Connective tissue fibers Extracellular matrix

Acc. Prof. Sinan Özkavukcu

Department of Histology and Embryology

Lab Manager – Center for Assisted Reproduction – Department of Obstetrics and Gynecology

sinozk@gmail.com

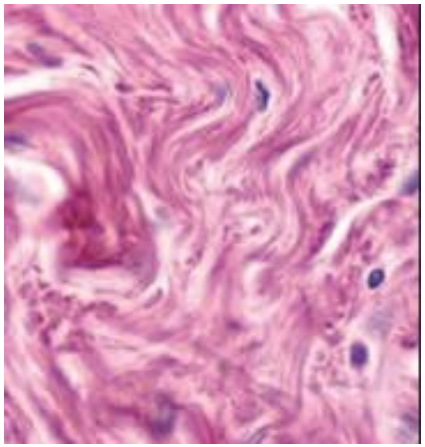
Connective tissue fibers

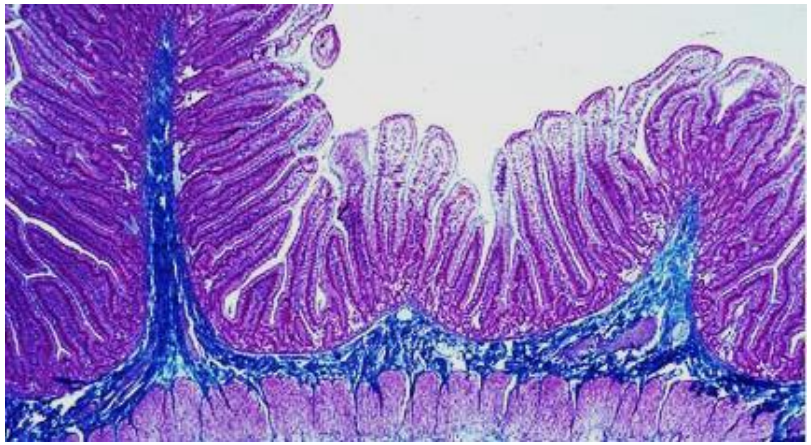
There are basically 3 types of fiber structures

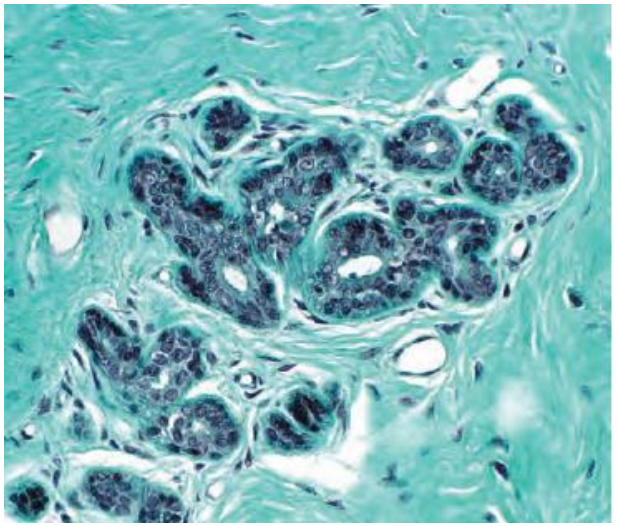
- Collagen Fibers
- Reticular Fibers
- Elastic Fibers

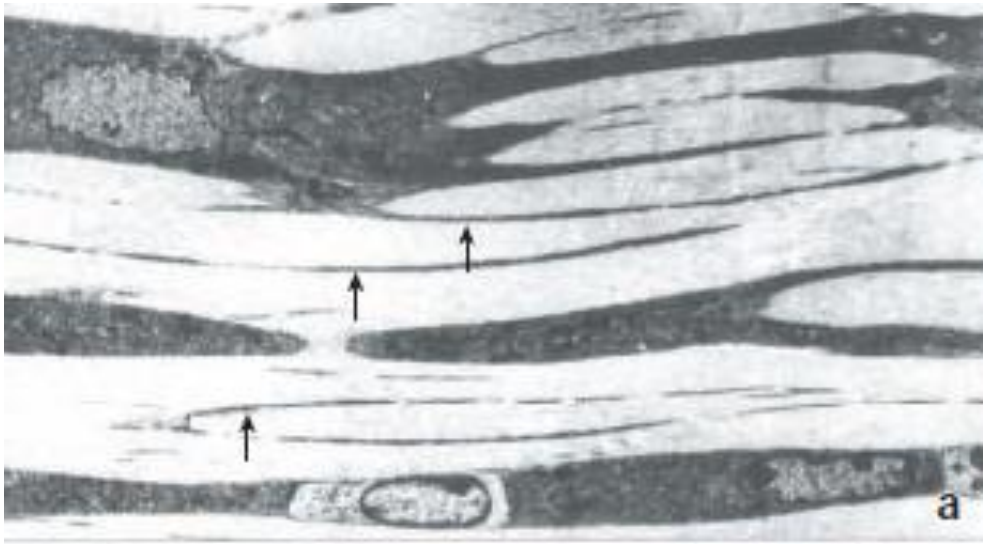
Collagen Fibers and Fibrils

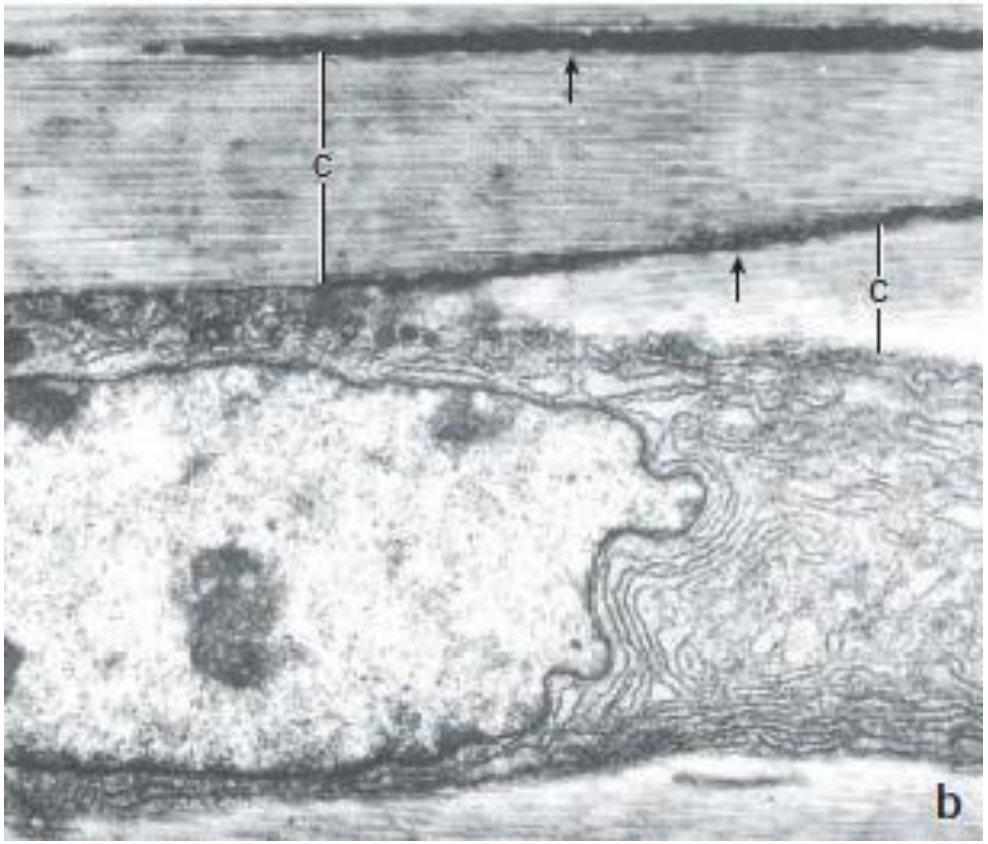
- They are the most common type of fibers in connective tissues.
- They are flexible, they are also tensile resistant.
- Under light microscope they observed wavy, indeterminate length and in variable thickness
- Stained with eosin and other acidic dyes
- Stained with aniline blue in Mallory connective tissue dye,
- Stained in light green in Masson dye



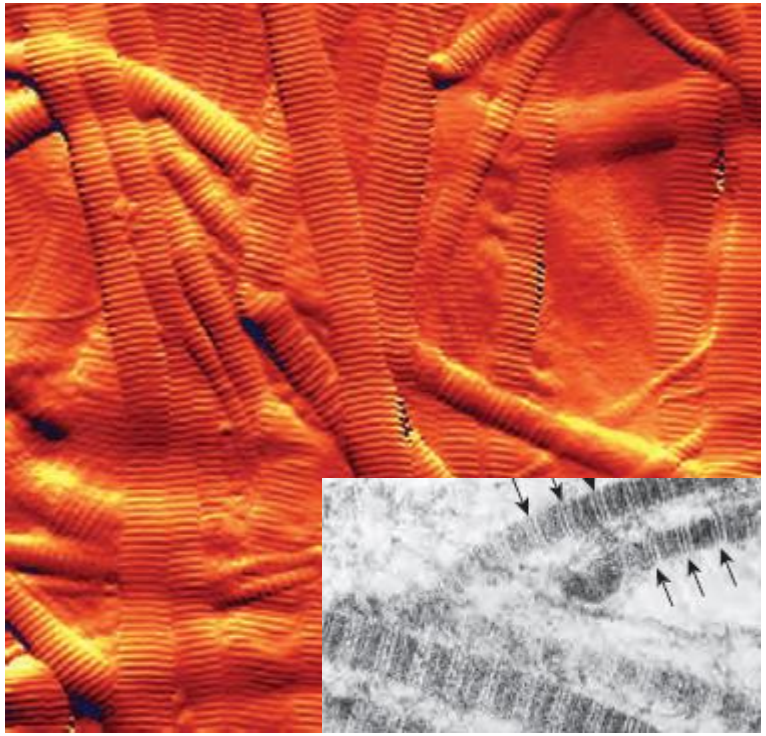






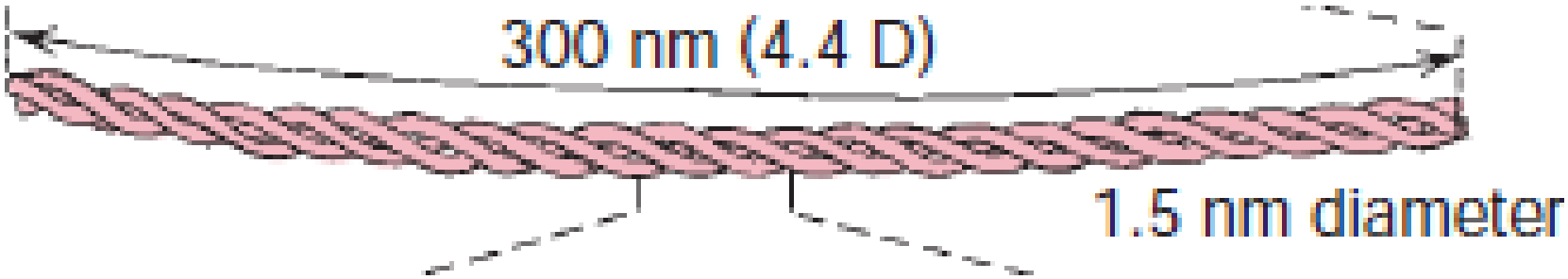


- When examined with the TEM, collagen fibers appear as bundles of fine, threadlike subunits. These subunits are **collagen fibrils**
- The diameter of the collagen fibrils may be from 15 to 300 nm thick, depending on the type of tissue.
- When the collagen strands are stained with osmium for TEM examinations, they show a transverse band sequence at 68 nm, along their length.
- Due to the structure of the collagen molecule, this band sequence can also be observed on Atomic Power Microscopy.



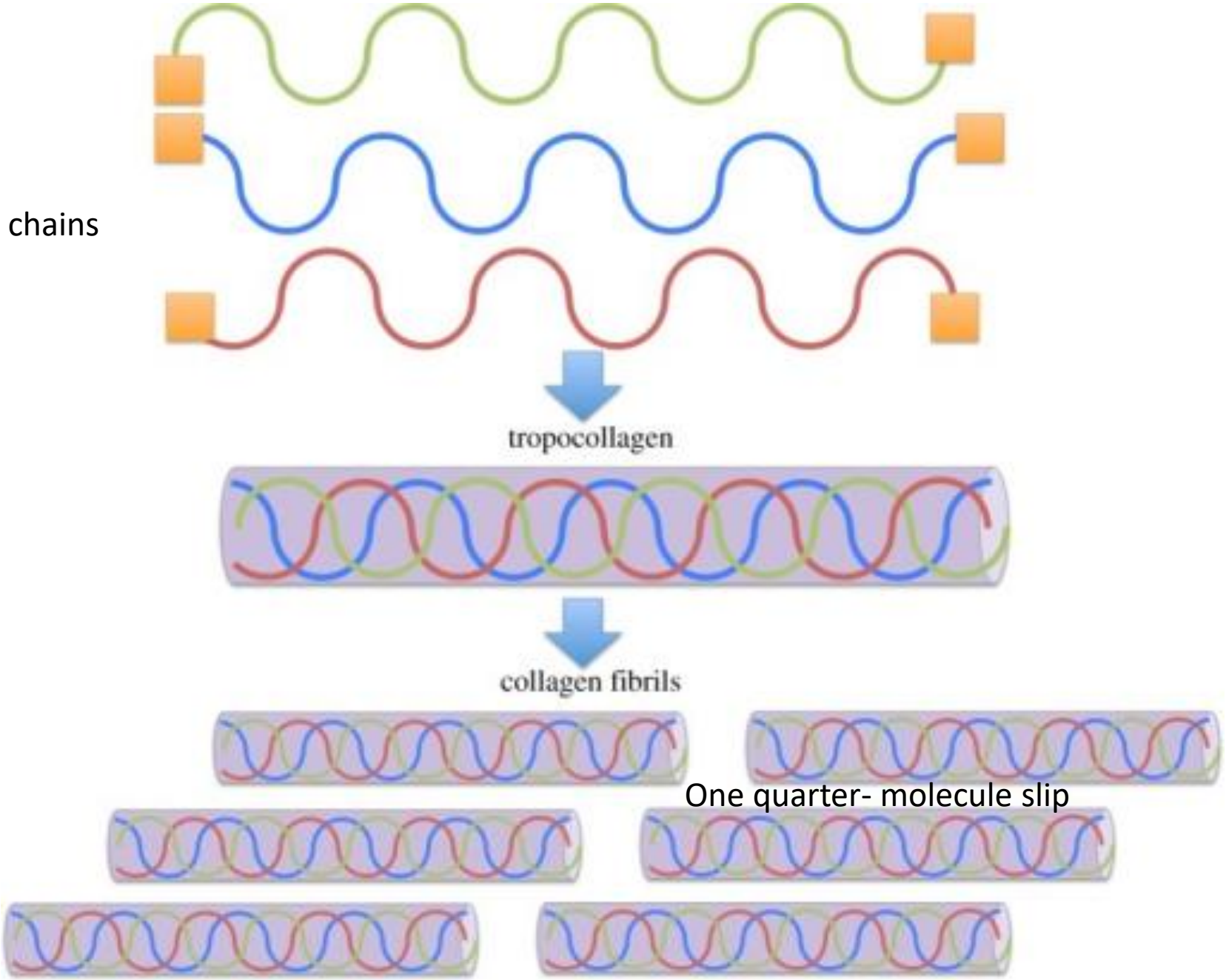
The collagen molecule

- Formerly called *tropocollagen*.
- Unit molecule measures about 300 nm long by 1.5 nm thick and has a head and a tail..

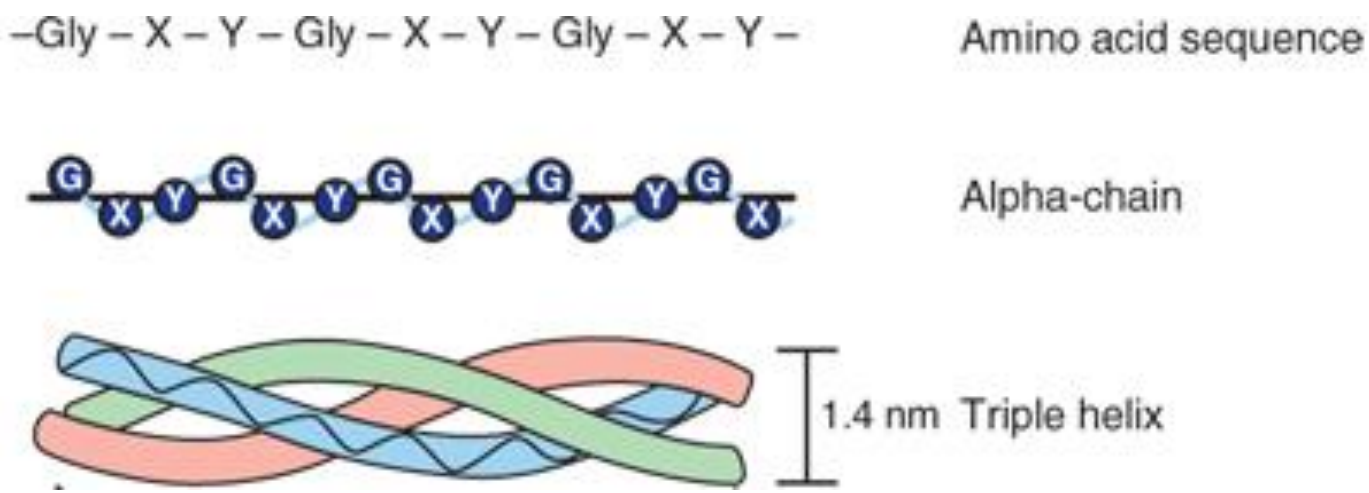


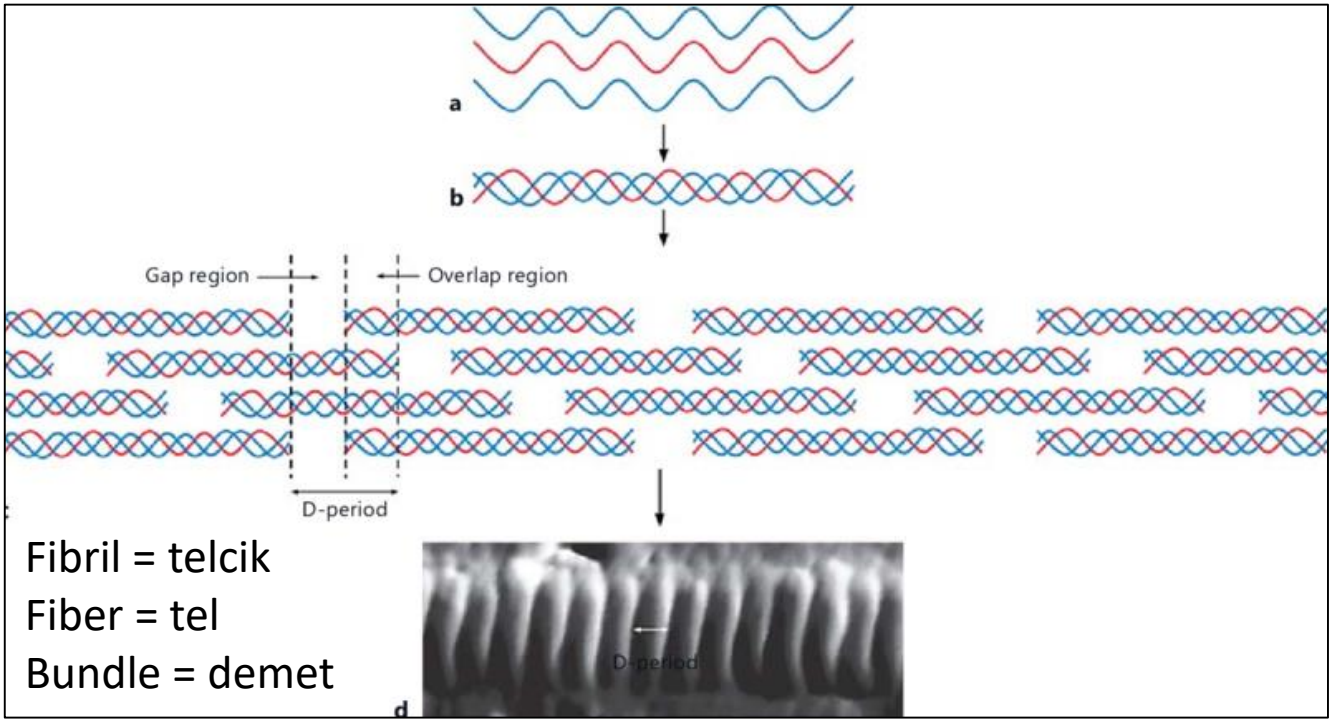
- Consists of 3 helix-encoded polypeptide chains = **α (alpha) chains**

Alpha chains



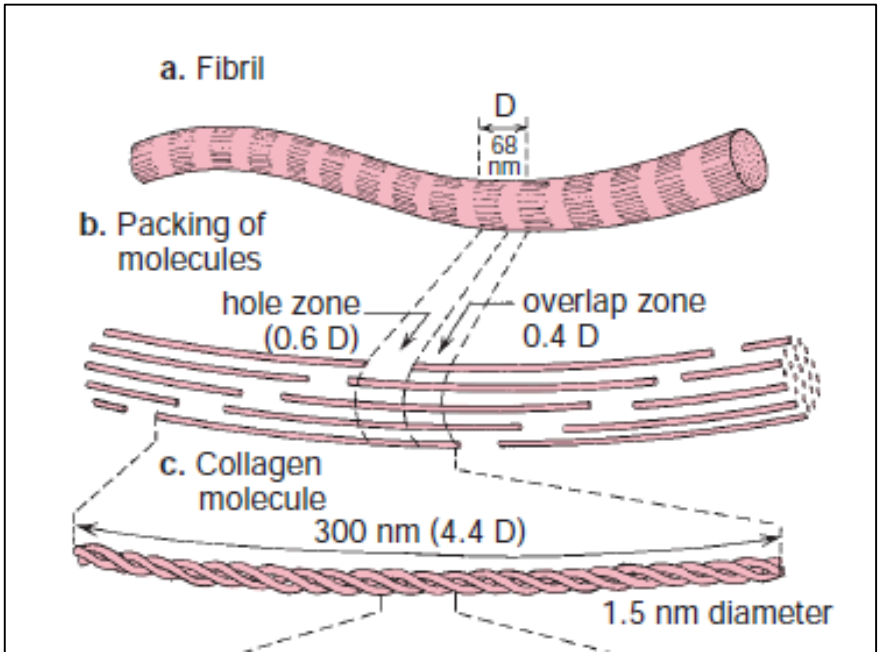
- Alpha chains; organize in helix structure.
- Glycine is one out of every three amino acids in the alpha chain. However, glycine cannot be the last amino acid of the chain.
- The glycine is usually chained first to hydroxyproline or hydroxylisine followed by the proline amino acid.
- In the collagen molecule hydroxyproline, proline and glycine are essential for the triple helix structure.
- There are sugar groups bound to the collagen molecule, so collagen is actually a glycoprotein structure.
- To date, over 40 alpha chain structures and their chromosomal loci for synthesis have been discovered

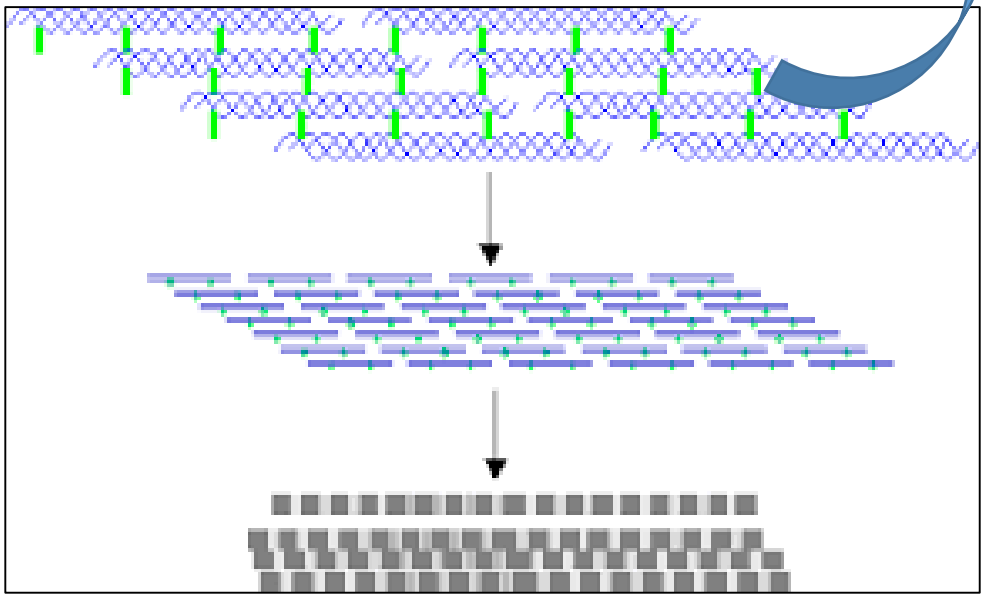


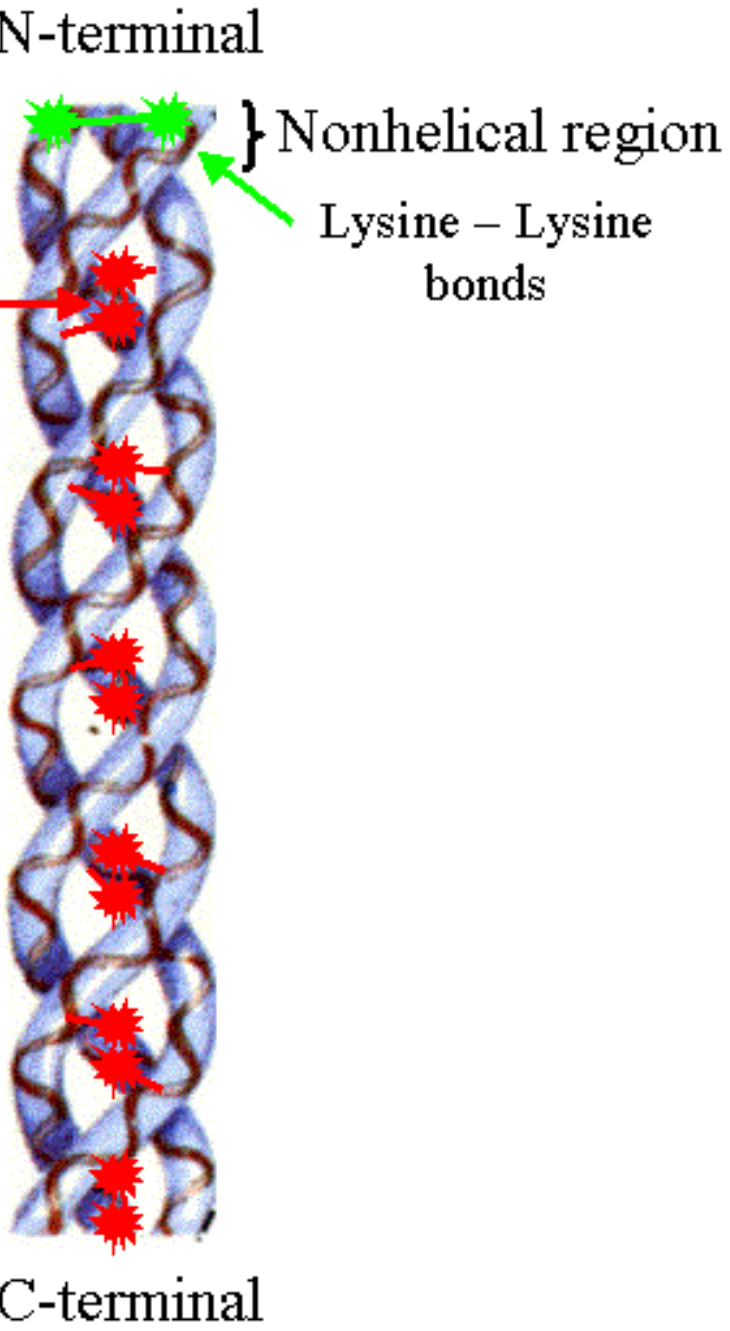


Fibril = telcik
Fiber = tel
Bundle = demet

The strength of the fibril is created by the covalent bonds between the collagen molecules of adjacent rows, not the head-to-tail attachment of the molecules in a row.

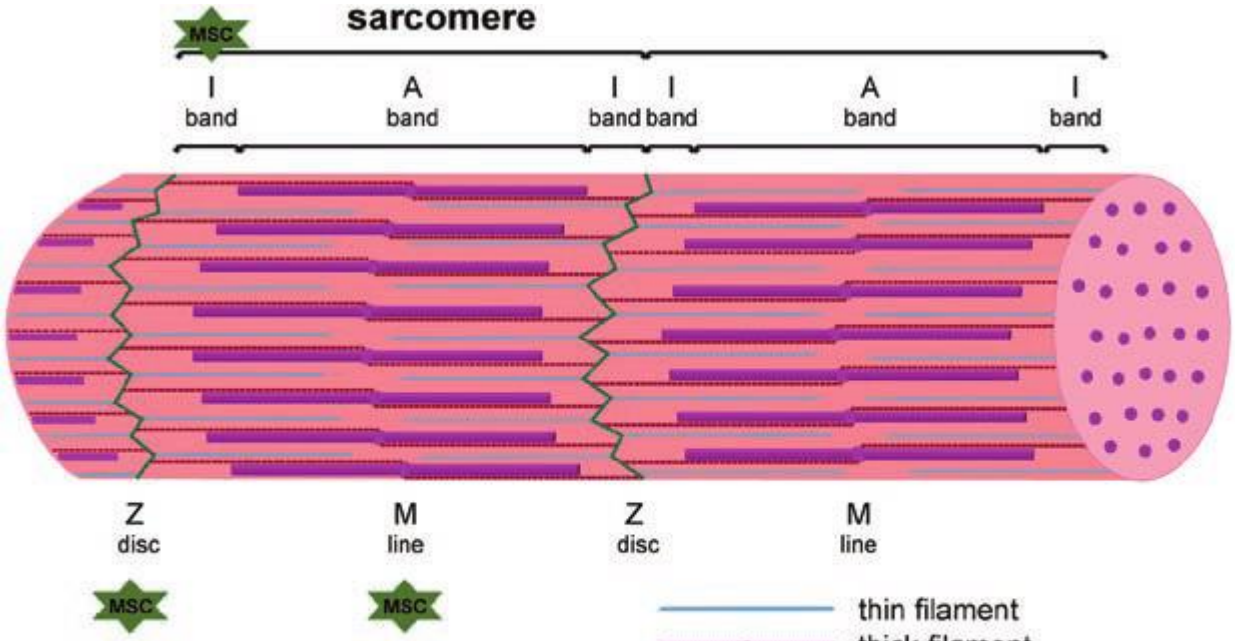


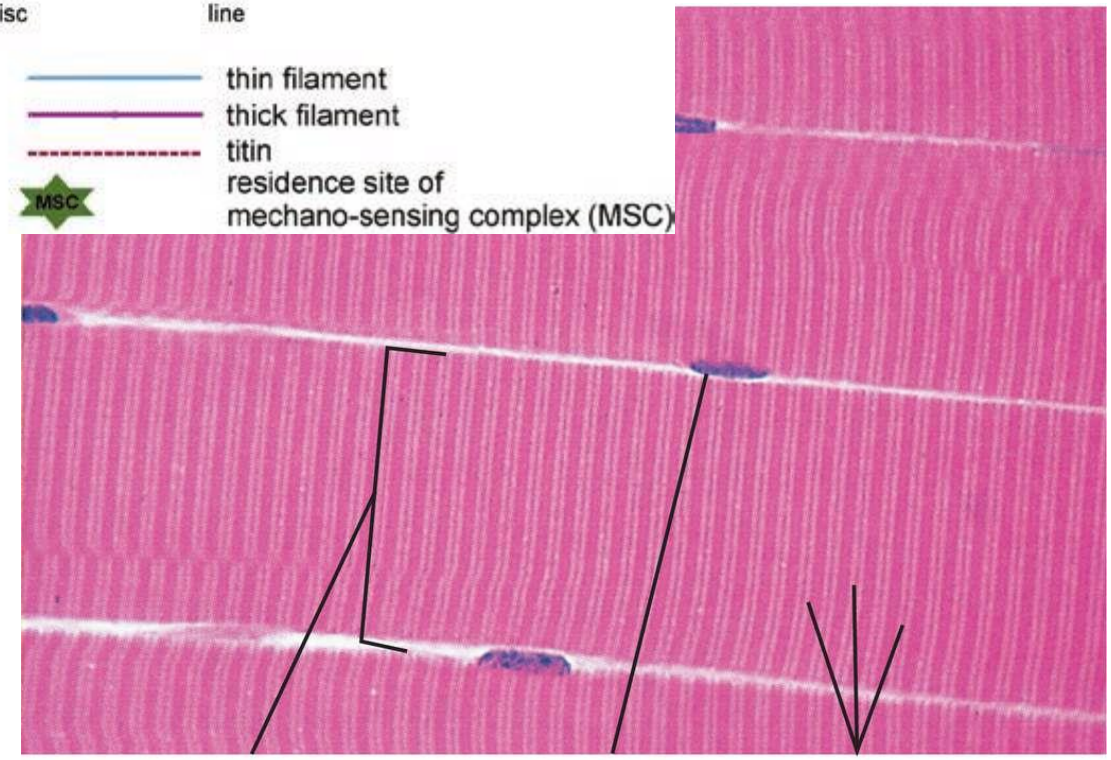




Intra-tropocollagen cross-links:

- Lysine-Lysine bonds
- Glycine(NH group)-x(CO group) hydrogen bonds (red line)
- Hydroxyproline hydrogen bonds





Skeletal muscle fiber

Nucleus

Striations

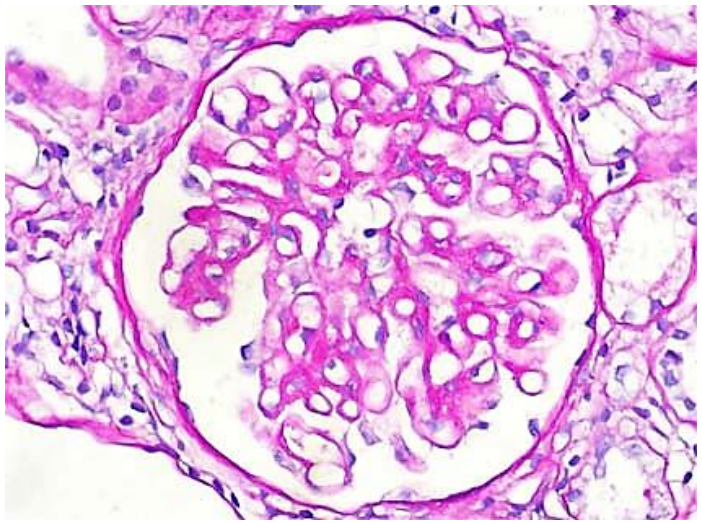
Collagen types

- There are at least 28 types of collagen, formed with different alpha chains, which are numbered according to the order of discovery in Roman numerals (I to XXVIII).
- Homotrimeric: consisting of three identical chains.
- Heterotrimeric: consisting of two or even three genetically distinct alpha chains).
- Type I collagen: Found in loose and tight connective tissue. Heterotrimeric. Expressed as $[\alpha 1\ (I)]_2\ \alpha 2\ (I)$. It is found in the bone, tendon, dentin, skin and provides tensile strength.
- Type II collagen : Homotrimeric. It is found in hyaline and elastic cartilage in the form of very fine fibers. Expressed as $[\alpha\ 1(II)]_3$

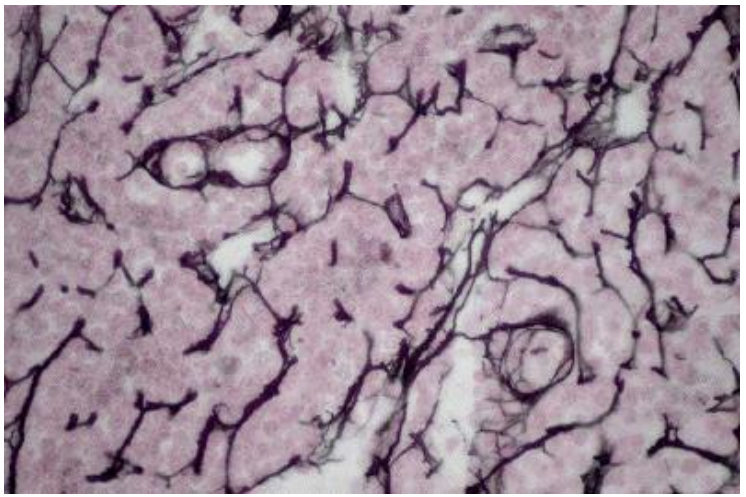
Collagen types

As reticular fibers and collagen in general, are in glycoprotein structure, can be well visualized by periodic acid-Schiff (PAS) reaction (because of the carbohydrate content)

- Type III collagen: Located in the reticular lamina of the basement membrane. They are called reticular fibers. They are the first structures produced during the wound healing process and later converted to type I collagen.
- They are argyrophilic. (=having an affinity for silver). Selectively reduce silver salts to metallic silver, stained black by silver salts.
- Type IV collagen: Located in the basal lamina. Connects to laminin.



PAS (+)



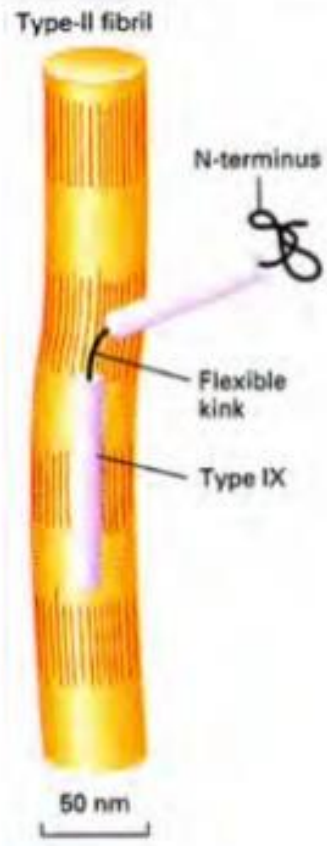
silver impregnation

Collagen groups according to function and polymerization pattern

- **Fibrillar collagens**: **Type I, II, III, V, XI.**
- **Fibril-associated collagens with interrupted triple helixes (FACITs)**: Accessory collagens that provide flexibility by their interrupted triple helix structure. Type **IX**, XII, XIV, XVI, XIX, XX, XXI, XXII
- **Hexagonal network–forming collagens** are represented by collagen types VIII and X.
- **Transmembrane collagens** are represented by types: XIII (found in the focal adhesions), XVII (found within the hemidesmosomes), XXIII (found in metastatic cancer cells), and XXV (a brain-specific collagen).
- **Multiplexins** (collagens with multiple triple-helix domains and interruptions) comprise collagen types XV and XVIII, which reside in the basement membrane zones.
- **Basement membrane–forming collagens: Type IV, VI, VII** collagen

FACIT: Fibril-Associated Collagens with Interrupted Triple helices

1. Triple helices interrupted by non-helical domains
2. Retain propeptides at ends
3. Do not aggregate into large fibrils
4. Bind collagen fibrils to each other and/or the ECM

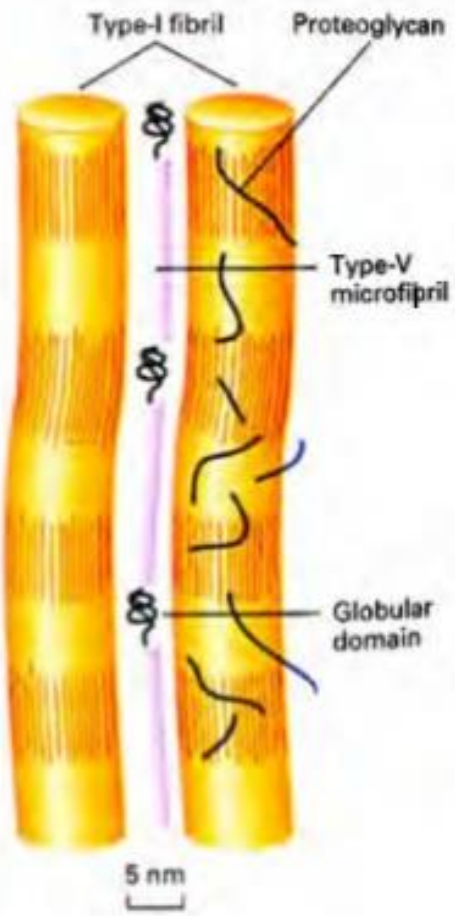


Type IX Collagen (left)

- Binds type II Fibrils to the ECM
- Globular N-terminus interacts with ECM
- Heparin-SO_4 at kink interacts with ECM
- Helical region interacts with type II fibril

Type VI Collagen (right)

Bundles type I fibrils into FIBERS
Binds fibrils via helical domains



 Alberts et. al. *Molecular Biology of the Cell*. Second Edition.

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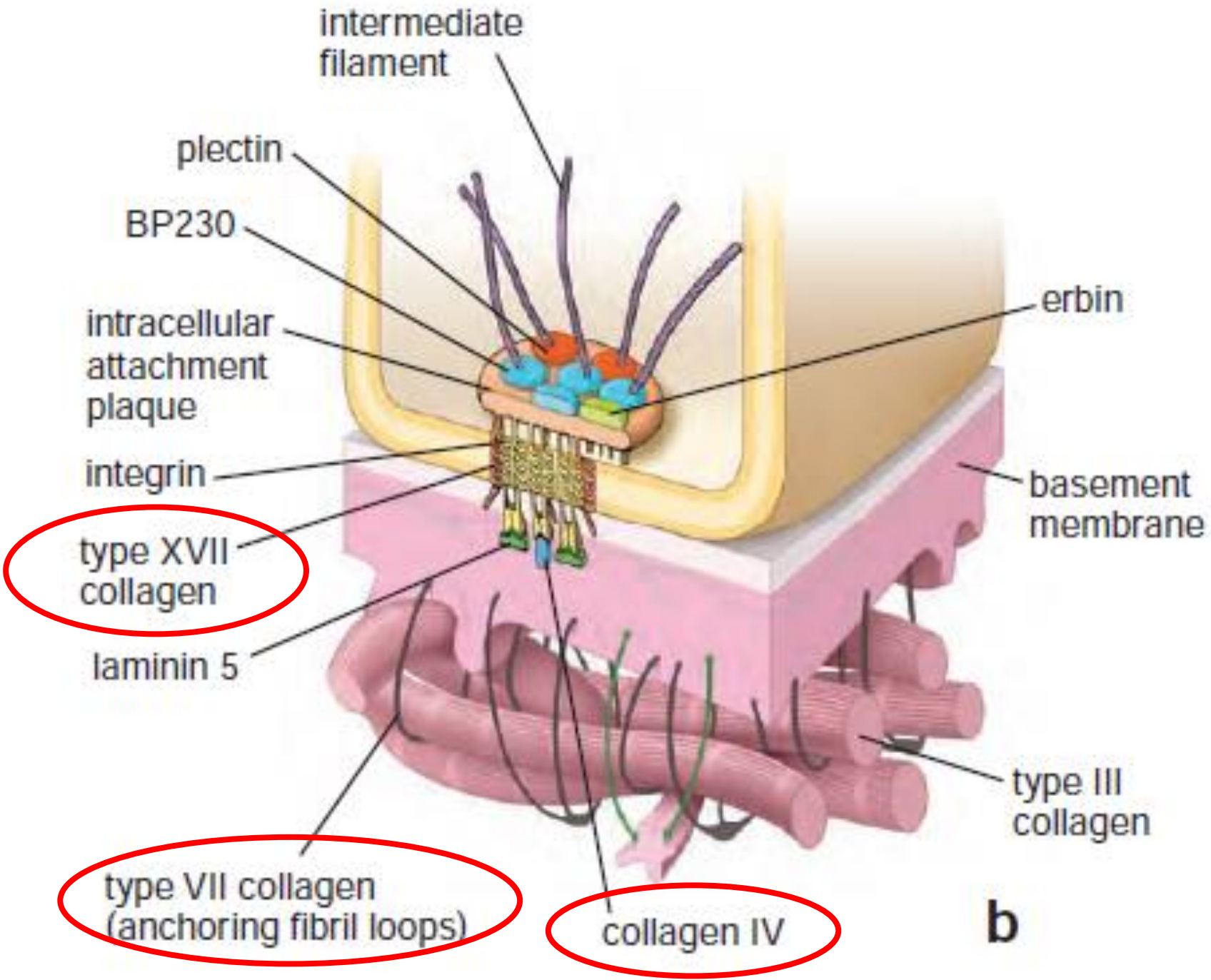

intermediate filament
plectin
BP230
intracellular attachment plaque
integrin
type XVII collagen
laminin 5
type VII collagen (anchoring fibril loops)
collagen IV
erbin
basement membrane
type III collagen
b

Type	Composition[a]	Location	Functions
I	$[\alpha1(I)]_2\alpha2(I)$	Connective tissue of skin, bone, tendon, ligaments, dentin, sclera, fascia, and organ capsules (accounts for 90% of body collagen)	Provides resistance to force, tension, and stretch
II	$[\alpha1(II)]_3$	Cartilage (hyaline and elastic), notochord, and intervertebral disk	Provides resistance to intermittent pressure
III	$[\alpha1(III)]_3$	Prominent in loose connective tissue and organs (uterus, liver, spleen, kidney, lung, etc.); smooth muscle; endoneurium; blood vessels; and fetal skin	Forms reticular fibers, arranged as a loose meshwork of thin fibers, provides a supportive scaffolding for the specialized cells of various organs and blood vessels.
IV	$[\alpha1(IV)]_2\alpha2(IV)$ or $\alpha3(IV)$ $\alpha4(IV)$ $\alpha5(IV)$ or $[\alpha5(IV)]_2\alpha6(IV)$	Basal laminae of epithelia, kidney glomeruli, and lens capsule	Provides support and filtration barrier
V	$[\alpha1(V)]_2\alpha2(V)$ or $\alpha1(V)\alpha2(V)\alpha3(V)$	Distributed uniformly throughout connective tissue stroma; may be related to reticular network	Localized at the surface of type I collagen fibrils along with type XII and XIV collagen to modulate biomechanical properties of the fibril
VI	$[\alpha1(VI)]_2\alpha2(VI)$ or $\alpha1(VI)$ $\alpha2(VI)$ $\alpha3(VI)$	Forms part of the cartilage matrix immediately surrounding the chondrocytes	Attaches the chondrocyte to the matrix; covalently bound to type I collagen fibrils
VII	$[\alpha1(VII)]_3$	Present in anchoring fibrils of skin, eye, uterus, and esophagus	Secures basal lamina to connective tissue fibers
VIII	$[\alpha1(VIII)]_2\alpha2(VIII)$	Product of endothelial cells	Facilitates movement of endothelial cells during angiogenesis

Type	Composition[a]	Location	Functions
IX	$\alpha1(IX)\alpha2(IX)\alpha3(IX)$	Found in cartilage associated with type II collagen fibrils	Stabilizes network of cartilage type II collagen fibers by interaction with proteoglycan molecules at their intersections
X	$[\alpha1(X)]_3$	Produced by chondrocytes in the zone of hypertrophy of normal growth plate	Contributes to the bone mineralization process by forming hexagonal lattices necessary to arrange types II, IX, and XI collagen within cartilage
XI	$[\alpha1(XI)]_2\alpha2(XI)$ or $\alpha1(XI)\ \alpha2(XI)\ \alpha3(XI)$	Produced by chondrocytes; associated with type II collagen fibrils, forms core of type I collagen fibrils	Regulates size of type II collagen fibrils; it is essential for cohesive properties of cartilage matrix
XII	$[\alpha1(XII)]_3$	Isolated from skin and placenta; abundant in tissues in which mechanical strain is high	Localized at the surface of type I collagen fibrils along with type V and XIV collagen to modulate biomechanical properties of the fibril
XIII	$[\alpha1(XIII)]_3$	An unusual transmembrane collagen detected in bone, cartilage, intestine, skin, placenta, and striated muscles	Associated with the basal lamina along with type VII collagen

Type	Composition[a]	Location	Functions
XIV	$[\alpha1(XIV)]_3$	Isolated from placenta; also detected in the bone marrow	Localized at the surface of type I collagen fibrils along with type V and XII collagen to modulate biomechanical properties of the fibril; has a strong cell–cell binding property
XV	$[\alpha1(XV)]_3$	Present in tissues derived from mesenchyme; expressed in heart and skeletal muscles	Involved in adhesion of basal lamina to the underlying connective tissue
XVI	$[\alpha1(XVI)]_3$	Broad tissue distribution; associated with fibroblasts and arterial smooth muscle cells, but not associated with type I collagen fibrils	Contributes to structural integrity of connective tissue
XVII	$[\alpha1(XVII)]_3$	Another unusual transmembrane collagen found in epithelial cell membranes	Interacts with integrins to stabilize hemidesmosome structure
XVIII	$[\alpha1(XVIII)]_3$	Found in epithelial and vascular basement membrane	Represents a basement membrane heparan sulfate proteoglycan thought to inhibit endothelial cell proliferation and angiogenesis
XIX	$[\alpha1(XIX)]_3$	Discovered from the sequence of human rhabdomyosarcoma cDNA; present in fibroblasts and liver	Pronounced vascular and stromal interaction suggests involvement in angiogenesis
XX	$[\alpha1(XX)]_3$	Discovered from chick embryonic tissue; also in corneal epithelium, sternal cartilage, and tendons	Binds to the surface of other collagen fibrils
XXI	$[\alpha1(XXI)]_3$	Found in human gingiva, heart and skeletal muscle, and other tissues containing type I collagen fibrils	Plays a role in maintaining three-dimensional architecture of dense connective tissues

Type	Composition[a]	Location	Functions
XXII	$[\alpha1(XXII)]_3$	Found in myotendinous junction, skeletal and heart muscle, articular cartilage–synovial fluid junction, at the border between hair follicle and dermis	Belongs to FACIT family Expressed at tissue junctions In skin, influences epithelial-mesenchymal interactions during hair follicle morphogenesis and cycling
XXIII	$[\alpha3(XXIII)]_3$	Discovered in metastatic tumor cells Also expressed in heart, retina, and metastatic prostate cancer cells	Transmembrane collagen Interacts with ECM proteins (collagen XIII and XXV, fibronectin, heparin) Increased expression in patient with metastatic prostate cancer
XXIV	$[\alpha1(XXIV)]_3$	Found co-expressed with type I collagen in the developing bone and eye	Fibrillarlike collagen Regarded as an ancient molecule that regulates type I collagen fibrillogenesis in bone and eye during fetal development
XXV	$[\alpha1(XXV)]_3$	A brain-specific transmembrane collagen Discovered in amyloid plaques in brains of patients with Alzheimer's disease Overexpressed in neurons	Binds to fibrillized β-amyloid peptide of amyloid plaques in Alzheimer's disease

[a]Each collagen molecule is composed of three polypeptide α chains intertwined in a helical configuration. The Roman numerals in the parentheses in the Composition column indicate that the α chains have a distinctive structure that differs from the chains with different numerals. Thus, collagen type I has two identical $\alpha1$ chains and one $\alpha2$ chain; collagen type II has three identical $\alpha1$ chains.

fibrillar collagen; FACITs; basement membrane–forming collagen; hexagonal network–forming collagen; transmembrane collagens; multiplexins

Collagen Biosynthesis

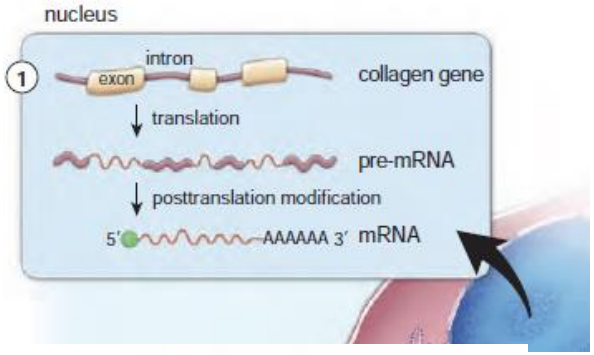
- **Collagen producing cells:**
  - Fibroblast (connective tissue)
  - Reticular cells (type III, bone marrow, lymphoid organs)
  - Osteoblast (bone)
  - Chondroblast (cartilage)
  - Odontoblast (tooth)
  - Epithelial cell (Type IV)
  - Pericytes (blood vessels)

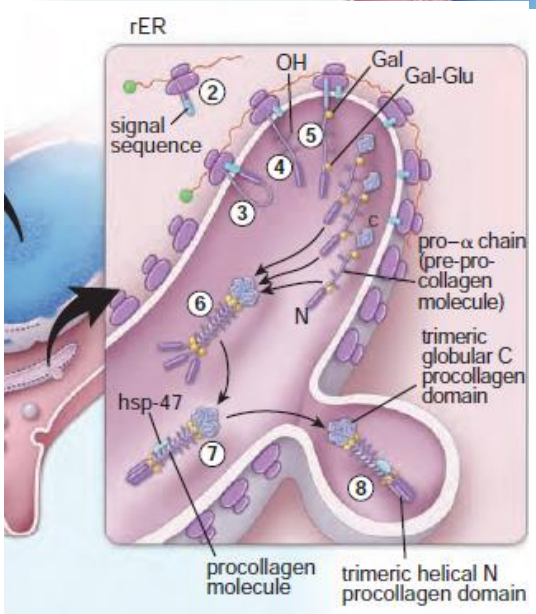
Transforming growth factor β (TGF- β) and platelet-derived growth factor (PDGF) increase collagen synthesis while glucocorticoids (steroids) reduce.

- **It is a series of events that take place inside and outside of fibroblasts.**
- Inside fibroblast, the production of protocollagen, the precursor of the collagen molecule, is carried out.
- Fiber formation is then carried out by the activity of enzymes present in the cell membrane outside the cell.
- The construction required for fiber formation occurs under the supervision of the cell in the extracellular matrix.

Collagen Biosynthesis

- Nuclear mRNA formation from the relevant DNA sequence

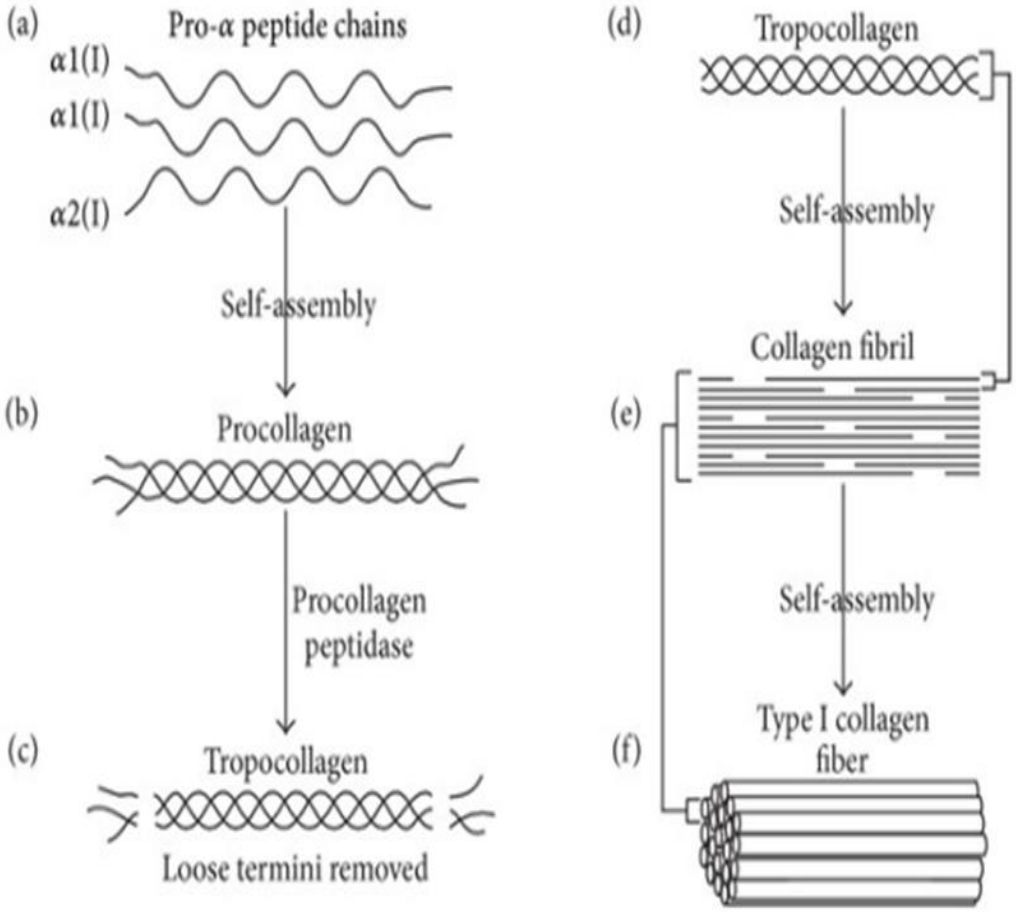


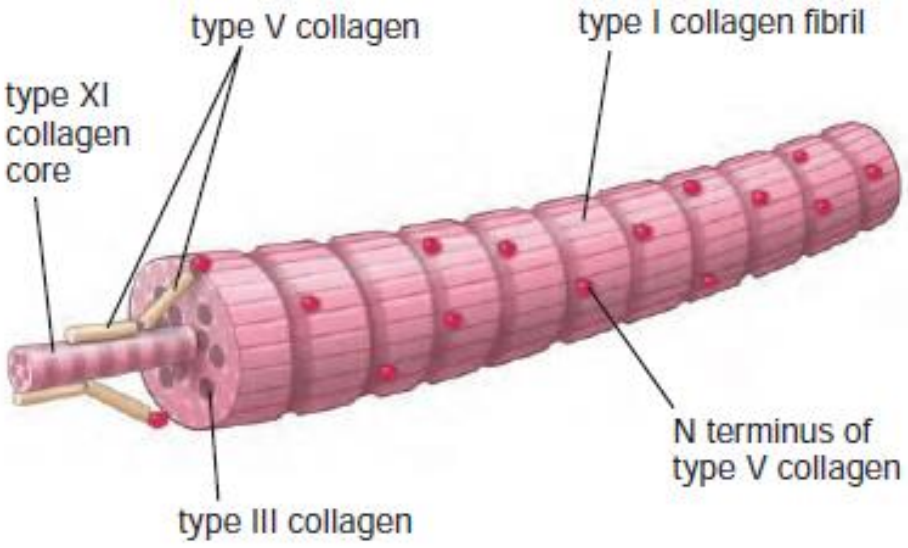


- Translocation of mRNA from the nucleus to GER and formation of pro-α chains (pre-procollagen)
- Hydroxylation of the proline and lysine residues takes place before the formation of the helix. (prolyl hydroxylase and lysyl hydroxylase enzymes) (**Vitamin C dependent-Scurvy-*skorbüt***) (required for hydrogen bonds)
- Glycosylation of specific hydroxylysyl residues
- Formation of the procollagen triple helix structure from the C-terminus to the N-terminus
- Procollagen transport to the Golgi body and transport outside the cell

Collagen Biosynthesis

- Cutting the globular C-terminus and helical N-terminus of procollagen carried **outside the cell** by «procollagen N- and C-peptidase»
- Polymerization (self-assembly) of collagen molecules into collagen fibrils (in cove of fibroblast) with development of covalent cross-linking
- Addition of other collagen (FACIT)

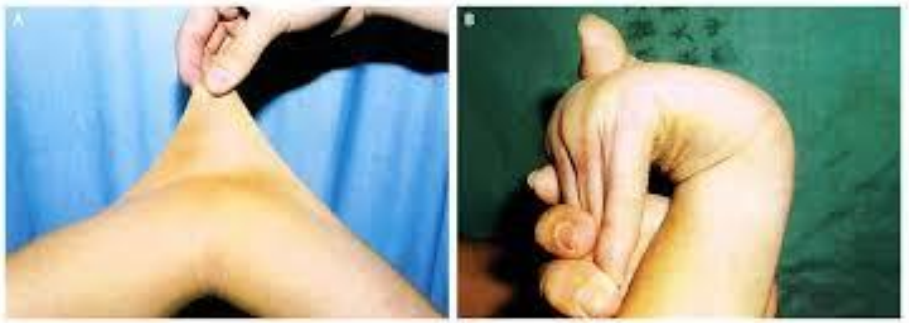




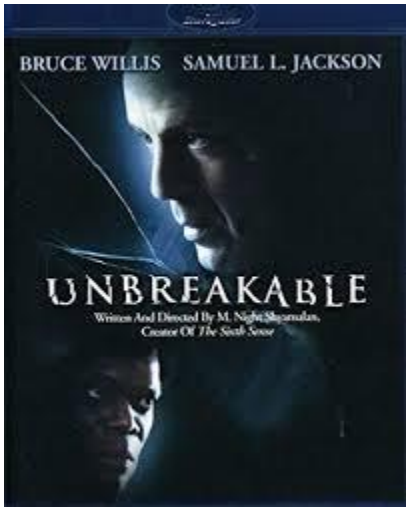
- Formation of type V and XI collagen is the first step in the production of type I collagen.
- Type I is added to this fibrillar mold
- Type II and III collagen form an integrated structure to type I collagen
- Type V and XI control the thickness and prevent the addition of fibers when the thickness is sufficient

- Collagen production and destruction is an ongoing event. Proteinases break down collagen and these fragments are removed by phagocytosis.
- It is performed by **matrix metalloproteinases** in the extracellular matrix (**MMPs**).
- Tissue inhibitors of metalloproteinases (**TIMPs**) limit MMP effects
- They are secreted by fibroblasts, chondrocytes, monocytes, neutrophils, macrophages, epithelial and cancer cells.
- Collagenase (cleaves I, II, III, X), gelatinase (degrades laminin, fibronectin, elastin, denatured collagen), stromelysin (degrades proteoglycan, fibronectin denatured collagen), matrilysins (degrades IV and proteoglycan fragments), macrophage metalloelastases (degrades elastin, IV, laminin)

Collagenopathies



Ehlers–Danlos Sendrome

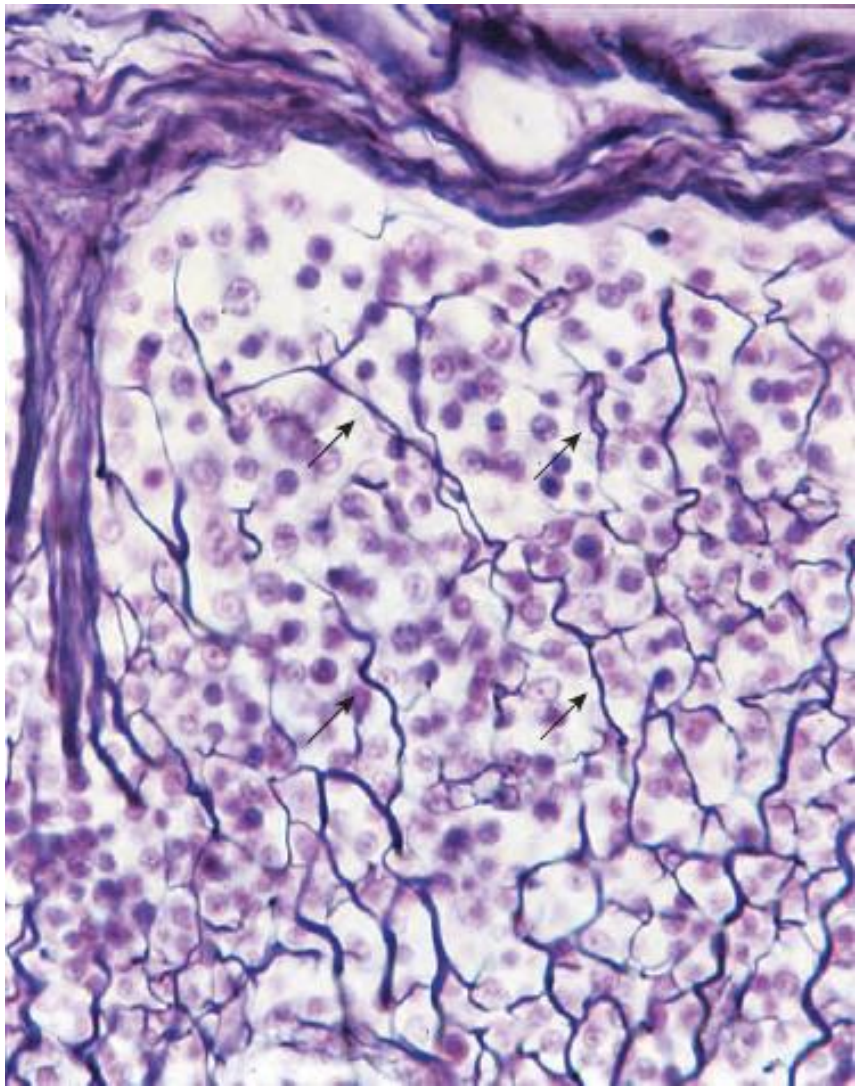


Osteogenesis imperfecta

Type of Collagen	Disease	Symptoms
I	Osteogenesis imperfecta	Repeated fractures after minor trauma, brittle bones, abnormal teeth, thin skin, weak tendons, blue sclerae, progressive hearing loss
II	Kniest dysplasia; Achondrogenesis, type 2	Short stature, restricted joint mobility, ocular changes leading to blindness, wide metaphyses, and joint abnormality seen in radiographs
III	Ehlers-Danlos type IV	Hypermobility of joints of digits, pale thin skin, severe bruisability, early morbidity and mortality, resulting from rupture of vessels and internal organs
IV	Alport's syndrome	Hematuria resulting from structural changes in the glomerular basement membrane of the kidney, progressive hearing loss, and ocular lesions
VII	Kindler's syndrome	Severe blistering and scarring of the skin after minor trauma, resulting from absence of anchoring fibrils
IX	Multiple ephiphyseal dysplasia (MED)	Skeletal deformations resulting from impaired endochondral ossification and dysplasia (MED), premature degenerative joint disease
X	Schmid metaphysal chondrodysplasia	Skeletal deformations characterized by modifications of the vertebral bodies and chondrodysplasia metaphyses of the long bone
XI	Weissenbacher-Zweymuller syndrome Stickler's syndrome (includes also additional mutations of type II collagen gene)	Similar clinical features to type II collagenopathies in addition to craniofacial and skeletal deformations, severe myopia, retinal detachment, and progressive hearing loss
XVII	Generalized atrophic benign epidermolysis bullosa (GABEB)	Blistering skin disease with mechanically induced dermal–epidermal separation, epidermolysis bullosa resulting from faulty hemidesmosomes, skin atrophy, nail dystrophy, and alopecia

Reticular Fibers

- Reticular fibers are composed of **type III collagen**.
- exhibit a 68-nm banding pattern
- have a narrow diameter (about 20 nm)
- exhibit a branching pattern, and typically do not bundle to form thick fibers
- reticular fibers cannot be identified in H&E preparations,
- Since they contain more sugar groups than collagen, they are observed by PAS reaction.
- They are argirophilic (silver precipitation methods)



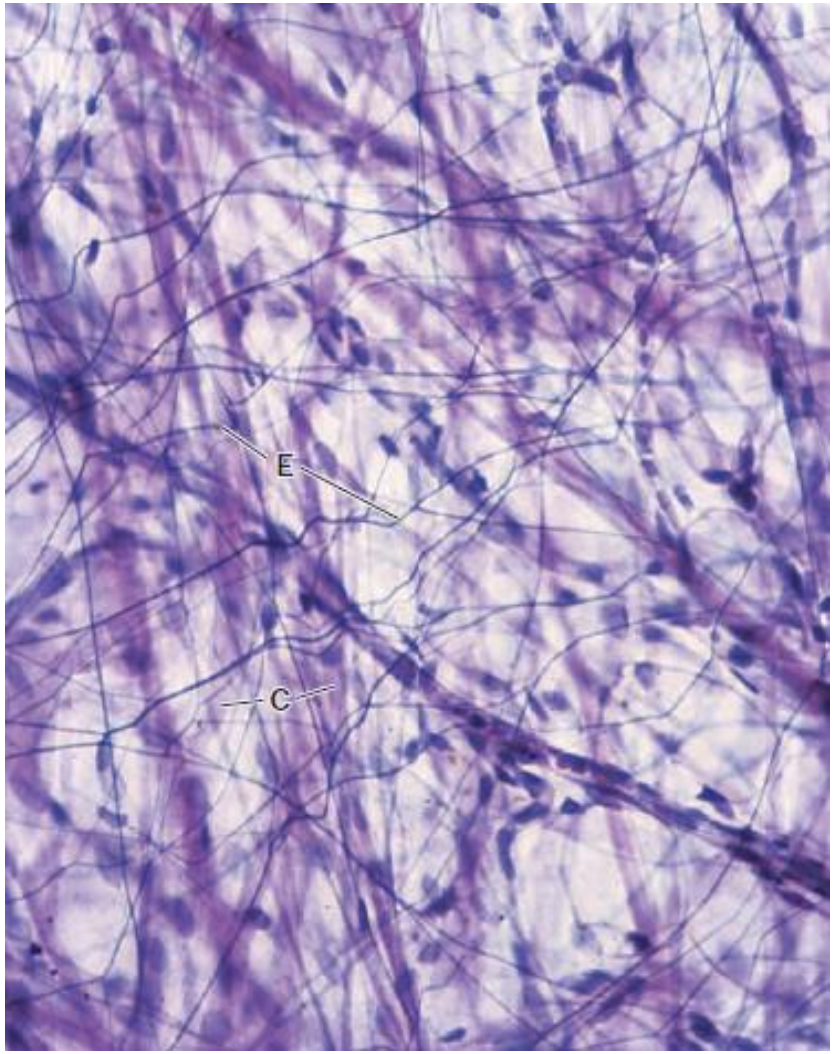
Lymph node, silver impregnation

Reticular Fibers

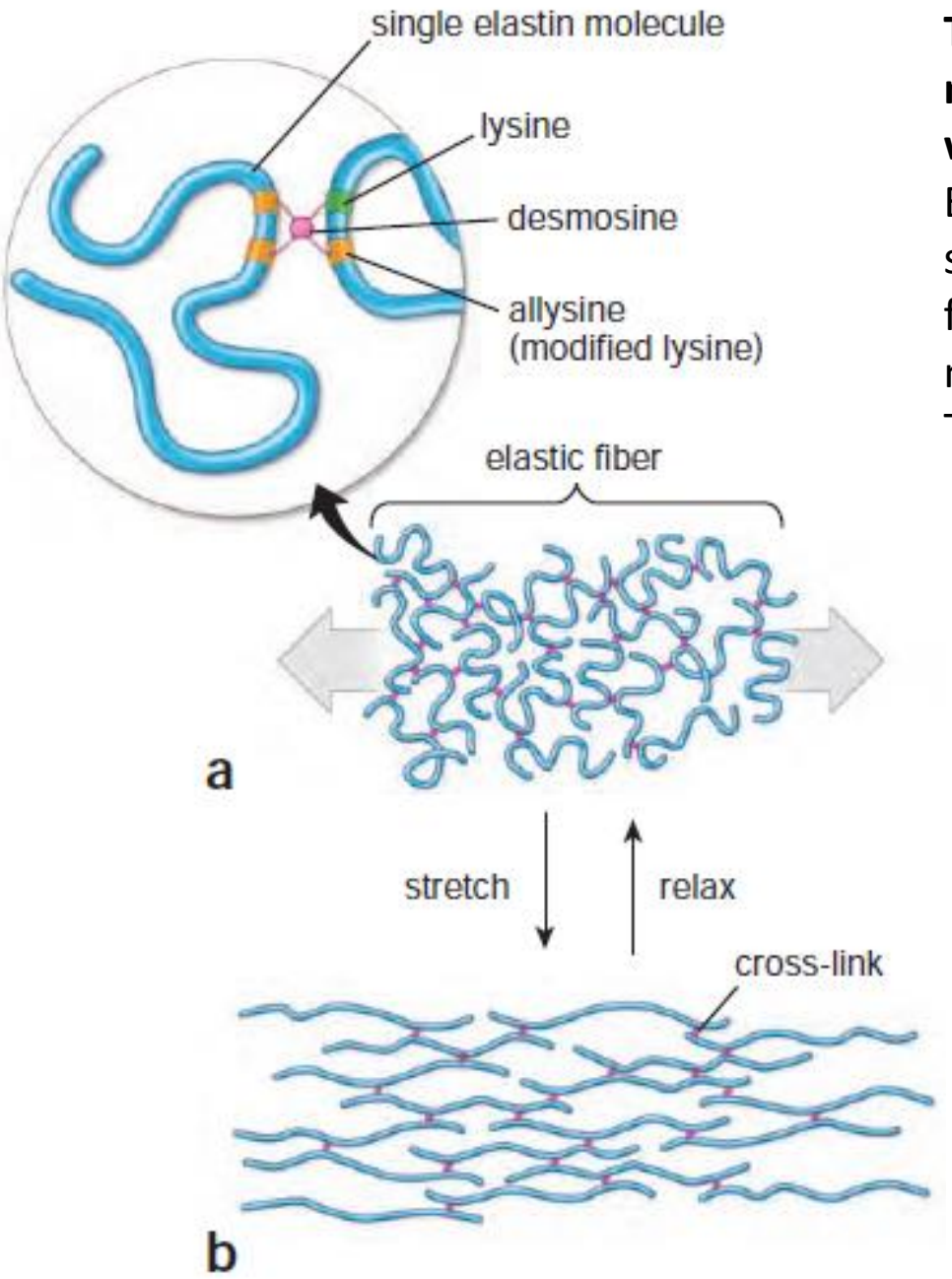
- Found abundant on the border of epithelium and underlying connective tissue, around adiposites and small blood vessels
- It is found in embryonic tissues and areas of healing tissue (replaced with type I)
- It forms the supporting connective tissue in **hematopoietic and lymphatic organs (except thymus).** It is synthesized by **reticulum cells** in these organs.
- Except in peripheral nerve endoneurium (Schwann hc) and tunica media (smooth muscle cell) of blood vessels it is produced by fibroblasts

Elastic Fibers

- They are finer fibers than collagen which are organized in a branching structure to form a three-dimensional network structure.
- The fibers are interwoven with collagen fibers to limit the distensibility of the tissue and prevent tearing from excessive stretching
- Since it is stained eosinophilic in H&E, it is indistinguishable from collagen. They are examined with special dyes such as orsein, resorcin-fuxin.



Mesentery, resorcin-fuxin



The elastic property of the elastin molecule is related to its unusual polypeptide backbone, which causes random coiling.

Elastic fibers are produced by many of the same cells that produce collagen and reticular fibers, particularly fibroblasts and smooth muscle cells.

They have two major structural component

- Central core of **elastin**
- Surrounding network of **fibrillin**
- **Fibulin** connects these two

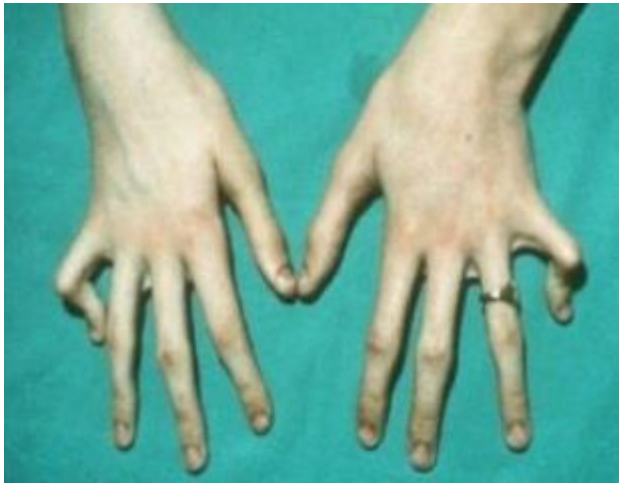
Elastin:

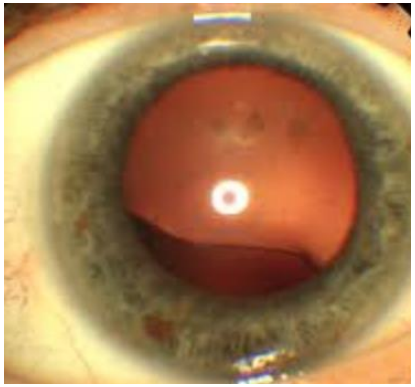
- It is rich in proline and glycine like collagen
- Less hydroxyproline
- Hydroxylysine is never found.
- Glycine was randomly located. The molecule is therefore hydrophobic and tends to randomly curl.
- Elastin-specific desmosin and isodesmosin covalently bond 4 elastins together

Fibrillin-1:

- is a glycoprotein that forms fine microfibrils measuring 10 to 12 nm in diameter
- Elastin-associated **fibrillin microfibrils** play a major role in organizing elastin into fibers
- Without fibrillin, microfibrils during elastogenesis results in the formation of elastin sheets or lamellae, as found in blood vessels.

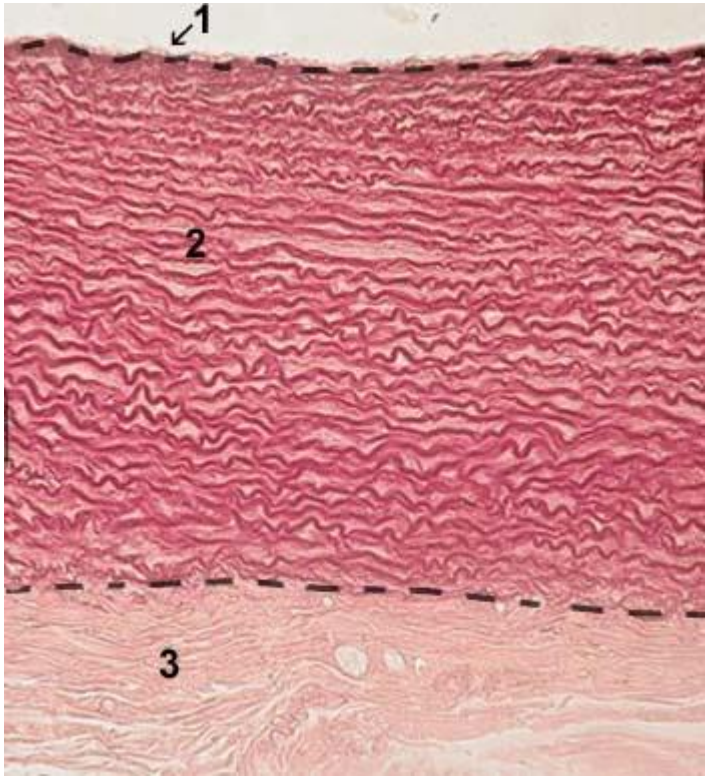
Abnormal expression of the fibrillin gene (FBN1) is linked to Marfan's syndrome, a complex, autosomal dominant, connective tissue disorder

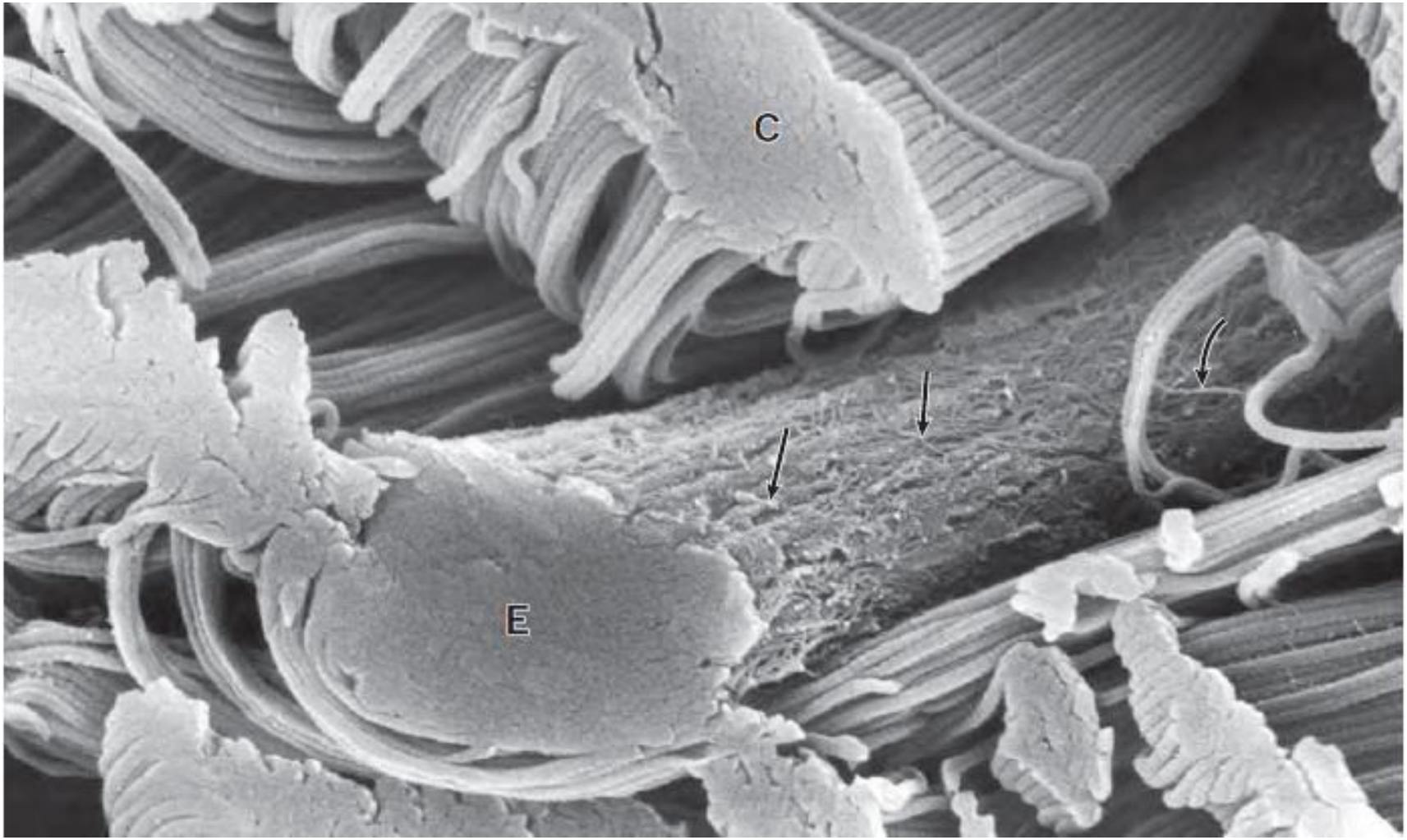




Elastic Fibers

- It is the main component of extracellular material in vertebral ligaments, larynx and elastic (large) arteries.
- Lig. flava is rich in elastic fibers. The fibers here are thicker and associate with collagen.
- The fibers are thin in the larynx.
- In elastic arteries, the elastic material is in the form of fenestrated lamellae, sheets of elastin with gaps or openings. They are synthesized by smooth muscle cells.




C
E

Extracellular matrix

- It is a complex, intricate network that surrounds and supports cells in connective tissue.
- It contains reticular, elastic and collagen fibers.
- In addition; It contains the following 3 groups of substances that make up the **ground substance:**
- **Proteoglycans** (aggrecan, syndecan)
- **Multi-adhesive glycoproteins** (fibronectin and laminin)
- **Glycosaminoglycans** (dermatan sulfate, keratan sulfate, hyaluronan)

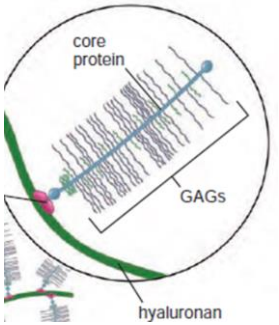
Extracellular matrix = Ground substance + fibers

- The extracellular matrix composition may be different in each tissue. Cartilage, bone, loose connective tissue components are not the same. It is secreted by cells in a tissue-specific manner.
- Its function is communication between the cells with mechanical and structural support.
- It regulates and locates the metabolic functions of cells. Provides the essential routes for migration.
- Cell-ECM linking complexes stabilize cells.
- It has regulatory tasks for embryonic development and differentiation. Growth factors are bound and maintained.

Ground substance

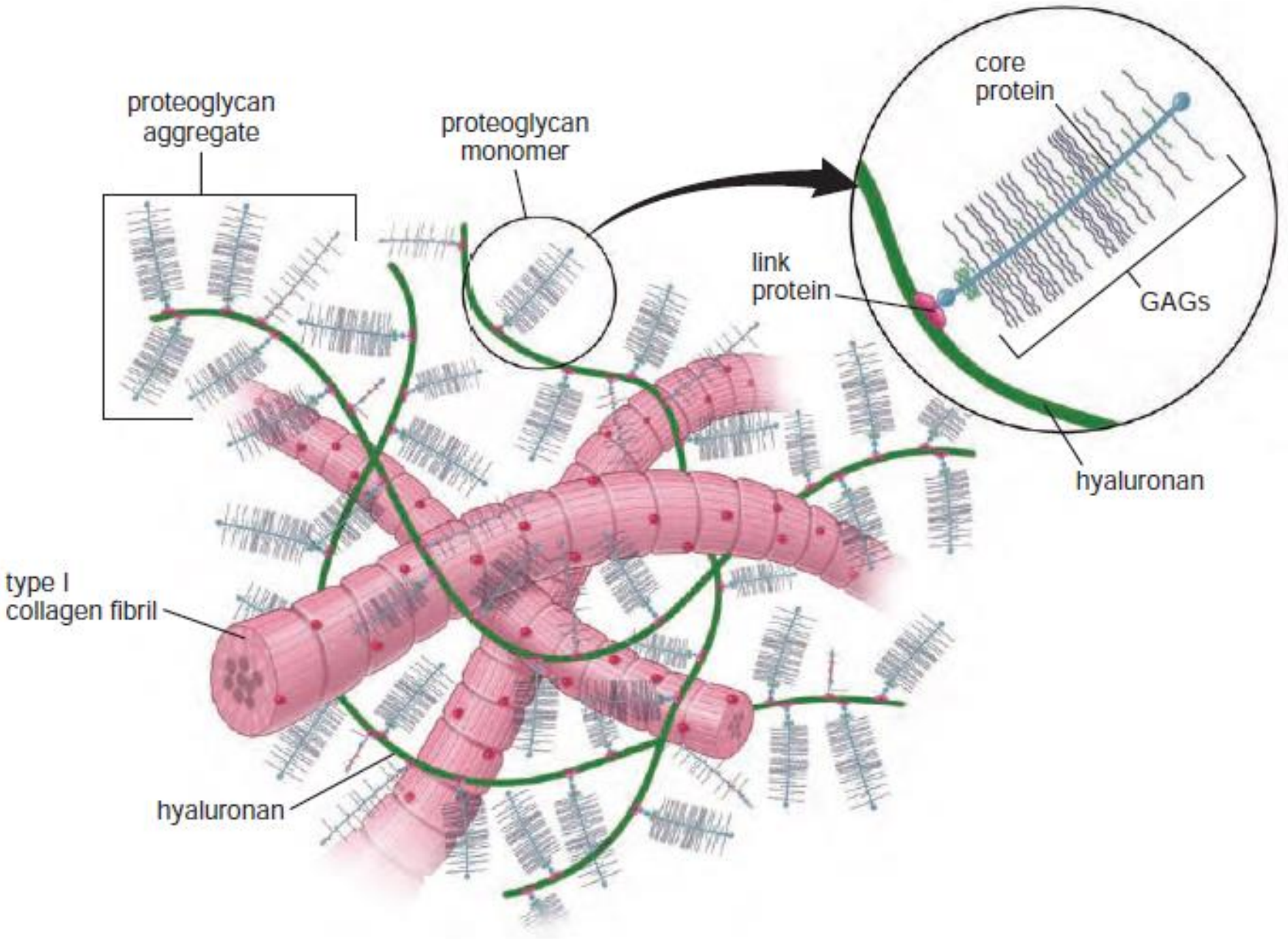
- **Ground substance** is a viscous, clear substance with a slippery feel and high water content.

Glycosaminoglycans (GAG)



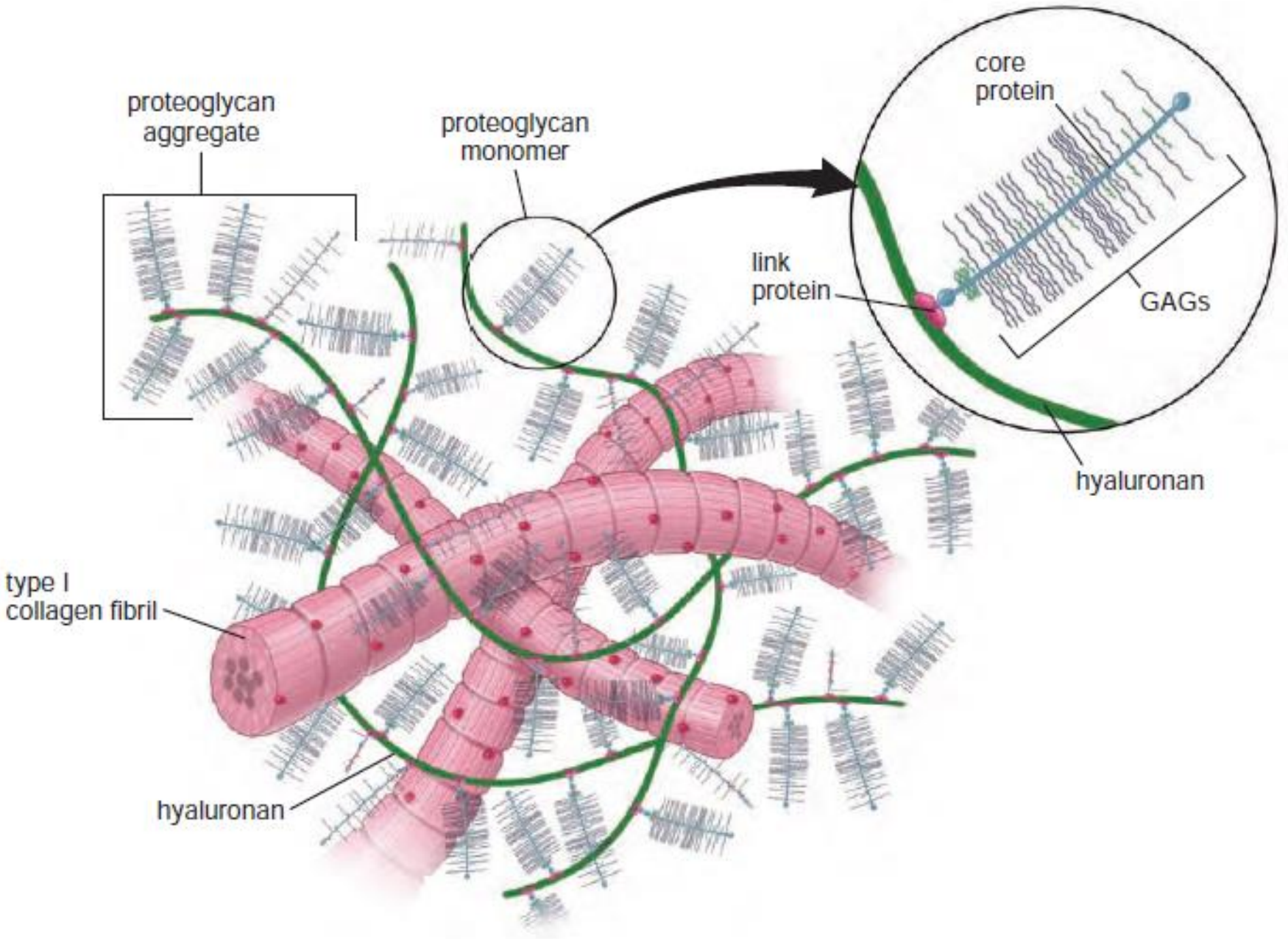
- Creates the physical properties of the ground substance
- Highest amount of heteropolysaccharide in ECM
- It is a polysaccharide consisting of long chain, non-branching, repeating disaccharide units.
- Disaccharide units consist of one of 2 modified sugars: N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc) and a uronic acid (glucuronate or iduronate).
- They take basic dyes because they are negatively charged (sulfate and carboxyl groups)
- They draw water into the environment and form a jelly consistency.

- Since the glycosaminoglycan molecule has many negative radicals (polyanion), it can combine with a large number of cations.
- The most cation bound to glycosaminoglycan is sodium.
- Glycosaminoglycans have an important role in regulating the amount of water in the connective tissue due to the aforementioned properties.
- Since almost all of the water in the ground substance is bound to glycosaminoglycans, the water in the connective tissue does not move by changing the body posture.


proteoglycan
aggregate
proteoglycan
monomer
core
protein
link
protein
GAGs
hyaluronan
type I
collagen fibril
hyaluronan

Hyaluronan (hyaluronic acid)

- A very long, rigid GAG consisting of thousands of sugar molecules (a free carbohydrate chain) *
- They are produced by enzymes on the cell surface, they do not undergo post-translational modification *
- Has a very intensive water holding capacity
- Sulfate free *
- They are not bound to proteins, they are free, so they do not form proteoglycans.
- It forms the binding region for many growth factors.
- Limits diffusion and inhibits passage of macromolecules (eg plasma proteins)

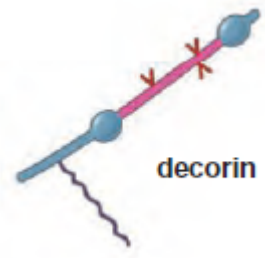

proteoglycan
aggregate
proteoglycan
monomer
core
protein
link
protein
GAGs
hyaluronan
type I
collagen fibril
hyaluronan

GAGs

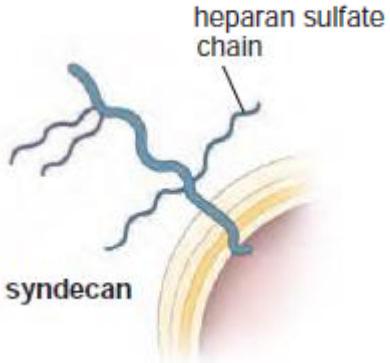
- Water retention
- Lubricant
- Shock absorbers
- Substance exchange
- Growth Factor Binding

Name	Molecular Weight (kDa)	Disaccharide Composition	Localization	Function
Hyaluronan	100–10,000	D-Glucuronic acid + *N*-acetylglucosamine	Synovial fluid, vitreous humor, ECM of connective tissues	Large polymers of hyaluronan can displace a large volume of water. Thus this polymer is excellent lubricant and shock absorber
Chondroitin 4-sulfate	25	D-Glucuronic acid + *N*-acetylgalactosamine 4-sulfate	Cartilage, bone, heart valves	Chondroitin sulfates and hyaluronan are fundamental components of aggrecan found in articular cartilage. Aggrecan confers on articular cartilage shock-absorbing properties
Chondroitin 6-sulfate	25	D-Glucuronic acid + *N*-acetylgalactosamine 6-sulfate		
Dermatan sulfate	35	L-Iduronic acid + *N*-acetylgalactosamine 4-sulfate	Skin, blood vessels, heart valves	Dermatan sulfate proteoglycans have been implicated in cardiovascular disease, tumorigenesis, infection, wound repair, fibrosis, and as a modulator in cell behavior
Keratan sulfate	10	Galactose or galactose 6-sulfate + *N*-acetylglucosamine 6-sulfate	Bone, cartilage, cornea	Keratan sulfate proteoglycans function in cellular recognition of protein ligands, axonal guidance, cell motility, corneal transparency, and embryo implantation
Heparan sulfate	15	Glucuronic acid or L-iduronic acid 2-sulfate + *N*-sulfamylglucosamine or *N*-acetylglucosamine	Basal lamina, normal component of cell surface	Facilitates interactions with fibroblastic growth factor (FGF) and its receptor
Heparin	40	Glucuronic acid or L-iduronic acid 2-sulfate + N-sulfamylglucosamine or N-acetylglucosamine 6-sulfate	Limited to granules of mast cells and basophiles	Functions as an anticoagulant, facilitates interactions with FGF and its receptor

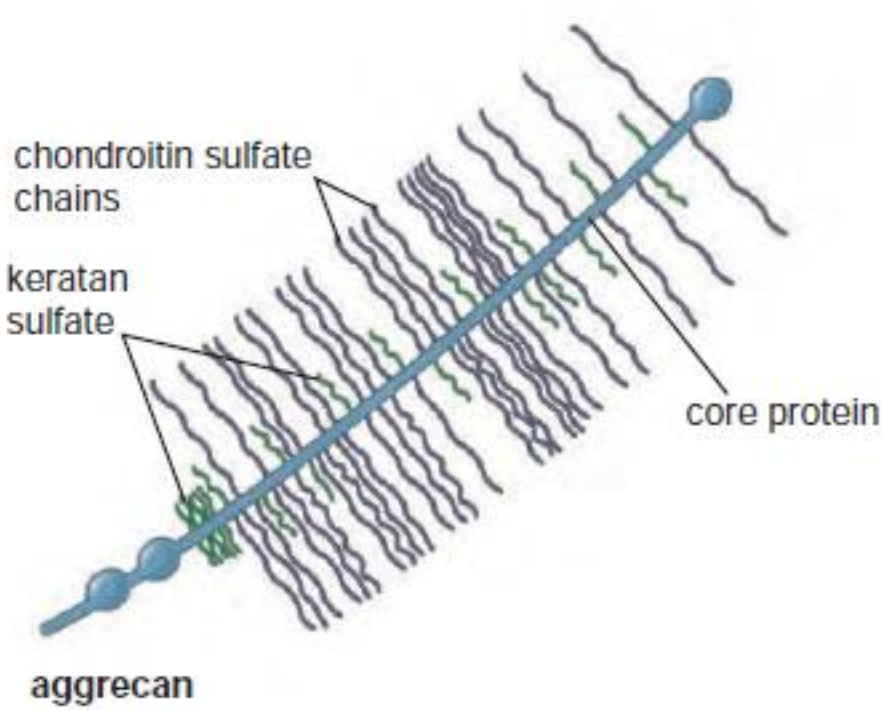
Proteoglycans



- Proteoglycans are composed of GAGs covalently attached to core proteins
- Single GAG → decorin
- GAGs can be uniform (figroglican or versican), or multple type (aggrecan, sindecan) on a proteoglycan
- Sindecan is a transmembrane proteoglycan. Binds cells to ECM. (eg. B lymphocytes ve plasma cells)



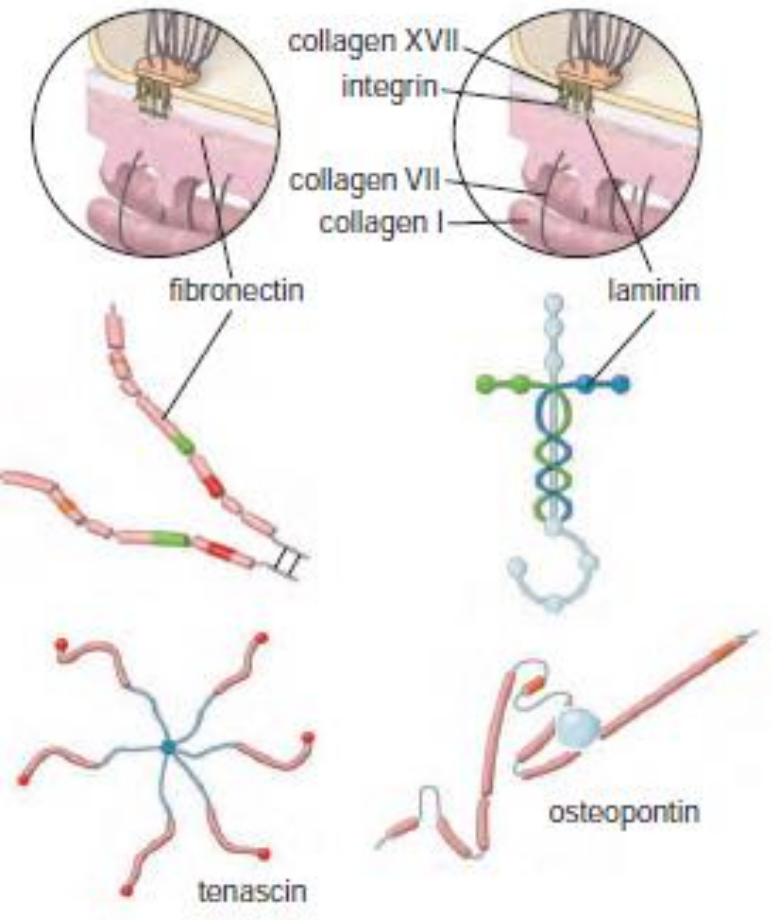
- **Aggrecan** is another important extracellular proteoglycan.
- Its molecules are noncovalently bound to the long molecule of hyaluronan



Proteoglycans

Name	Molecular Weight (kDa)	Molecular Composition	Localization	Function
Aggrecan	250	Linear molecule; binds via a link protein to hyaluronan; contains 100 to 150 molecules of keratan sulfate and chondroitin sulfate chains	Cartilage, Chondrocytes	Responsible for hydration of extracellular matrix of cartilage
Decorin	38	Small protein that contains only one chondroitin sulfate or dermatan sulfate chain	Connective tissue, fibroblasts, cartilage, and bone	Functions in collagen fibrillogenesis; by attaching to neighboring collagen molecules, helps to orient fibers. Regulates the thickness of the fibril and interacts with transforming growth factor β (TGF-β)
Versican	260	Associated with a link protein; contains main and 12–15 chains of chondroitin sulfate attached to core protein	Fibroblasts, skin, smooth muscle, brain, and mesangial cells of the kidney	Possesses EGF-like domains on the core protein; participates in cell-to-cell and cell-to-extracellular matrix interactions; binds to fibulin-1
Syndecan	33	Family of at least four different types of transmembrane proteoglycans, containing varying amounts of both heparan sulfate and chondroitin sulfate molecules	Embryonic epithelia, mesenchymal cells, developing lymphatic tissue cells, lymphocytes, and plasma cells	The extracellular domain binds collagens, heparin, tenascin, and fibronectin, intracellular domain binds to cytoskeleton via actin

Multiadhesive glycoproteins

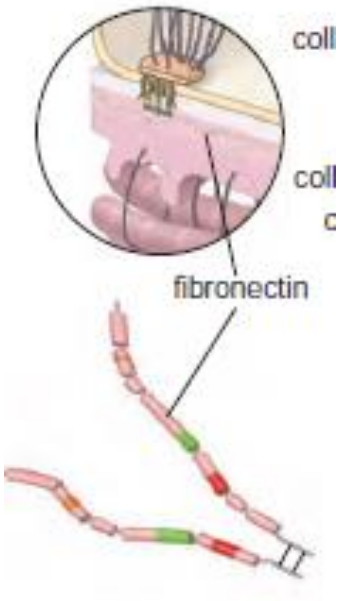


- They stabilize ECM and bind to cell membranes.
- They bind to both ECM elements (PG, GAG, collagen) and cells (integrin).

- **Fibronectin**
- **Laminin**
- **Tenascin**
- **Osteopontin**

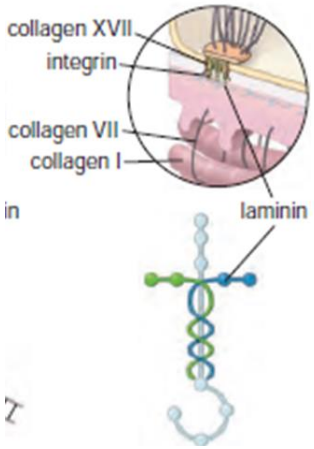
Glycoproteins

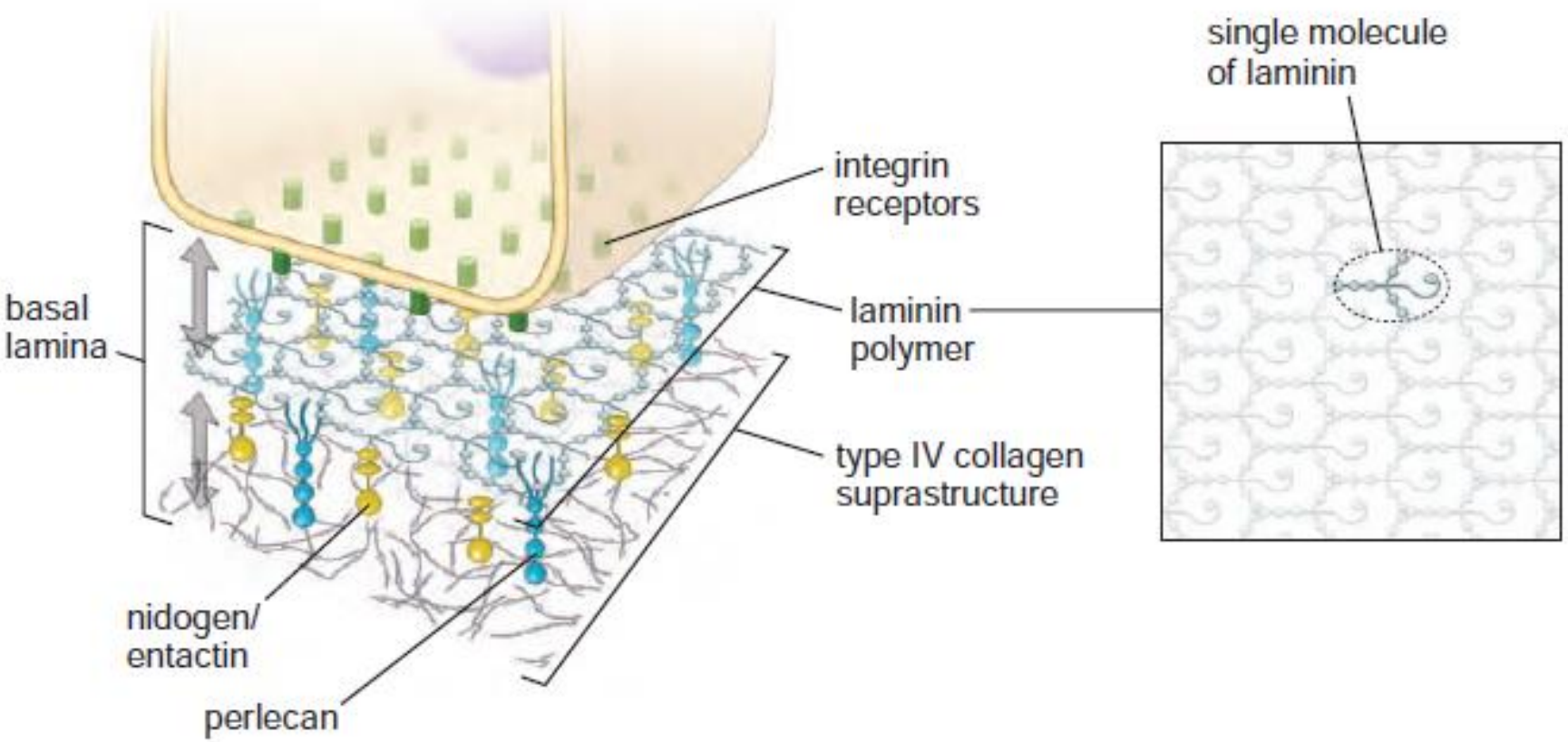
- **Fibronectin:**
- The most abundant glycoprotein in connective tissue. Dimer structure.
- There are many binding centers on it for different ECM elements. (heparan sulphate, collagen type I, II, III, fibrin, hyaluronan, fibronectin)
- It binds to integrin on cells.
- Nearly twenty varieties have been identified
- Activated by binding to the cell surface creates a fiber structure.



Glycoproteins

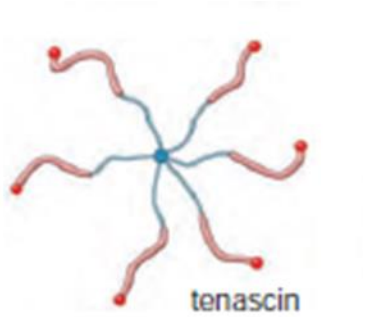
- **Laminin:**
  - Found in basement and external laminea
  - Connection points:
    - Collagen type IV
    - heparan sulfate
    - Heparin
    - Entactin
    - Laminin receptors on the cell surface



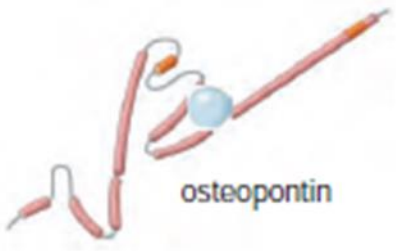

single molecule
of laminin
integrin
receptors
basal
lamina
laminin
polymer
type IV collagen
suprastructure
nidogen/
entactin
perlecan

Glycoproteins

- **Tenascin:**
- It plays an active role in embryogenesis, and its synthesis ends with the maturation of tissues.
- Takes part in wound healing
- Located in muscle-tendon junction area and malignant tumors
- Molecules it binds:
  - fibrinogen,
  - Heparin
- EGF-like growth factors
- Enables cell binding to ECM



Glycoproteins



- **Osteopontin:**
- Plays an important role in ECM of the bone
- It binds osteoclasts and fixes them to the bone surface.
- Plays an important role in calcium release and calcification
- It plays a role in the development of many malignant tumors

Multiadhesive glycoproteins

Name	Molecular Weight (kDa)	Molecular Composition	Localization	Function
Fibronectin	250–280	Dimer molecule formed from two similar peptides linked by a disulfide bond	Present in the ECM of many tissues	Responsible for cell adhesion and mediate migration; possesses binding sites for integrins, type IV collagen, heparin, and fibrin
Laminin	140–400	Cross-shaped molecule formed from three polypeptides (α chain and two β chains)	Present in basal laminae of all epithelial cells and external laminae of muscle cells, adipocytes, and Schwann cells	Anchors cell surfaces to the basal lamina. It possesses binding sites for collagen type IV, heparan sulfate, heparin, entactin, laminin, and integrin receptors on the cell surface
Tenascin	1,680	Giant protein formed from six chains connected by disulfide bonds	Embryonic mesenchyme, perichondrium, periosteum, musculotendinous junctions, wounds, tumors	Modulates cell attachments to the ECM; possesses binding sites for fibronectin, heparin, EGF-like growth factors, integrins, and CAMs
Osteopontin	44	Single-chain glycosylated polypeptide	Bone	Binds to osteoclasts; possesses binding sites for calcium, hydroxyapatite, and integrin receptor on the osteoclast membrane
Entactin/ Nidogen	150	Single-chain rodlike sulfated glycoprotein	Basal lamina–specific protein	Links laminin and type IV collagen; has binding sites for perlecan and fibronectin