# Connective Tissue

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Contributor: Gustavo Egea

This is an overview of the main molecular components, structural organization and main functions of the connective tissue, which is constitutively present in tissues and organs of the body. Connective tissue is known to provide structural and functional “glue” properties to other tissues. It contains cellular and molecular components that are arranged in several dynamic organizations. Connective tissue is the focus of numerous genetic and nongenetic diseases. Genetic diseases of the connective tissue belong to minority or rare diseases, but no less important than the nongenetic diseases.

Keywords: connective tissue ; collagens ; fibrilins ; fibroblasts ; glucosaminoglycans ; extracellular matrix ; proteoglycans ; histology

## 1. Introduction

Connective tissue (CT) is the structural support of the body and a dynamic site for other important functions. For example, it is a medium for the exchange of metabolites; the defense, protection, and repair of the body; the storage and mobilization of energy (fat); the regulation and integration of mechanical and cell-signaling responses; the storage and mobilization of growth and differentiation factors; and a guide and barrier for cell locomotion and migration [1]. CT tightly interacts with other tissues to maintain functional organs. Most CTs originate from the mesoderm. From this embryonic layer, pluripotent mesenchymal cells are formed that migrate throughout the embryo, giving rise to adult CT cells, such as cartilage, bone, tendons, blood, and hematopoietic and lymphoid cells. CT is a major meeting point of metabolic and catabolic reactions of tissues and organs and a large platform of signaling that regulates them.

## 2. Basic Structural Organization, Function, and Cellular and Molecular Components of Connective Tissue

CT is composed of cells and their surrounding extracellular matrix (ECM), which in turn consists of ground substance (proteoglycans, glycosaminoglycans (GAGs), and nonfibrotic/cell adhesion glycoproteins) and fibers (collagen and elastic fibers). Depending on the CT, cells, ground substance, or fibers are the predominant component and determine the histological classification. Fibroblasts are predominant in loose CT, fibers in tendons and ligaments, and ground substance in embryonic CT. Nonetheless, all three components are critical for the function of CT(s) in organs.

### 2.1. Cellular Components

The CT is composed of resident and transient cellular components [2]. The most representative of the former group is the fibroblast [3]. Transient cells are those that (relatively) freely wander and move in and out of the tissue. Transient cells are almost exclusively represented by leukocytes and macrophages. Fibroblasts are the most abundant resident cell type of proper CT and are responsible for synthesizing almost all ECM components. Fibroblasts undergo different states of activity. Those that are highly active have an elongated morphology, with high transcriptomic activity. In contrast, when cells are scarcely active (called fibrocytes) they become smaller and have low transcriptomic activity. In both physiological states, cells are tightly associated with ground substance components and with collagen and elastic fibers (see below). Fibroblasts undergo cell division and restricted movement and can differentiate to other cell types such as adipocytes, osteoblasts, and myofibroblasts. In pathological circumstances, they can also be converted into epithelioid cells through the mesenchymal–epithelial transition (MET) mechanism. The reverse process, called epithelial–mesenchymal transition (EMT) also occurs and is relevant in cancer [4][5]. Myofibroblasts are modified fibroblasts that express some characteristic proteins of smooth muscle cells (SMCs) (some actin-based cytoskeleton proteins). Myofibroblasts acquire special relevance in wound healing and fibrotic processes [6].

## 2.2. ECM Components

ECM is composed of a large variety of complex macromolecules localized in the extracellular space of the cells [7]. The extent of ECM varies with the tissue type. Cells maintain their associations with the ECM by forming specialized junctions that hold them to the surrounding macromolecules. ECM is not only the skeleton of tissues but also (1) modulates and determines the morphology and function of fixed and resident cells (see above), (2) influences their development and differentiation state, (3) regulates their migration and mitotic activity, (4) senses and transduces mechanical forces (compression and tensile) to cells, (5) facilitates junctional associations among cells, and (6) provides a biological field for immune defense. As indicated above, ECM is composed of a hydrated gel-like ground substance embedded with fibers. Ground substance resists compression forces and facilitates a quick exchange of metabolites and catabolites, whereas fibers support tensile forces.

### 2.2.1 Ground Substance

It is composed of GAGs, proteoglycans (GAGs linked to a protein core), and cell adhesive glycoproteins, also called nonfibrotic glycoproteins. GAGs are long, inflexible, unbranched polysaccharides composed of chains of repeating disaccharide units, an amino sugar (*N*-acetylglucosamine or *N*-acetylgalactosamine), and a uronic acid (iduronic or glucuronic) [8]. GAGs are classified into four groups, depending on their core disaccharide constituents [9]. GAGs are strongly negatively charged, attracting cations (such as $K^+$, $Na^+$), which, in turn, attract water that hydrates ECM and helps to resist compression forces. Unlike hyaluronic acid, GAGs are sulfated and usually consist of fewer than 300 repeating disaccharide units. The main sulfated GAGs include keratan sulfate, heparan sulfate, heparin, chondroitin 4-sulfate, chondroitin 6-sulfate, and dermatan sulfate. These GAGs are usually linked covalently to a core protein to form proteoglycans. An exception is hyaluronic acid that contains up to 10,000 repeating disaccharide units but does not form covalent links to some protein molecules. All GAGs are synthesized in the Golgi apparatus with the exception again of hyaluronic acid, which is synthesized as a polymer at the cytoplasmic face of the plasma membrane by hyaluronan synthases. Hyaluronic acid also has intracellular functions such as helping chromosome alignment during mitosis.

Proteoglycans are large structures that look like a bottle brush. They range from about 50,000 Da (decorin and betaglycan) to as large as 3 million Da (aggrecan) [9][10]. Aggrecan is responsible for the gel state of the ECM and acts as a barrier to fast diffusion of molecules [11]. Proteoglycans resist compression and can facilitate normal cellular locomotion of migrating cells to move between these hydrated macromolecules. At the same time, they can limit the migration of invasive microorganisms and metastatic cells. Proteoglycans also bind some signaling molecules and assist in the formation of collagen fibers (decorin). Syndecans are proteoglycans that remain attached to the cell membrane. Syndecans and betaglycans also act as low-affinity receptors (co-receptors) binding growth factors such as fibroblast growth factor (FGF) and tumor growth factor-beta (TGF-β), respectively, presenting them to their respective high-affinity receptors located in the vicinity at the plasma membrane. Moreover, they also act as hijackers of growth factors, regulating their availability for high-affinity signaling receptors [12][13][14][15].

Nonfiber glycoproteins or cell adhesive glycoproteins are also large macromolecules that have several domains in their 3D structure. At least one of the domains binds to the cell surface. The most representative of these glycoproteins are integrins, which bind to collagen fibers and proteoglycans [16][17]. In this manner, cell adhesion glycoproteins help cells to adhere to the extracellular matrix and hold various components of tissues to each other. Other major types of adhesive glycoproteins are fibronectin, laminin, entactin, tenascin, chondronectin, and osteonectin.

### 2.2.2 Fibers

Fibers of ECM provide tensile strength and elasticity. From the molecular perspective, there are only two types of fibers (collagenous and elastic), whereas from the histochemical point of view three types are defined (collagenous, reticular, and elastic fibers) [18].

### 2.2.3 Collagens

Collagen fibers are responsible for compressive forces, together with GAGs and proteoglycans. Collagen is a hard, inelastic glycoprotein that constitutes an abundant, large family of macromolecules with over 30 members. The most known and widely expressed are types I, II, III, IV, VII, VIII, IX, XI, XII, XV, and XVIII [19][20]. Collagen fiber is the result of the regular assembly of tropocollagen molecules, which are composed of three polypeptide α-chains. Alpha-chains are highly enriched in glycine, proline, hydroxyproline, and hydroxylysine, and each chain is coded by a single gene [21].

As indicated above, 30 types of collagens have been reported so far and they are grouped into four categories [22]. The first category is fibril-forming collagens, which have been taken as a model to report the basic structure and synthesis. Characteristic collagens of this group are types I, II, III, V, and XI [23]. The second category is fibril-associated collagens,

which stabilize the previous group because they form molecular bridges between fibril-forming collagens and components of the ground substance. They are composed of types IX and XII. The third is network-forming collagens, which are synthesized by epithelial cells. As indicated above, they are not subjected to the action of procollagen peptidase and, consequently, form a network of thin 3D sheets. Examples are collagens IV (characteristic of basement membrane) and VII, which assist as anchoring fibers in the stabilization of the basement membrane. The fourth category is transmembrane collagens or collagen-like proteins, which are integral membrane proteins that participate in adhesion between tissues. This is the case of collagen type XVII that acts at the epidermis and the dermis, at the level of hemidesmosomes. Other collagens of this category are types XIII, XXIII, and XXV.

Collagens are synthetized in the endoplasmic reticulum (ER) by translation of the respective mRNA transcripts, generating a preprocollagen molecule whose proline and lysine residues are co-translationally hydroxylated by peptidyl proline and lysine hydroxylase, respectively [24]. Three preprocollagen molecules are aligned and assembled with the help of chaperones in the lumen of ER to form the procollagen molecule. Next, procollagen molecules leave the ER to the Golgi apparatus using large and pleomorphic transport carriers, where they are additionally glycosylated to be finally packaged in the *trans*-Golgi network (TGN) and transported to the extracellular space. As procollagen is released to outside of the cell, extracellular plasma membrane-attached procollagen peptidases remove both amino and carboxyl ends of propeptides, resulting in a tropocollagen moiety. Tropocollagen molecules spontaneously self-assemble and align into a regular fibril array only in fibril-forming collagens. The resulting extracellular basic fibrillar structure of these collagens is subsequently thickened and stabilized (3D self-assembling) by covalent bonds between lysine and hydroxylysine residues of neighboring tropocollagen molecules by lysyl oxidases (LOXes) [25]. Importantly, the alignment of collagen fibrils and fiber bundles is determined by fibroblasts at the plasma membrane level, which act as a mold for the final correct direction of collagen fibrils. Subsequently, mechanical forces to cells will finally rearrange the orientation and organization of fibrils and bundles in the tissue [26]. Importantly, the aforementioned fibrillar structure for fibril-forming collagens is absent in types IV and VII collagen because propeptides are not removed from procollagen. In this case, the procollagen molecules assemble only into dimers, forming net-like structures.

#### 2.2.4 Elastic Fibers

Elastic fibers provide most of the elasticity of CT. Elastic fibers are differently organized depending on the tissue to form long, worm-like, thin fibers, fenestrated sheets (the tunica media of large elastic arteries and internal elastic lamina of small arteries), or coarse bundles in dermis and elastic cartilage [27][28]. Fibroblasts and vascular SMCs (VSMCs) synthesize all components of elastic fibers.

Elastin is a glycoprotein that is rich in glycine, lysine, alanine, valine, proline, and desmosine (only in elastin) residues. However, unlike collagens, elastin does not contain hydroxylysine [29]. Like collagen, elastin comes from a soluble protein precursor, tropoelastin, which becomes insoluble because of cross-linking of lysine residues by LOXes [25]. Desmosine is highly deformable and, consequently, provides elasticity to elastic fibers, which explains cycles of stretching and recoiling. Elastin does not form elastic fibers unless the amorphous central elastin core is surrounded by a fibrillin-1 microfibril sheath [30]. During elastogenesis, besides fibrillin-1, several fibrillin-binding proteins facilitate the assembly of elastic fibers and their function, such as latent TGF-β binding proteins, fibulins, microfibril-associated glycoproteins (MAGPs), a disintegrin and metalloprotease with thrombospondin type-1 repeats (ADAMTS) and ADAMTS-like (ADAMTSL) proteins, and type VIII collagen, which limits the amount of stretching of elastic fibers. Transglutaminases and LOXes are also essential determinants of the final assembly and cross-linking of elastin and deposition onto microfibril scaffolds. Fibrillin-1 microfibrils interact with growth factors (TGF-βs and BMPs) and integrins. Fibrilin-1 mutations cause heritable connective tissue diseases, grouped as fibrillinopathies. Several fibrillin-binding proteins have been reported. The most representative are latent TGFβ protein, fibulins 4 and 5, ADAMTS 6 and 10, ADAMTSL 2, aggrecan, MAGP-1 and 2, perlecan, aggecan, integrins αV, and LOX [31].

#### 2.2.5 Other ECM Components

Finally, other parts of ECM are (1) the basement membrane, which forms the interface between epithelium and CT, and (2) integrins and dystroglycans, transmembrane glycoproteins that act as nonsignaling receptors of nonfibrillar/cell adhesive glycoproteins of the ECM and assist in the structure of basement membrane and CTs. Integrins function in adhesion and signal transduction from extracellular to intracellular media, activating second messengers at the focal adhesions.

## 3. Maintenance and Turnover of ECM

ECM is slowly but continuously (re)modelled for maintenance and adaptation to local homeostasis and pathological environments. Major components that are responsible for maintenance and turnover of ECM are a large family of proteases and their inhibitors, which are both secreted by fibroblasts, local and transient macrophages, some translocated leukocytes, and metastatic cells. Metalloproteases (MMPs), transmembrane inhibitors of proteases (TIMPS), soluble cathepsins, and other types of proteases belong to this group of ECM components [32][33][34][35].

## 4. Pathologies Associated with the Connective Tissue

As in any other tissue and organ, connective tissue is susceptible to damage, which is primary if it originates in some of the cell components or in any of the numerous ECM components and secondary because of alterations in any of the associated functions such as the metastatic process, immune overreactions, etc.

### References


1. Kierszenbaum, A.L.; Tres, L. Histology and Cell Biology: An Introduction to Pathology; Elsevier: Philadelphia, PA, USA, 2019; ISBN 9780323673211.
2. Ross, R. Connective tissue cells, cell proliferation and synthesis of extracellular matrix-a review. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 1975, 271, 247–259.
3. Shaw, T.J.; Rognoni, E. Dissecting Fibroblast Heterogeneity in Health and Fibrotic Disease. Curr. Rheumatol. Rep. 2020, 22, 33.
4. Ribatti, D.; Tamma, R.; Annese, T. Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. Transl. Oncol. 2020, 13, 100773.
5. Sun, N.-Y.; Yang, M.-H. Metabolic Reprogramming and Epithelial-Mesenchymal Plasticity: Opportunities and Challenges for Cancer Therapy. Front. Oncol. 2020, 10, 792.
6. Pakshir, P.; Noskovicova, N.; Lodyga, M.; Son, D.O.; Schuster, R.; Goodwin, A.; Karvonen, H.; Hinz, B. The myofibroblast at a glance. J. Cell Sci. 2020, 133.
7. Karamanos, N.K. Extracellular matrix: Key structural and functional meshwork in health and disease. FEBS J. 2019, 286, 2826–2829.
8. Sugahara, K.; Mikami, T.; Uyama, T.; Mizuguchi, S.; Nomura, K.; Kitagawa, H. Recent advances in the structural biology of chondroitin sulfate and dermatan sulfate. Curr. Opin. Struct. Biol. 2003, 13, 612–620.
9. Lindahl, U.; Couchman, J.; Kimata, K.; Esko, J.D. Proteoglycans and Sulfated Glycosaminoglycans; Varki, A., Cummings, R.D., Esko, J.D., Stanley, P., Hart, G.W., Aebi, M., Darvill, A.G., Kinoshita, T., Packer, N.H., Prestegard, J.H., et al., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, USA, 2015.
10. Walimbe, T.; Panitch, A. Proteoglycans in Biomedicine: Resurgence of an Underexploited Class of ECM Molecules. Front. Pharmacol. 2019, 10, 1661.
11. Kiani, C.; Chen, L.; Wu, Y.J.; Yee, A.J.; Yang, B.B. Structure and function of aggrecan. Cell Res. 2002, 12, 19–32.
12. Bilandzic, M.; Stenvers, K.L. Betaglycan: A multifunctional accessory. Mol. Cell. Endocrinol. 2011, 339, 180–189.
13. Afratis, N.A.; Nikitovic, D.; Multhaupt, H.A.B.; Theocharis, A.D.; Couchman, J.R.; Karamanos, N.K. Syndecans—Key regulators of cell signaling and biological functions. FEBS J. 2017, 284, 27–41.
14. Gondelaud, F.; Ricard-Blum, S. Structures and interactions of syndecans. FEBS J. 2019, 286, 2994–3007.
15. Kim, S.K.; Henen, M.A.; Hinck, A.P. Structural biology of betaglycan and endoglin, membrane-bound co-receptors of the TGF-beta family. Exp. Biol. Med. (Maywood) 2019, 244, 1547–1558.
16. Kechagia, J.Z.; Ivaska, J.; Roca-Cusachs, P. Integrins as biomechanical sensors of the microenvironment. Nat. Rev. Mol. Cell Biol. 2019, 20, 457–473.
17. Bachmann, M.; Kukkurainen, S.; Hytönen, V.P.; Wehrle-Haller, B. Cell adhesion by integrins. Physiol. Rev. 2019, 99, 1655–1699.
18. Ushiki, T. Collagen fibers, reticular fibers and elastic fibers. A comprehensive understanding from a morphological viewpoint. Arch. Histol. Cytol. 2002, 65, 109–126.
19. Gordon, M.K.; Hahn, R.A. Collagens. Cell Tissue Res. 2010, 339, 247–257.

20. Mienaltowski, M.J.; Birk, D.E. Structure, physiology, and biochemistry of collagens. Adv. Exp. Med. Biol. 2014, 802, 5–29.
21. Fidler, A.L.; Boudko, S.P.; Rokas, A.; Hudson, B.G. The triple helix of collagens—An ancient protein structure that enabled animal multicellularity and tissue evolution. J. Cell Sci. 2018, 131.
22. Kadler, K.E.; Baldock, C.; Bella, J.; Boot-Handford, R.P. Collagens at a glance. J. Cell Sci. 2007, 120, 1955–1958.
23. Bella, J.; Hulmes, D.J.S. Fibrillar Collagens. Subcell. Biochem. 2017, 82, 457–490.
24. Gelse, K.; Pöschl, E.; Aigner, T. Collagens - Structure, function, and biosynthesis. Adv. Drug Deliv. Rev. 2003, 55, 1531–1546.
25. Vallet, S.D.; Ricard-Blum, S. Lysyl oxidases: From enzyme activity to extracellular matrix cross-links. Essays Biochem. 2019, 63, 349–364.
26. Muiznieks, L.D.; Keeley, F.W. Molecular assembly and mechanical properties of the extracellular matrix: A fibrous protein perspective. Biochim. Biophys. Acta 2013, 1832, 866–875.
27. Goldfischer, S.; Coltoff-Schiller, B.; Schwartz, E.; Blumenfeld, O.O. The infrastructure of aortic elastic fibers. Tissue Cell 1983, 15, 429–435.
28. Midwood, K.S.; Schwarzbauer, J.E. Elastic fibers: Building bridges between cells and their matrix. Curr. Biol. 2002, 12, R279–R281.
29. Vindin, H.; Mithieux, S.M.; Weiss, A.S. Elastin architecture. Matrix Biol. 2019, 84, 4–16
30. Kielty, C.M.; Sherratt, M.J.; Marson, A.; Baldock, C. Fibrillin microfibrils. Adv. Protein Chem. 2005, 70, 405–436.
31. Thomson, J.; Singh, M.; Eckersley, A.; Cain, S.A.; Sherratt, M.J.; Baldock, C. Fibrillin microfibrils and elastic fibre proteins: Functional interactions and extracellular regulation of growth factors. Semin. Cell Dev. Biol. 2019, 89, 109–117.
32. Stamenkovic, I. Extracellular matrix remodelling: The role of matrix metalloproteinases. J. Pathol. 2003, 200, 448–464.
33. Lu, P.; Takai, K.; Weaver, V.M.; Werb, Z. Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harb. Perspect. Biol. 2011, 3.
34. Arpino, V.; Brock, M.; Gill, S.E. The role of TIMPs in regulation of extracellular matrix proteolysis. Matrix Biol. 2015, 44–46, 247–254.
35. Vizovišek, M.; Fonović, M.; Turk, B. Cysteine cathepsins in extracellular matrix remodeling: Extracellular matrix degradation and beyond. Matrix Biol. 2019, 75–76, 141–159.