M, Orsini E, Ottani V. Collagen structure of tendon relates to function. TheScientificWorldJournal. 2007; 7: 404–420. https://doi.org/10.1100/tsw.2007.92

[161] Thorpe CT, Screen HRC. Tendon Structure and Composition. Advances in Experimental Medicine and Biology. 2016; 920: 3–10. https://doi.org/10.1007/978-3-319-33943-6_1

[162] Kannus P. Structure of the tendon connective tissue. Scandinavian Journal of Medicine & Science in Sports. 2000; 10: 312–320. https://doi.org/10.1034/j.1600-0838.2000.010006312.x

[163] Franchi M, Ottani V, Stagni R, Ruggeri A. Tendon and ligament fibrillar crimps give rise to left-handed helices of collagen fibrils in both planar and helical crimps. Journal of Anatomy. 2010; 216: 301–309. https://doi.org/10.1111/j.1469-7580.2009.01188.x

[164] Franchi M, Fini M, Quaranta M, De Pasquale V, Raspanti M, Giavaresi G, et al. Crimp morphology in relaxed and stretched rat Achilles tendon. Journal of Anatomy. 2007; 210: 1–7. https://doi.org/10.1111/j.1469-7580.2006.00666.x

[165] Beach ZM, Bonilla KA, Dekhne MS, Sun M, Adams TH, Adams SM, et al. Biglycan has a major role in maintenance of mature tendon mechanics. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 2022; 40: 2546–2556. https://doi.org/10.1002/jor.25299

[166] Trotter JA. Structure-function considerations of muscle-tendon junctions. Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology. 2002; 133: 1127–1133. ht

tps://doi.org/10.1016/s1095-6433(02)00213-1
[167] François RJ, Braun J, Khan MA. Entheses and enthesitis: a histopathologic review and relevance to spondyloarthritides. Current Opinion in Rheumatology. 2001; 13: 255–264. https://doi.org/10.1097/00002281-200107000-00003
[168] Gill SS, Turner MA, Battaglia TC, Leis HT, Balian G, Miller MD. Semitendinosus regrowth: biochemical, ultrastructural, and physiological characterization of the regenerate tendon. The American Journal of Sports Medicine. 2004; 32: 1173–1181. https://doi.org/10.1177/0363546503262159
[169] Schatzker J, Brånemark PI. Intravital observations on the microvascular anatomy and microcirculation of the tendon. Acta Orthopaedica Scandinavica. Supplementum. 1969; 126: 1–23. https://doi.org/10.3109/ort.1969.40.suppl-126.01
[170] Gaut L, Duprez D. Tendon development and diseases. Wiley Interdisciplinary Reviews. Developmental Biology. 2016; 5: 5–23. https://doi.org/10.1002/wdev.201
[171] Leonardi L, Strocchi R, Castellani PP, Guizzardi S, Ottani V. Ultrastructural findings on collagen fibers of tendon sheaths from the rat tail. Bollettino Della Societa Italiana Di Biologia Sperimentale. 1982; 58: 1478–1484.
[172] Jozsa L, Kannus P, Balint JB, Reffy A. Three-dimensional ultrastructure of human tendons. Acta Anatomica. 1991; 142: 306–312. https://doi.org/10.1159/000147207
[173] Rowe RW. The structure of rat tail tendon. Connective Tissue Research. 1985; 14: 9–20. https://doi.org/10.3109/03008208509089839
[174] Kvist M, Józsa L, Järvinen M, Kvist H. Fine structural alterations in chronic Achilles paratenonitis in athletes. Pathology, Research and Practice. 1985; 180: 416–423. https://doi.org/10.1016/S0344-0338(85)80115-1
[175] Benjamin M, Kaiser E, Milz S. Structure-function relationships in tendons: a review. Journal of Anatomy. 2008; 212: 211–228. https://doi.org/10.1111/j.1469-7580.2008.00864.x
[176] Myerson MS, McGarvey W. Disorders of the Achilles tendon insertion and Achilles tendinitis. Instructional Course Lectures. 1999; 48: 211–218.
[177] Frank CB. Ligament structure, physiology and function. Journal of Musculoskeletal & Neuronal Interactions. 2004; 4: 199–201.
[178] Parmar K. Tendon and ligament: basic science, injury and repair. Orthopaedics and Trauma. 2018; 32: 241–244. https://doi.org/10.1016/j.mporth.2018.05.008
[179] Benjamin M, Ralphs JR. Entheses–the bony attachments of tendons and ligaments. Italian Journal of Anatomy and Embryology = Archivio Italiano Di Anatomia Ed Embriologia. 2001; 106: 151–157.
[180] Gelse K, Pöschl E, Aigner T. Collagens–structure, function, and biosynthesis. Advanced Drug Delivery Reviews. 2003; 55: 1531–1546. https://doi.org/10.1016/j.addr.2003.08.002
[181] Al-Qudsy L, Hu YW, Xu H, Yang PF. Mineralized Collagen Fibrils: An Essential Component in Determining the Mechanical Behavior of Cortical Bone. ACS Biomaterials Science & Engineering. 2023; 9: 2203–2219. https://doi.org/10.1021/acsbiomaterials.2c01377
[182] Georgiadis M, Müller R, Schneider P. Techniques to assess bone ultrastructure organization: orientation and arrangement of mineralized collagen fibrils. Journal of the Royal Society, Interface. 2016; 13: 20160088. https://doi.org/10.1098/rsif.2016.0088
[183] Hert J, Fiala P, Petrtýl M. Osteon orientation of the diaphysis of the long bones in man. Bone. 1994; 15: 269–277. https://doi.org/10.1016/8756-3282(94)90288-7
[184] Green M, Isaac DH, Jenkins GM. Bone microstructure by collagenase etching. Biomaterials. 1985; 6: 150–152. https://doi.org/10.1016/0142-9612(85)90002-x
[185] Fang M, Holl MMB. Variation in type I collagen fibril nanomorphology: the significance and origin. BoneKEy Reports. 2013; 2: 394. https://doi.org/10.1038/bonekey.2013.128
[186] Hart NH, Newton RU, Tan J, Rantalainen T, Chivers P, Siafarikas A, et al. Biological basis of bone strength: anatomy, physiology and measurement. Journal of Musculoskeletal & Neuronal Interactions. 2020; 20: 347–371.
[187] Takano Y, Turner CH, Owan I, Martin RB, Lau ST, Forwood MR, et al. Elastic anisotropy and collagen orientation of osteonal bone are dependent on the mechanical strain distribution. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 1999; 17: 59–66. https://doi.org/10.1002/jor.1100170110
[188] Kalmey JK, Lovejoy CO. Collagen fiber orientation in the femoral necks of apes and humans: do their histological structures reflect differences in locomotor loading? Bone. 2002; 31: 327–332. https://doi.org/10.1016/s8756-3282(02)00828-1
[189] Ascenzi MG, Roe AK. The osteon: the micromechanical unit of compact bone. Frontiers in Bioscience (Landmark Edition). 2012; 17: 1551–1581. https://doi.org/10.2741/4003
[190] Stockhausen KE, Qwamizadeh M, Wölfel EM, Hemmatian H, Fiedler IAK, Flenner S, et al. Collagen Fiber Orientation Is Coupled with Specific Nano-Compositional Patterns in *Dark* and *Bright* Osteons Modulating Their Biomechanical Properties. ACS Nano. 2021; 15: 455–467. https://doi.org/10.1021/acsnano.0c04786
[191] Warshaw J, Bromage TG, Terranova CJ, Enlow DH. Collagen Fiber Orientation in Primate Long Bones. Anatomical Record (Hoboken, N.J.: 2007). 2017; 300: 1189–1207. https://doi.org/10.1002/ar.23571
[192] Florencio-Silva R, Sasso GRDS, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. BioMed Research International. 2015; 2015: 421746. https://doi.org/10.1155/2015/421746
[193] Miguez PA. Evidence of biglycan structure-function in bone homeostasis and aging. Connective Tissue Research. 2020; 61: 19–33. https://doi.org/10.1080/03008207.2019.1669577
[194] Hua R, Jiang JX. Small leucine-rich proteoglycans in physiological and biomechanical function of bone. Matrix Biology Plus. 2021; 11: 100063. https://doi.org/10.1016/j.mbplus.2021.100063
[195] Mostafa H. Structure and Function of Periosteum with Special Reference to its Clinical Application. Egyptian Journal of Histology. 2019; 42: 1–9. https://doi.org/10.21608/ejh.2018.6331.1045
[196] Patro BP, Rath M, Mohapatra D, Kumar Patra S, Chandra Sahu M, Das G, et al. Traumatized periosteum: Its histology, viability, and clinical significance. Orthopedic Reviews. 2021; 14: 30044. https://doi.org/10.52965/001c.30044
[197] Manon J, Evrard R, Maistriaux L, Fievé L, Heller U, Magnin D, et al. Periosteum and fascia lata: Are they so different? Frontiers in Bioengineering and Biotechnology. 2022; 10: 944828. https://doi.org/10.3389/fbioe.2022.944828
[198] Squier CA, Ghoneim S, Kremenak CR. Ultrastructure of the periosteum from membrane bone. Journal of Anatomy. 1990; 171: 233–239.
[199] Dwek JR. The periosteum: what is it, where is it, and what mimics it in its absence? Skeletal Radiology. 2010; 39: 319–323. https://doi.org/10.1007/s00256-009-0849-9
[200] Hirashima S, Ohta K, Kanazawa T, Uemura KI, Togo A, Yoshitomi M, et al. Anchoring structure of the calvarial periosteum revealed by focused ion beam/scanning electron microscope tomography. Scientific Reports. 2015; 5: 17511. https://doi.org/10.1038/srep17511
[201] Aaron JE. Periosteal Sharpey's fibers: a novel bone matrix regulatory system? Frontiers in Endocrinology. 2012; 3: 98.

https://doi.org/10.3389/fendo.2012.00098
[202] Christodoulou C, Spencer JA, Yeh SCA, Turcotte R, Kokkaliaris KD, Panero R, et al. Live-animal imaging of native haematopoietic stem and progenitor cells. Nature. 2020; 578: 278–283. https://doi.org/10.1038/s41586-020-1971-z
[203] Nitsevich TP, Domashevskaia EI. Features of the femur periosteum and endosteum structure in rodents and hares. TSitologiia i Genetika. 1991; 25: 5–11.
[204] Nahian A, Chauhan PR. Histology, Periosteum And Endosteum. StatPearls. 2023.
[205] Modrowski D, Miravet L, Feuga M, Marie PJ. Increased proliferation of osteoblast precursor cells in estrogen-deficient rats. The American Journal of Physiology. 1993; 264: E190–E196. https://doi.org/10.1152/ajpendo.1993.264.2.E190
[206] Šromová V, Sobola D, Kaspar P. A Brief Review of Bone Cell Function and Importance. Cells. 2023; 12: 2576. https://doi.org/10.3390/cells12212576
[207] Bentley SA, Alabaster O, Foidart JM. Collagen heterogeneity in normal human bone marrow. British Journal of Haematology. 1981; 48: 287–291.
[208] Kanniyappan H, Chathurika Rathnayake RA, Osamor J, Islam M, Wang RR. The role of collagen and collagen I/III ratio in pathological conditions: insights into molecular mechanisms and therapeutic approaches. Frontiers in Bioengineering and Biotechnology. 2025; 13: 1679625. https://doi.org/10.3389/fbioe.2025.1679625
[209] Gao J, Guo Z, Zhang Y, Liu Y, Xing F, Wang J, et al. Age-related changes in the ratio of Type I/III collagen and fibril diameter in mouse skin. Regenerative Biomaterials. 2022; 10: rbac110. https://doi.org/10.1093/rb/rbac110
[210] Junge K, Klinge U, Rosch R, Mertens PR, Kirch J, Klosterhalfen B, et al. Decreased collagen type I/III ratio in patients with recurring hernia after implantation of alloplastic prostheses. Langenbeck's Archives of Surgery. 2004; 389: 17–22. https://doi.org/10.1007/s00423-003-0429-8
[211] Nasseri YY, Krott E, Van Groningen KM, Berho M, Osborne MC, Wollman S, et al. Abnormalities in collagen composition may contribute to the pathogenesis of hemorrhoids: morphometric analysis. Techniques in Coloproctology. 2015; 19: 83–87. https://doi.org/10.1007/s10151-014-1238-5
[212] Lin-Hui L, Yuan-Yuan Z, Ming-Yu L, Xu-Dong H, Yin-Jia D, Yue Z, et al. Recombinant Human Collagen Type III Improves Hypertrophic Scarring by Regulating the Ratio of Type I/III Collagen. Journal of Burn Care & Research: Official Publication of the American Burn Association. 2024; 45: 1269–1273. https://doi.org/10.1093/jbcr/irae040
[213] Qin L, Liu W, Cao H, Xiao G. Molecular mechanosensors in osteocytes. Bone Research. 2020; 8: 23. https://doi.org/10.1038/s41413-020-0099-y
[214] Choi JUA, Kijas AW, Lauko J, Rowan AE. The Mechanosensory Role of Osteocytes and Implications for Bone Health and Disease States. Frontiers in Cell and Developmental Biology. 2022; 9: 770143. https://doi.org/10.3389/fcell.2021.770143
[215] Marquardt K, Hartmann C, Wegener F, Park JY, Halbert D, Hsu S, et al. Microfocused Ultrasound With Visualization Induces Remodeling of Collagen and Elastin Within the Skin. Journal of Cosmetic Dermatology. 2025; 24: e16638. https://doi.org/10.1111/jocd.16638
[216] Mathioudaki E, Rallis M, Politopoulos K, Alexandratou E. Photobiomodulation and Wound Healing: Low-Level Laser Therapy at 661 nm in a Scratch Assay Keratinocyte Model. Annals of Biomedical Engineering. 2024; 52: 376–385. https://doi.org/10.1007/s10439-023-03384-x
[217] Woo K. Photobiomodulation as a multimodal therapy to enhance wound healing and skin regeneration. Medical Lasers; Engineering, Basic Research, and Clinical Application. 2024; 13: 173–184. https://doi.org/10.25289/ML.24.033
[218] Chen W, Wang N, Xie X, Liu H, Wang Y, Nie Y, et al. Recombinant type I & III chimeric collagen significantly enhances the vitality of fibroblasts and decelerates the skin aging process. BMC Biotechnology. 2025; 25: 116. https://doi.org/10.1186/s12896-025-01050-9
[219] Landscheidt K, Alabdulmohsen A, Hübscher M, Geber B, Hernekamp JF, Goertz O. Extracorporeal Shock Waves Therapy for the Treatment of Acute and Chronic Wounds-A Prospective, Monocentric Clinical Trial to Examine the Effect of Shock Waves on Wound Healing. Health Science Reports. 2025; 8: e70311. https://doi.org/10.1002/hsr2.70311
[220] Mittermayr R, Haffner N, Feichtinger X, Schaden W. The role of shockwaves in the enhancement of bone repair - from basic principles to clinical application. Injury. 2021; 52: S84–S90. https://doi.org/10.1016/j.injury.2021.02.081
[221] Lei M, Liu H, Zhong Q, Zhao L, Liu J, Mai H, et al. Hydroxybutyl chitosan-based thermosensitive hydrogel enhanced osteoporotic bone regeneration through sustained release of alendronate and BMP-2. Carbohydrate Polymers. 2026; 373: 124609. https://doi.org/10.1016/j.carbpol.2025.124609
[222] Diller RB, Tabor AJ. The Role of the Extracellular Matrix (ECM) in Wound Healing: A Review. Biomimetics (Basel, Switzerland). 2022; 7: 87. https://doi.org/10.3390/biomimetics7030087
[223] Fathke C, Wilson L, Hutter J, Kapoor V, Smith A, Hocking A, et al. Contribution of bone marrow-derived cells to skin: collagen deposition and wound repair. Stem Cells (Dayton, Ohio). 2004; 22: 812–822. https://doi.org/10.1634/stemcells.22-5-812