Genetic Disorders of Connective Tissue

- Marfan Syndrome
- Osteogenesis Imperfecta
- Ehlers-Danlos Syndrome

Types of connective tissue:

1. Loose (areolar) connective tissue (delicate thin layers between tissues; present in all mucous membranes)
2. Adipose tissue (fat)
3. Dense connective tissue (tendons/ligaments)
4. Hyaline cartilage (nose/ends of long bones/ribs)
5. Elastic cartilage (outer ear/epiglottis)
6. Fibrocartilage (between vertebrae/knee joints/pubic joint)
7. Bone (skeletal system)

8 Blood (bloodstream)

TABLE 4.1 Comparison of Classes of Connective Tissues

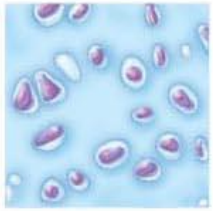
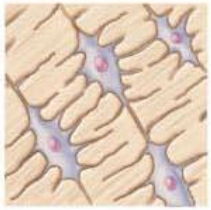
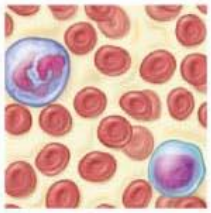
TISSUE CLASS AND EXAMPLE	SUBCLASSES	COMPONENTS: CELLS	COMPONENTS: MATRIX	GENERAL FEATURES
Connective Tissue Proper  *Dense regular connective tissue*	1. Loose connective tissue ▪ Areolar ▪ Adipose ▪ Reticular 2. Dense connective tissue ▪ Regular ▪ Irregular ▪ Elastic	Fibroblasts Fibrocytes Defense cells Fat cells	Gel-like ground substance All three fiber types: collagen, reticular, elastic	Six different types; vary in density and types of fibers Functions as a binding tissue Resists mechanical stress, particulary tension
Cartilage  *Hyaline cartilage*	1. Hyaline cartilage 2. Elastic cartilage 3. Fibrocartilage	Chondroblasts found in growing cartilage Chondrocytes	Gel-like ground substance Fibers: collagen, elastic fibers in some	Resists compression because of the large amounts of water held in the matrix Functions to cushion and support body structures

TABLE 4.1 Comparison of Classes of Connective Tissues

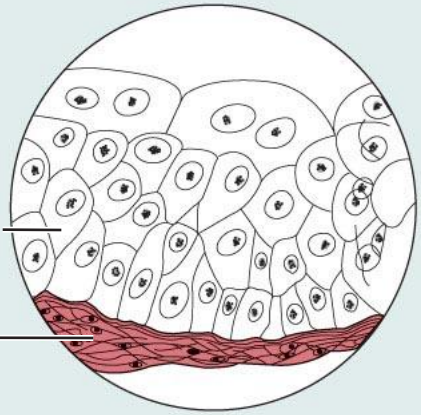
TISSUE CLASS AND EXAMPLE	SUBCLASSES	COMPONENTS: CELLS	COMPONENTS: MATRIX	GENERAL FEATURES
Bone Tissue  *Compact bone*	1. Compact bone 2. Spongy bone	Osteoblasts Osteocytes	Gel-like ground substance calcified with inorganic salts Fibers: collagen	Hard tissue that resists both compression and tension Functions in support
Blood 	Blood cell formation and differentiation are quite complex. Details are provided in Chapter 17.	Erythrocytes (RBC) Leukocytes (WBC) Platelets	Plasma No fibers	A fluid tissue Functions to carry O_2, CO_2, nutrients, wastes, and other substances (hormones, for example)

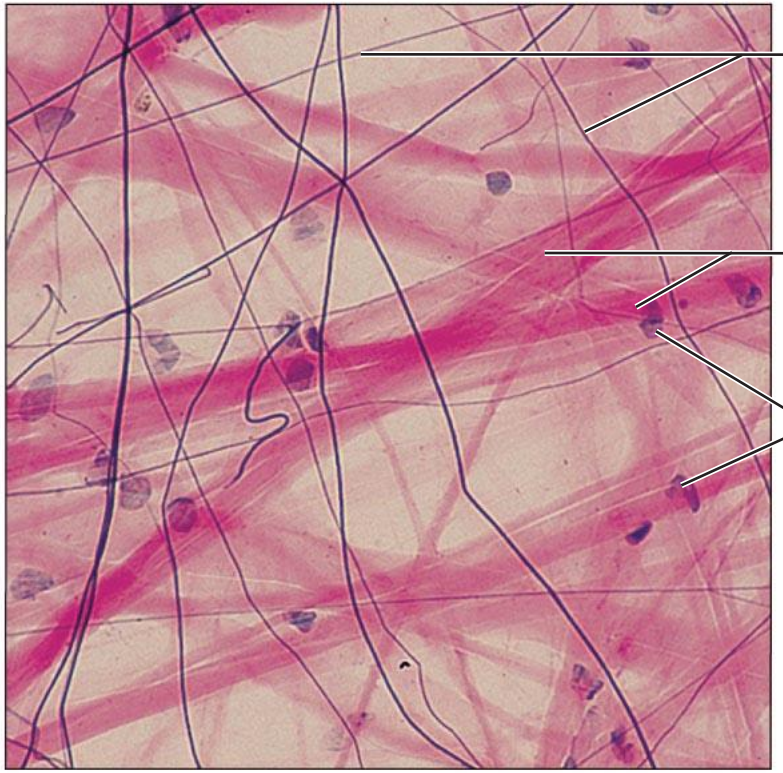
(a) Connective tissue proper: loose connective tissue, areolar

Description: Gel-like matrix with all three fiber types; cells: fibroblasts, macrophages, mast cells, and some white blood cells.

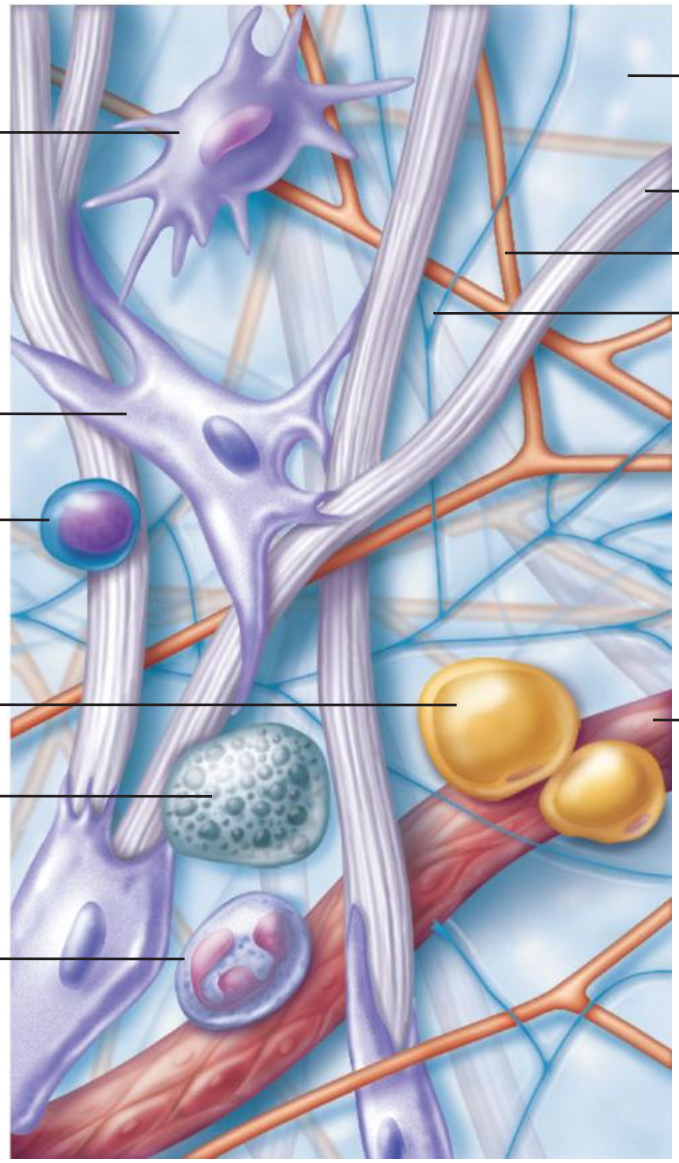
Function: Wraps and cushions organs; its macrophages phagocytize bacteria; plays important role in inflammation; holds and conveys tissue fluid.

Location: Widely distributed under epithelia of body, e.g., forms lamina propria of mucous membranes; packages organs; surrounds capillaries.





Photomicrograph: Areolar connective tissue, a soft packaging tissue of the body (300x).

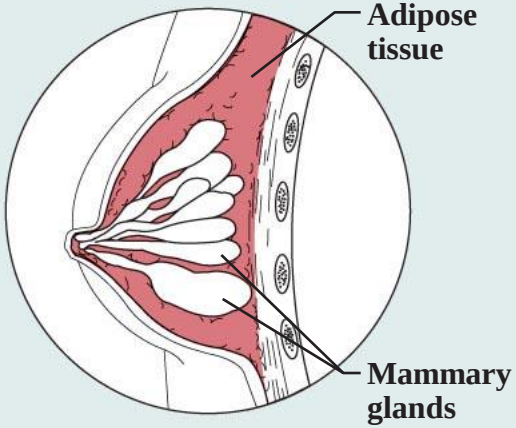


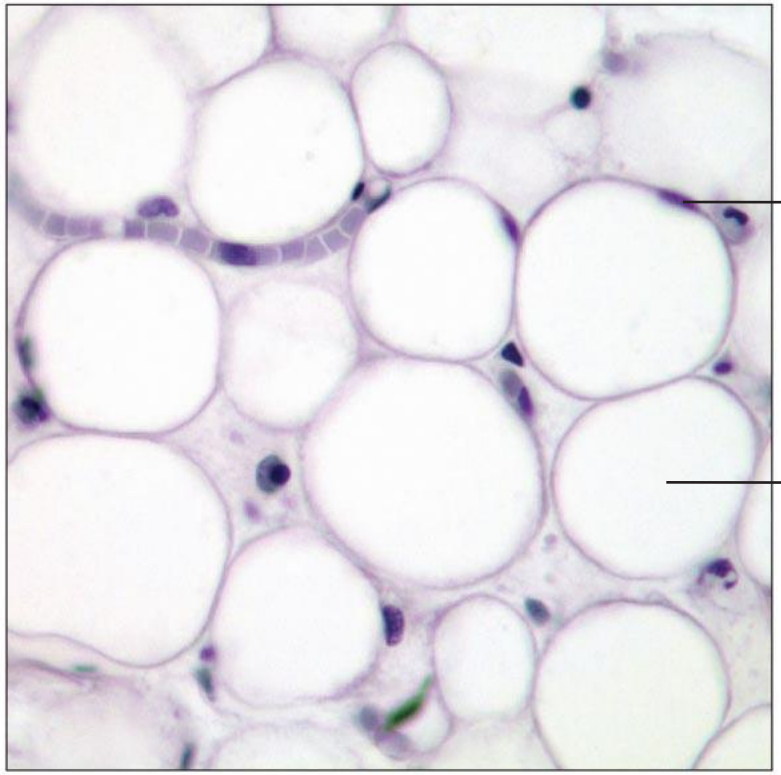
(b) Connective tissue proper: loose connective tissue, adipose

Description: Matrix as in areolar, but very sparse; closely packed adipocytes, or fat cells, have nucleus pushed to the side by large fat droplet.

Function: Provides reserve food fuel; insulates against heat loss; supports and protects organs.

Location: Under skin in the hypodermis; around kidneys and eyeballs; within abdomen; in breasts.





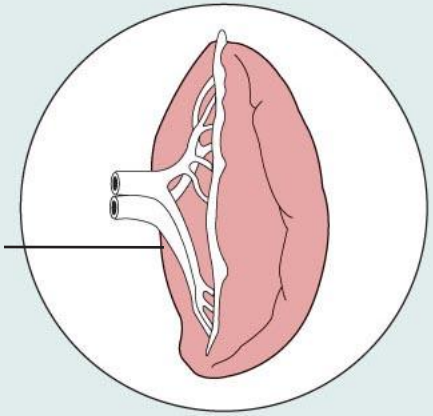
Photomicrograph: Adipose tissue from the subcutaneous layer under the skin (350x).

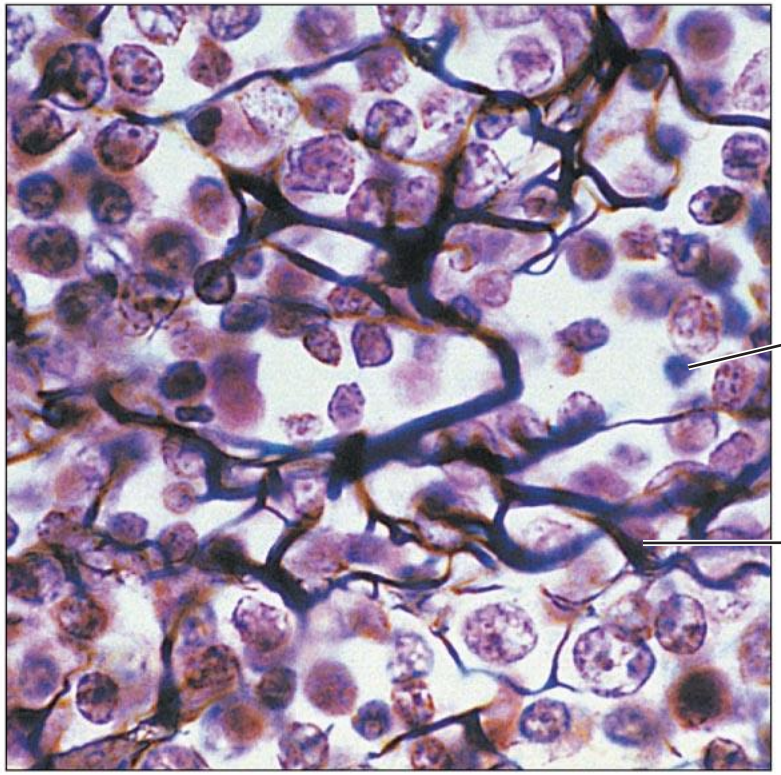
(c) Connective tissue proper: loose connective tissue, reticular

Description: Network of reticular fibers in a typical loose ground substance; reticular cells lie on the network.

Function: Fibers form a soft internal skeleton (stroma) that supports other cell types including white blood cells, mast cells, and macrophages.

Location: Lymphoid organs (lymph nodes, bone marrow, and spleen).





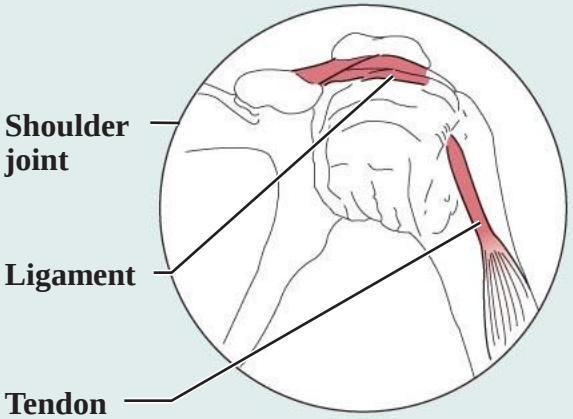
Photomicrograph: Dark-staining network of reticular connective tissue fibers forming the internal skeleton of the spleen (350x).

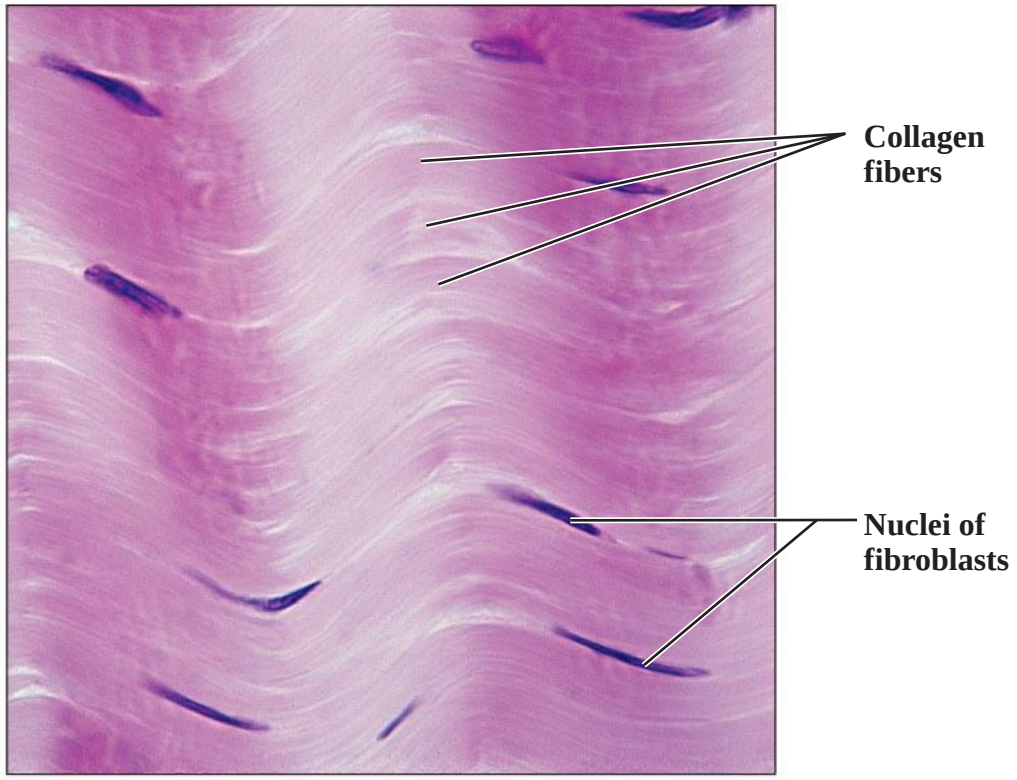
(d) Connective tissue proper: dense connective tissue, dense regular

Description: Primarily parallel collagen fibers; a few elastic fibers; major cell type is the fibroblast.

Function: Attaches muscles to bones or to muscles; attaches bones to bones; withstands great tensile stress when pulling force is applied in one direction.

Location: Tendons, most ligaments, aponeuroses.





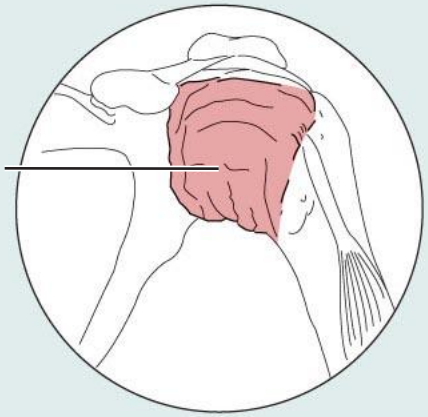
Photomicrograph: Dense regular connective tissue from a tendon (500x).

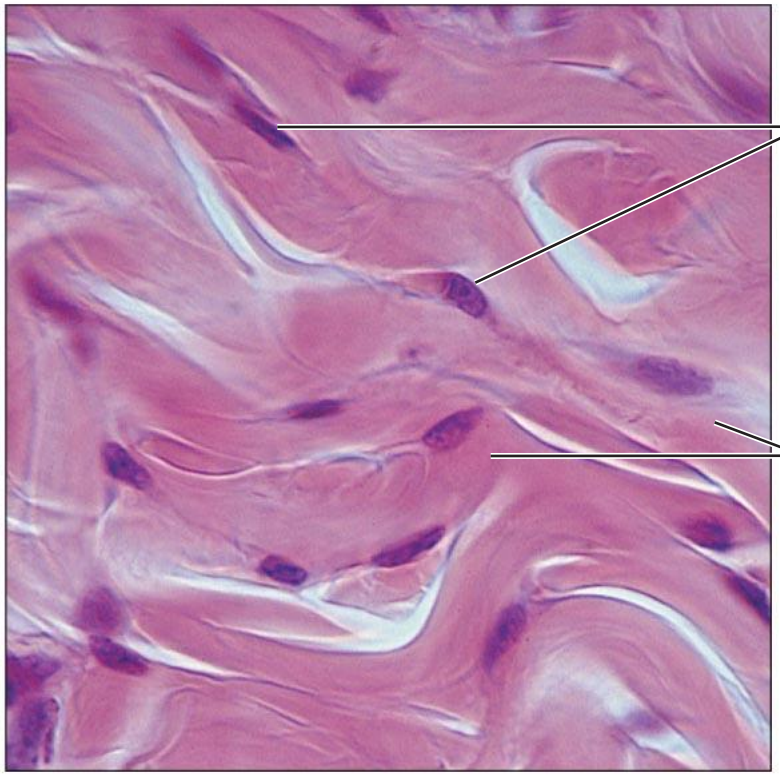
(e) Connective tissue proper: dense connective tissue, dense irregular

Description: Primarily irregularly arranged collagen fibers; some elastic fibers; major cell type is the fibroblast.

Function: Able to withstand tension exerted in many directions; provides structural strength.

Location: Fibrous capsules of organs and of joints; dermis of the skin; submucosa of digestive tract.





Photomicrograph: Dense irregular connective tissue from the dermis of the skin (400x).

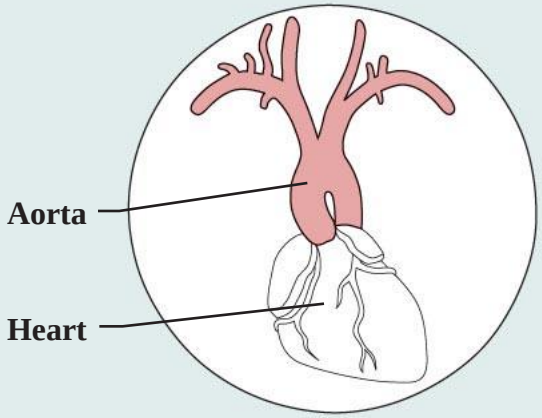
Figure 4.8f Connective tissues.

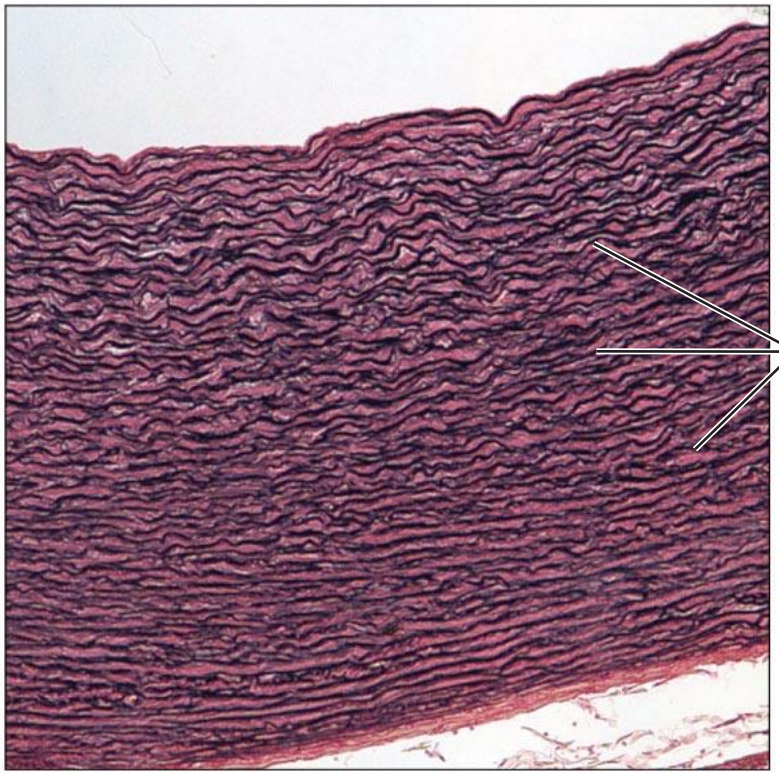
(f) Connective tissue proper: dense connective tissue, elastic

Description: Dense regular connective tissue containing a high proportion of elastic fibers.

Function: Allows recoil of tissue following stretching; maintains pulsatile flow of blood through arteries; aids passive recoil of lungs following inspiration.

Location: Walls of large arteries; within certain ligaments associated with the vertebral column; within the walls of the bronchial tubes.





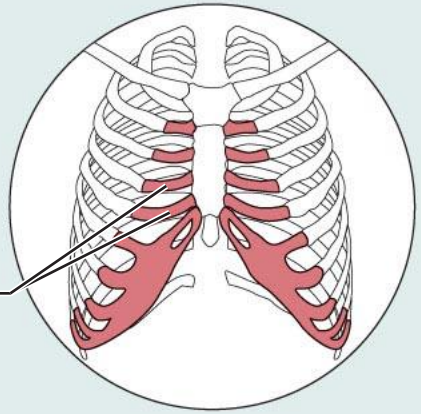
Photomicrograph: Elastic connective tissue in the wall of the aorta (250x).

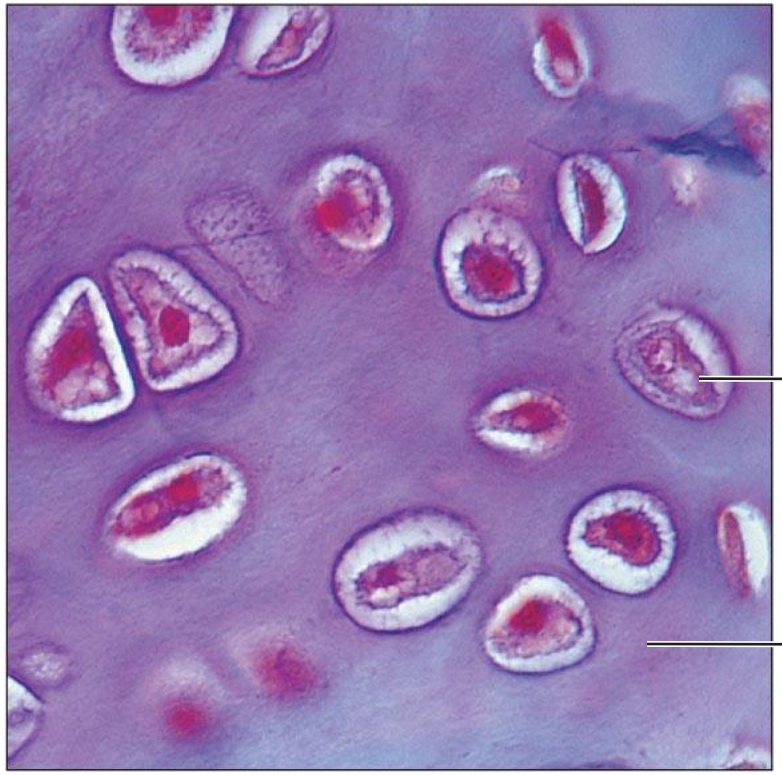
(g) Cartilage: hyaline

Description: Amorphous but firm matrix; collagen fibers form an imperceptible network; chondroblasts produce the matrix and when mature (chondrocytes) lie in lacunae.

Function: Supports and reinforces; has resilient cushioning properties; resists compressive stress.

Location: Forms most of the embryonic skeleton; covers the ends of long bones in joint cavities; forms costal cartilages of the ribs; cartilages of the nose, trachea, and larynx.





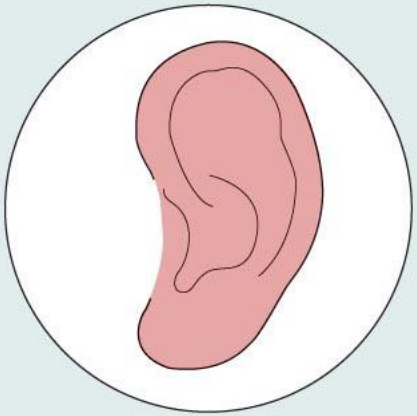
Photomicrograph: Hyaline cartilage from the trachea (750x).

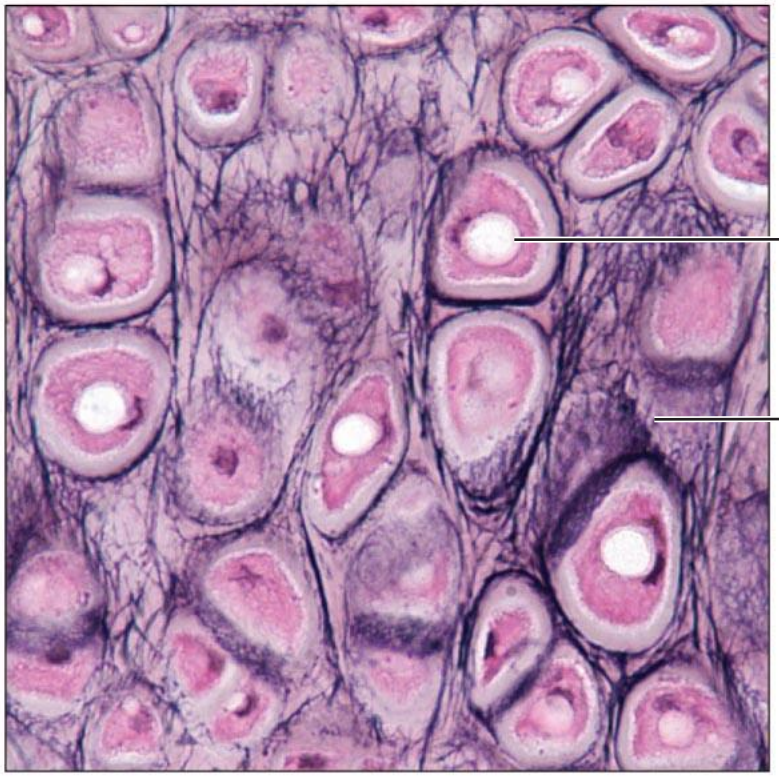
(h) Cartilage: elastic

Description: Similar to hyaline cartilage, but more elastic fibers in matrix.

Function: Maintains the shape of a structure while allowing great flexibility.

Location: Supports the external ear (pinna); epiglottis.





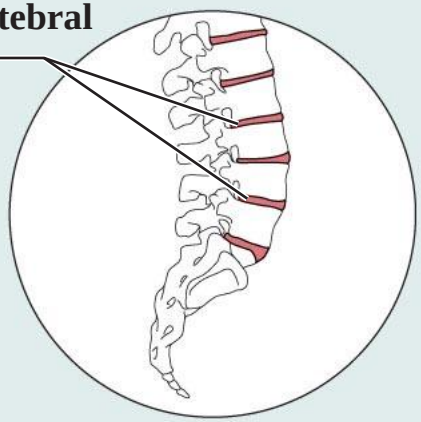
Photomicrograph: Elastic cartilage from the human ear pinna; forms the flexible skeleton of the ear (800x).

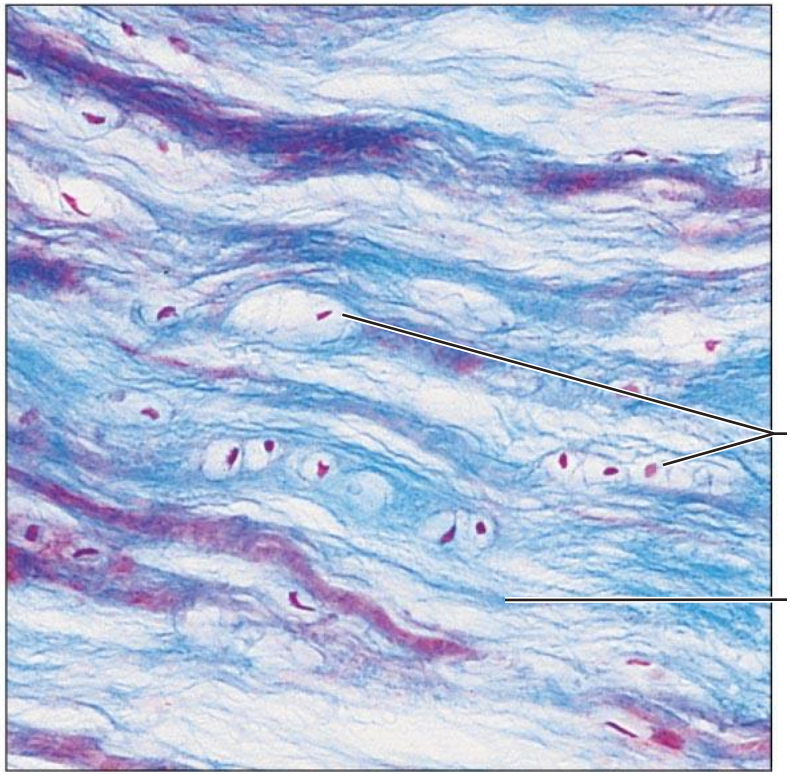
(i) Cartilage: fibrocartilage

Description: Matrix similar to but less firm than that in hyaline cartilage; thick collagen fibers predominate.

Function: Tensile strength with the ability to absorb compressive shock.

Location: Intervertebral discs; pubic symphysis; discs of knee joint.





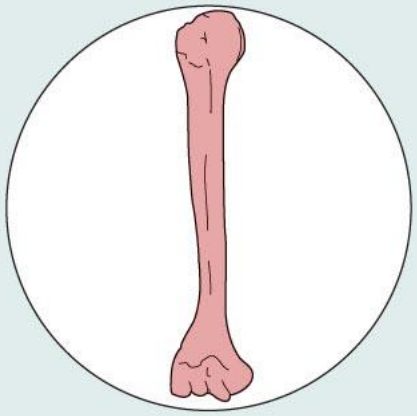
Photomicrograph: Fibrocartilage of an intervertebral disc (125x). Special staining produced the blue color seen.

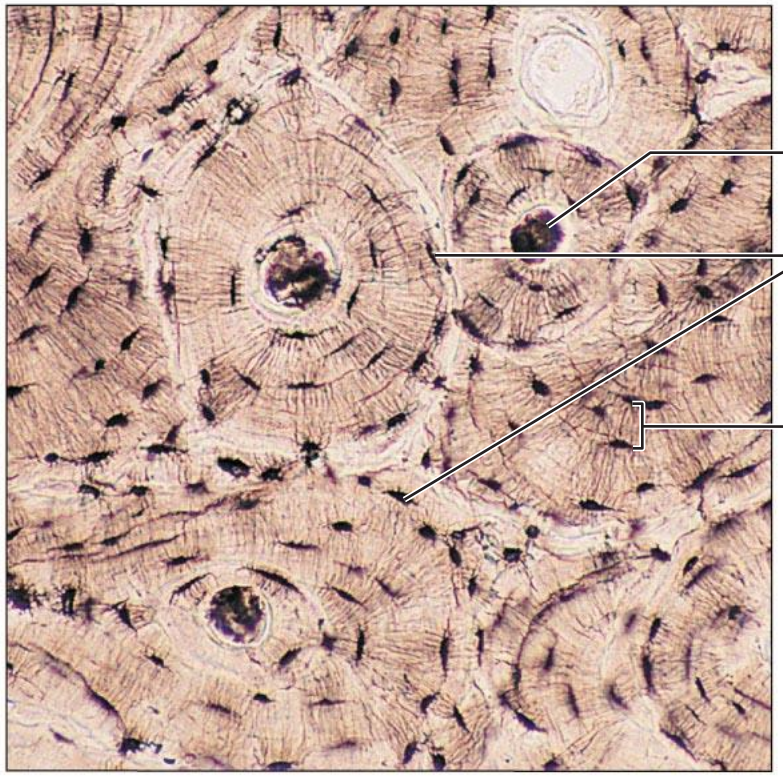
(j) Others: bone (osseous tissue)

Description: Hard, calcified matrix containing many collagen fibers; osteocytes lie in lacunae. Very well vascularized.

Function: Bone supports and protects (by enclosing); provides levers for the muscles to act on; stores calcium and other minerals and fat; marrow inside bones is the site for blood cell formation (hematopoiesis).

Location: Bones





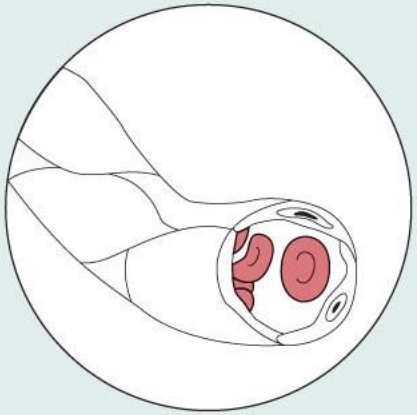
Photomicrograph: Cross-sectional view of bone (125x).

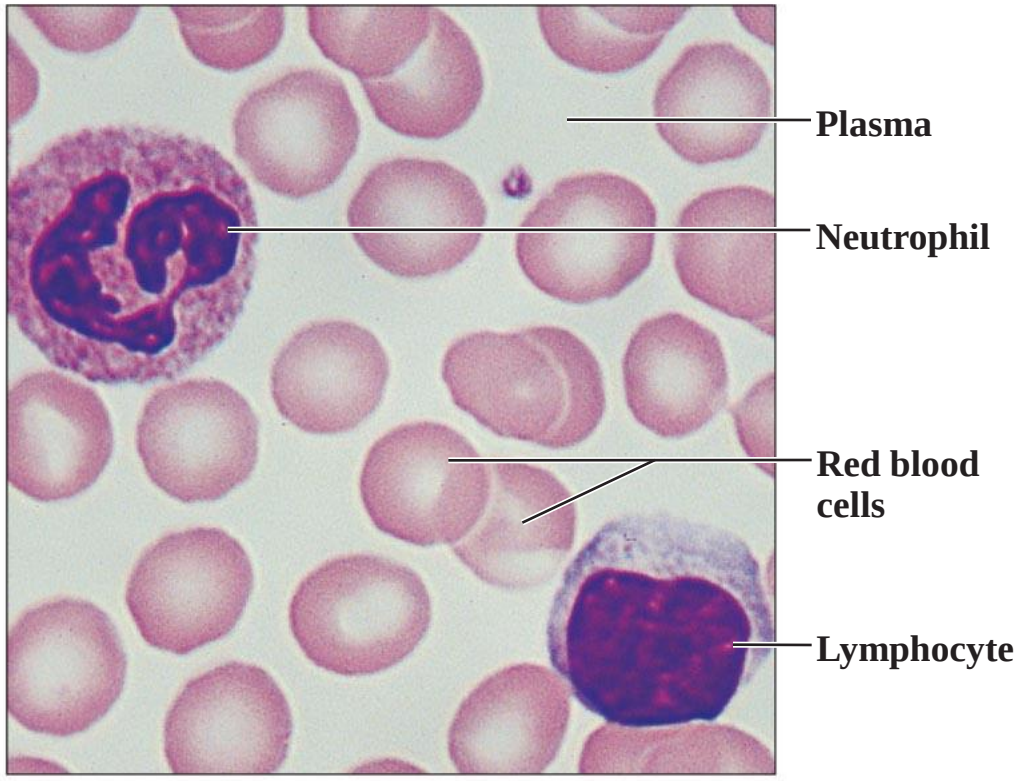
(k) Others: blood

Description: Red and white blood cells in a fluid matrix (plasma).

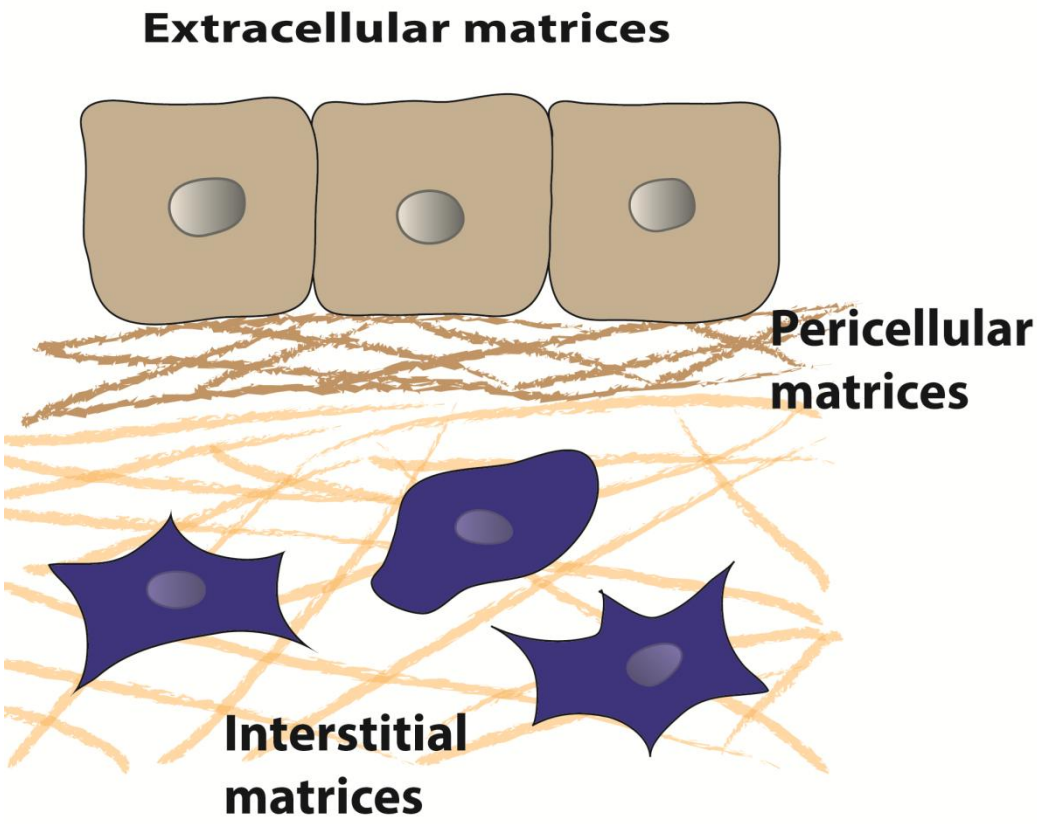
Function: Transport of respiratory gases, nutrients, wastes, and other substances.

Location: Contained within blood vessels.





Photomicrograph: Smear of human blood (1860x); two white blood cells (neutrophil in upper left and lymphocyte in lower right) are seen surrounded by red blood cells.

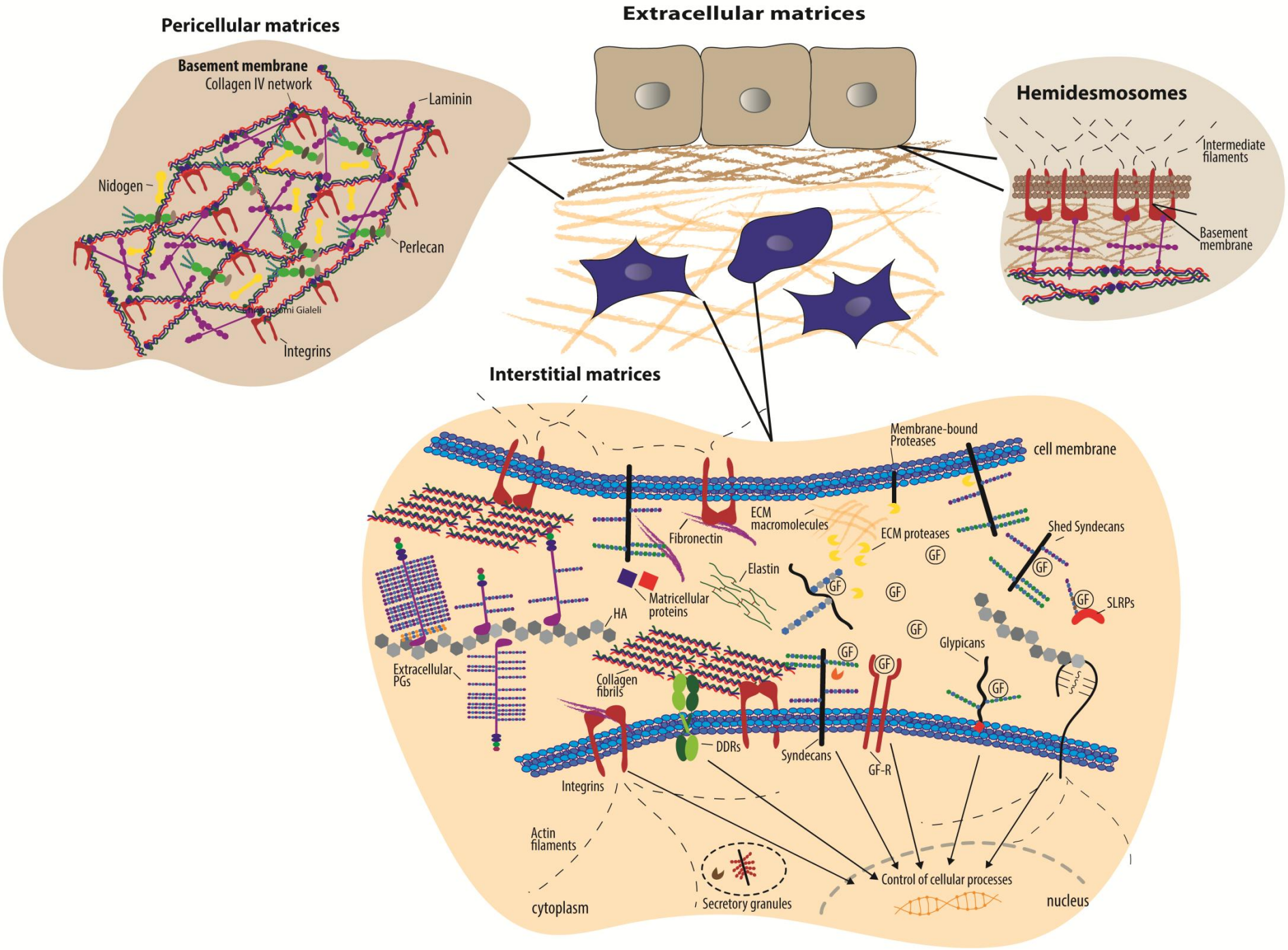


Extracellular Matrix (ECM) components

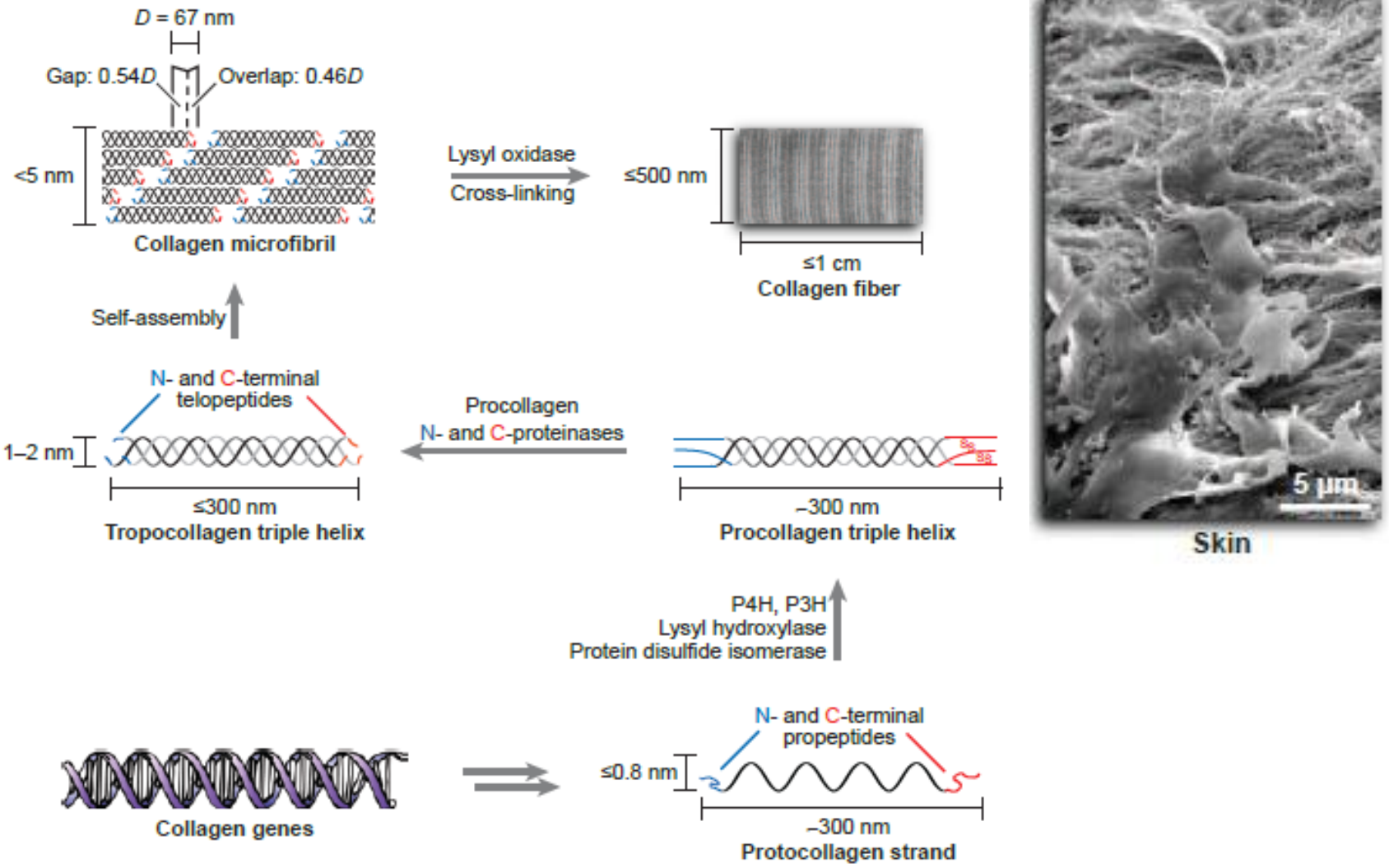
- Collagen
- Elastin
- Proteoglycans
- Hyaluronan
- Laminin
- Fibronectin
- Matricellular proteins
- ECM degrading enzymes
- Growth factors / Cytokines

ECM receptors

- Integrins
- Cell surface proteoglycans
- Discoidin domain receptors (DDRs)
- CD44 (Hyaluronan receptor)

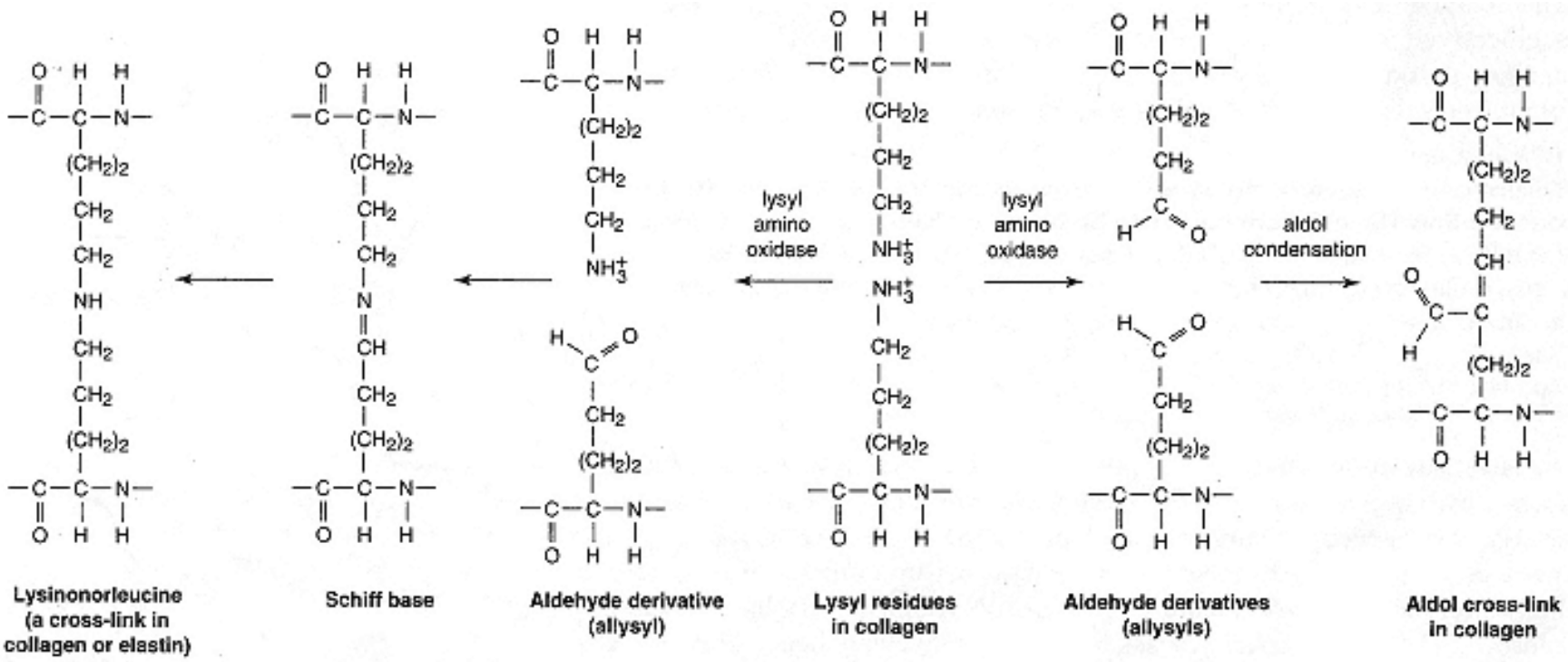

Pericellular matrices
Basement membrane
Collagen IV network
Laminin
Nidogen
Perlecan
Integrins
Extracellular matrices
Hemidesmosomes
Intermediate filaments
Basement membrane
Interstitial matrices
Membrane-bound Proteases
cell membrane
ECM macromolecules
Fibronectin
ECM proteases
Shed Syndecans
Elastin
Matricellular proteins
SLRPs
HA
Glypicans
Extracellular PGs
Collagen fibrils
DDRs
Syndecans
GF-R
Integrins
Actin filaments
Control of cellular processes
cytoplasm
Secretory granules
nucleus

Biosynthetic route of collagen



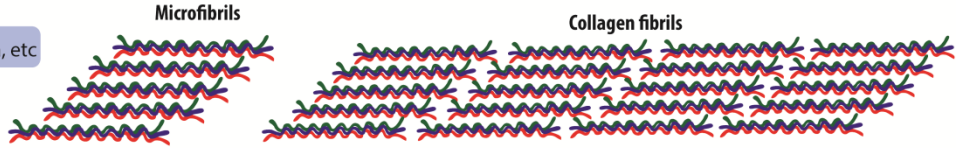
MD Shoulders and RT Raines, Annu. Rev. Biochem. 78, 929-59, 2009

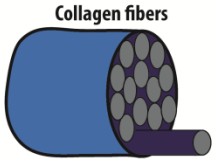
Collagen cross-linking

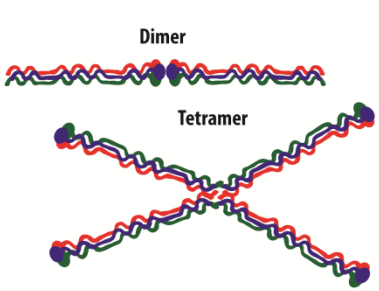


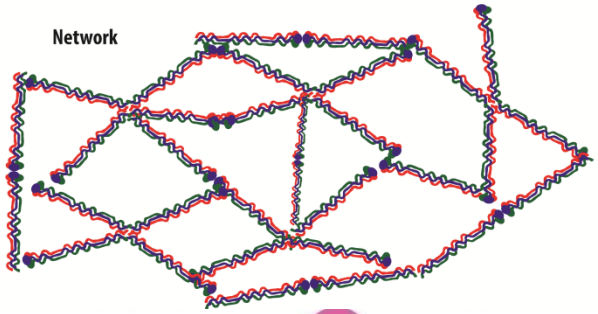
Classification, chain composition, distribution and structural features of vertebrate collagens

	Type	Composition	Distirbution
Fibrillar collagens	I	$\alpha1[I]_2\ \alpha2[I]$	Abundant and widespread: bone, dermis, tendon, ligament, cornea, etc
	II	$\alpha1[II]_3$	Cartilage, vitreous
	III	$\alpha1[III]_3$	Co-distribution with collagen I, skin, blood vessels, intestine
	V	$\alpha1[V]_3$ $\alpha1[V]_2\ \alpha2[V]$ $\alpha1[V]\ \alpha2[V]\ \alpha3[V]$	Widespread: co-distribution with collagen I, bone, dermis, cornea, placenta
	XI	$\alpha1[XI]\ \alpha2[XI]\ \alpha3[XI]$	Co-distribution with collagen II, cartilage, intervertebral disc
	XXIV		Bone, cornea
	XXVII		Cartilage
Network-forming collagens	IV	$\alpha1[IV]_2\ \alpha2[IV]$ $\alpha3[IV]\ \alpha4[IV]\ \alpha5[IV]$ $\alpha5[IV]_2\ \alpha6[IV]$	Basement membranes
	VIII	$\alpha1[VIII]_3$ $\alpha2[VIII]_3$ $\alpha1[VIII]_2\ \alpha2[VIII]$	Widespread: dermis, brain, heart, kidney
	X	$\alpha1[X]_3$	Cartilage



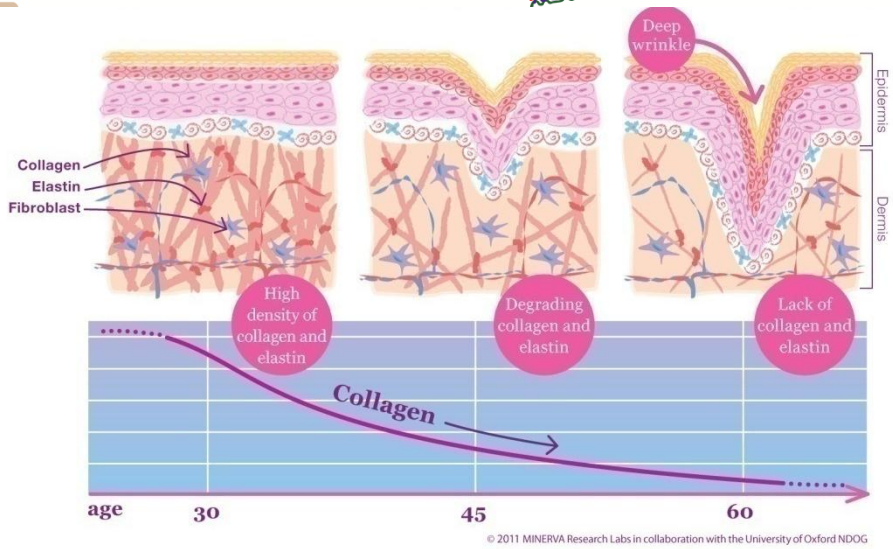






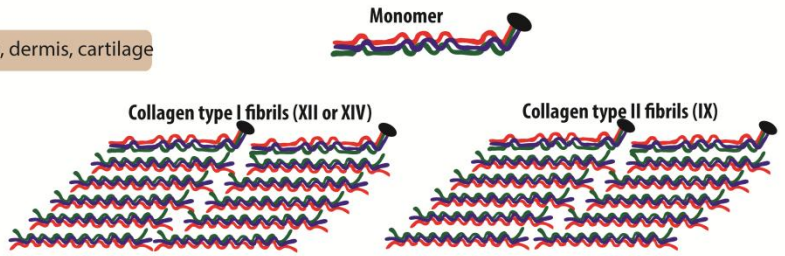
BONE MATRIX

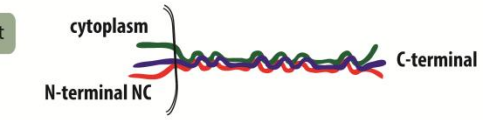
- The collagen and mineral components: Responsible for the major functional characteristics of bone.

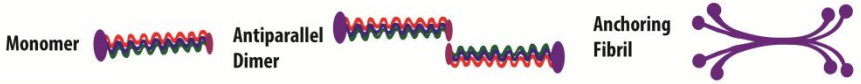


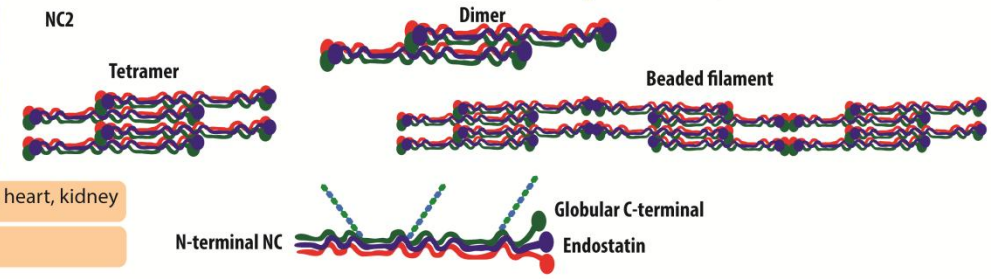
Classification, chain composition, distribution and structural features of vertebrate collagens

FACITs	IX	α1 [IX] α2 [IX] α3 [IX]	Co-distribution with collagen II, cartilage, vitreous, cornea
	XII	α1 $[XII]_3$	Found with collagen I, dermis, tendon
	XIV	α1 $[XIV]_3$	Widespread: found with collagen I, bone, dermis, cartilage
	XVI		Dermis, kidney
	XIX		Basement membrane
	XX		Cornea
	XXI		Stomach, kidney
	XXII		Tissue junctions
MACITs	XIII		Neuromuscular junctions, skin, endothelial cells, eye, heart
	XVII	α1 $[XVII]_3$	Hemidesmosomes in epithelia
	XXIII		Heart, retina
	XXV		Brain, heart, testis
Anchoring fibrils	VII	α1 $[VII]_2$ α2 [VII]	Dermal-epidermal junction, bladder
Beaded-filaments-forming collagens	VI	α1 [VI] α2 [VI] α3 [VI] α1 [VI] α2 [VI] α4 [VI]	Widespread: bone, cartilage, cornea, dermis, muscle
	XXVI		Testis, ovary
	XXVIII		Dermis, sciatic nerve
MULTIPLEXIN	XV		Basement membranes, eye, muscle, capillaries, testis, heart, kidney
	XVIII		Basement membranes, liver

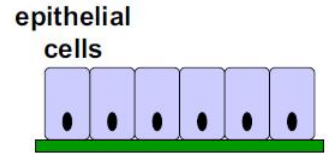


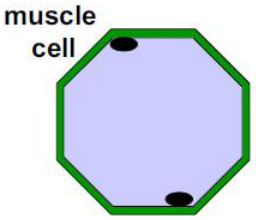


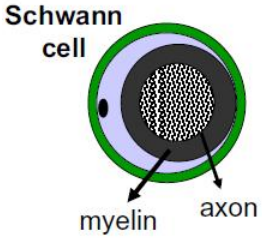


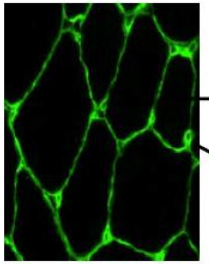


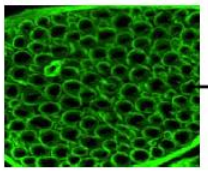
Laminins: localization, structure and functions

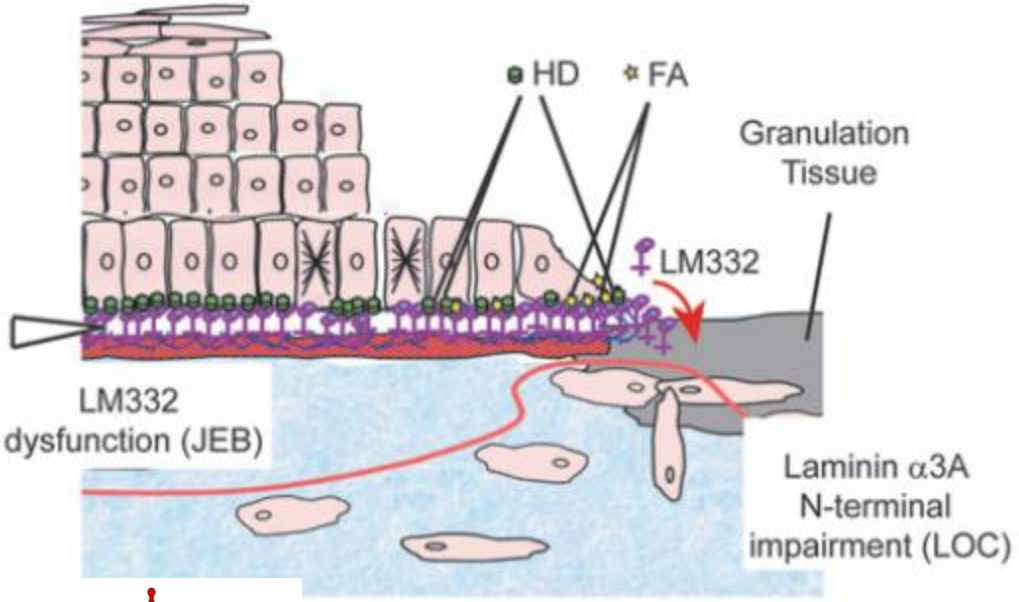


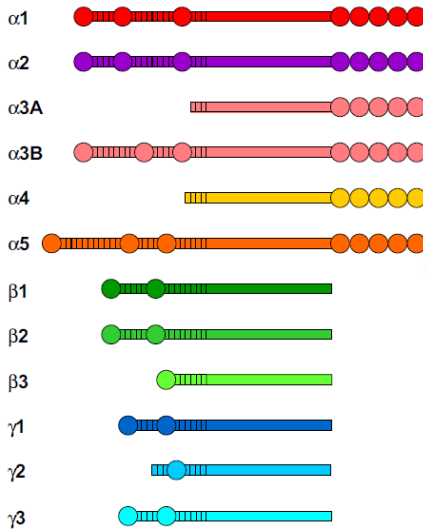


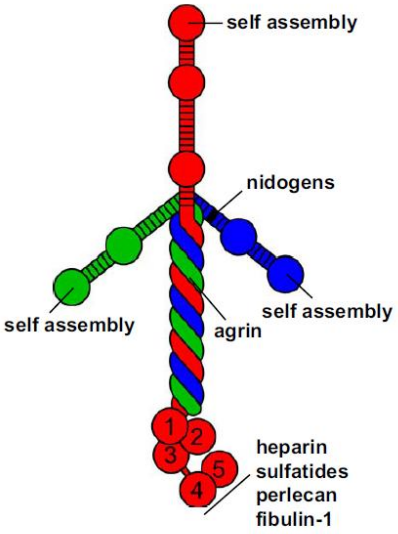


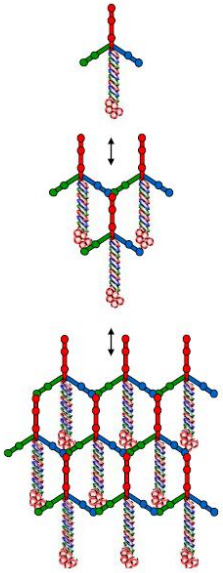


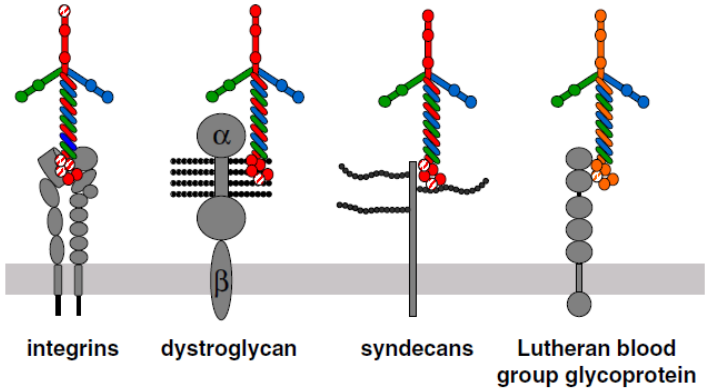






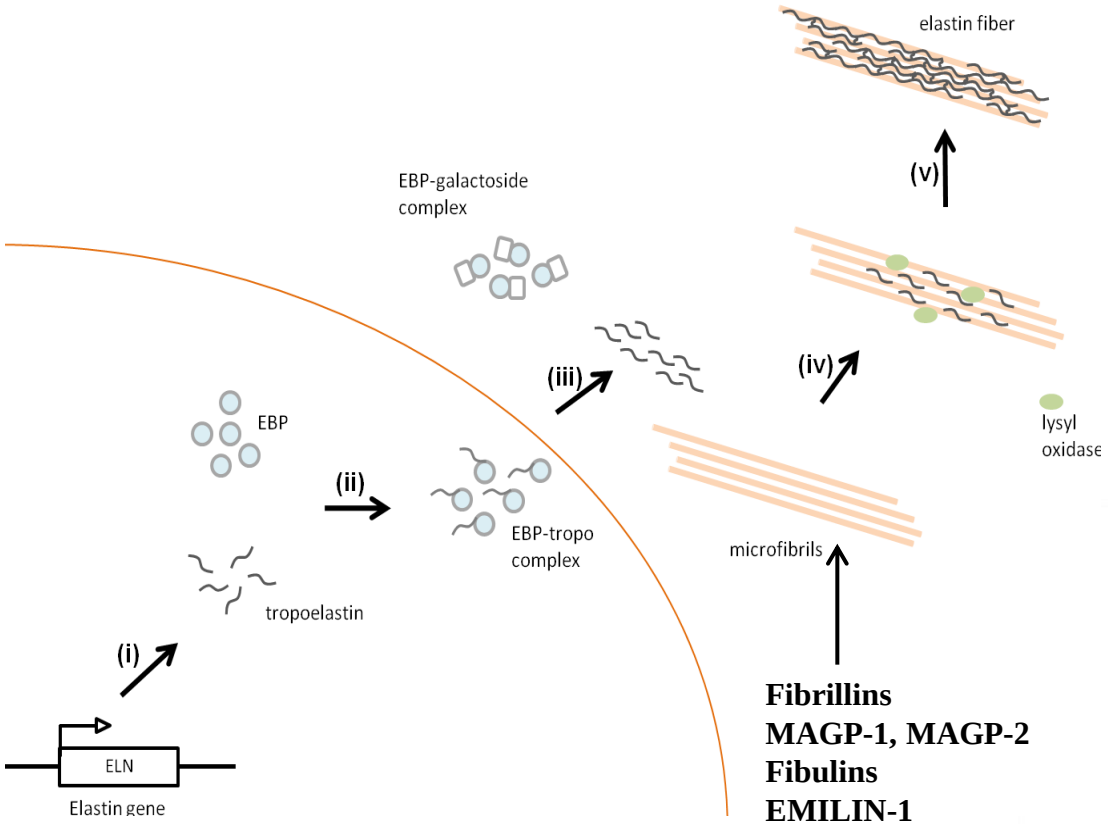




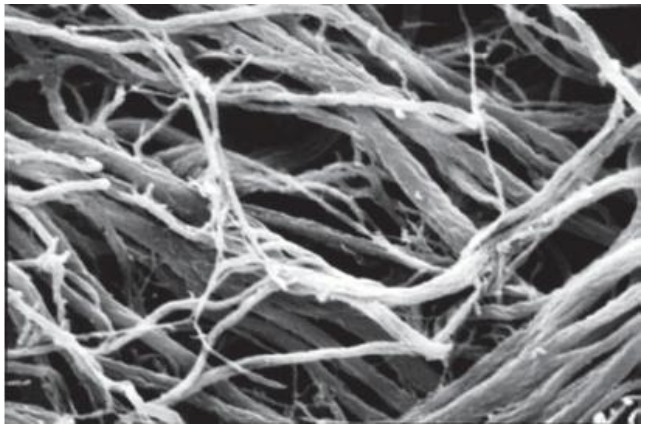


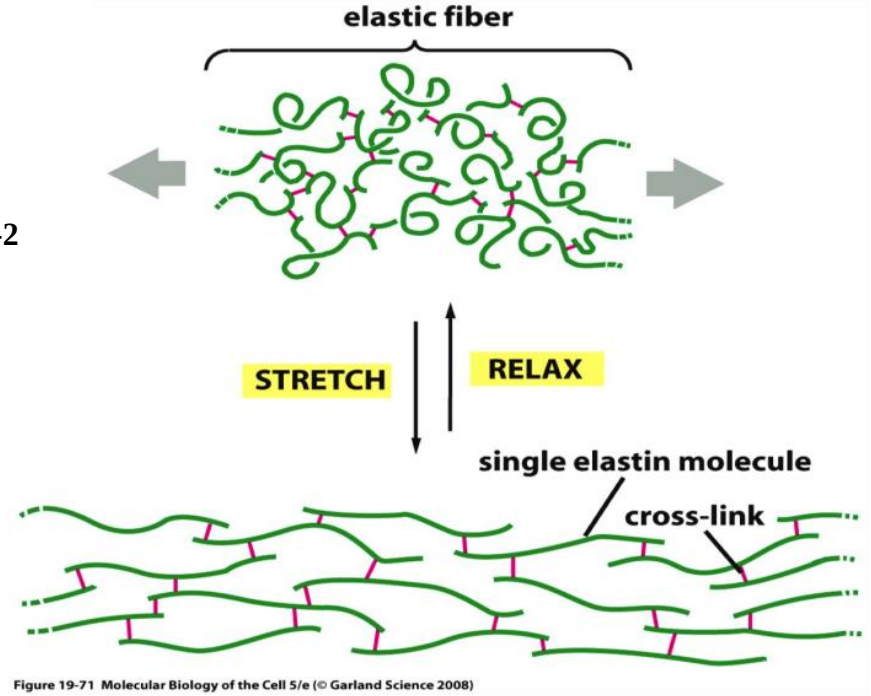
Madeleine Durbeej, Cell Tissue Res (2010) 339:259–268

Elastin biosynthesis



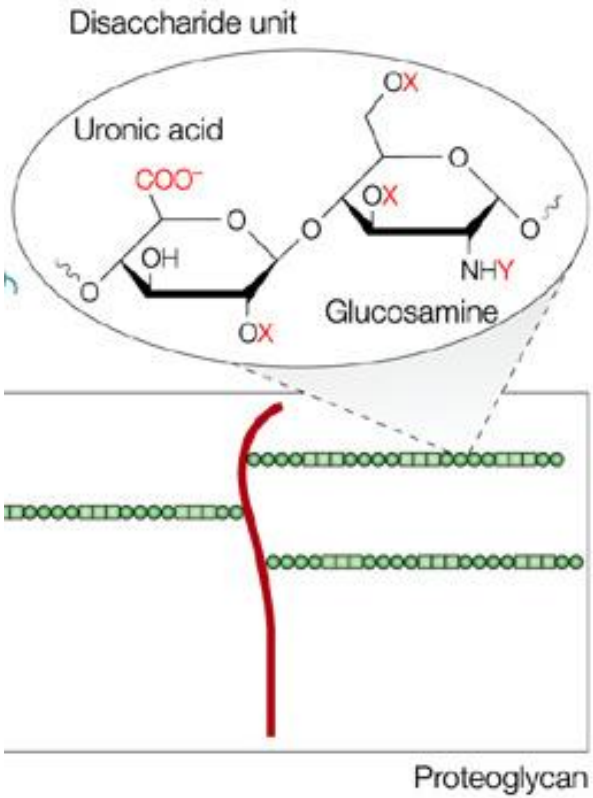
Fibrillins
MAGP-1, MAGP-2
Fibulins
EMILIN-1

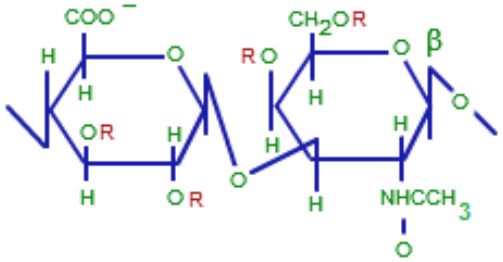




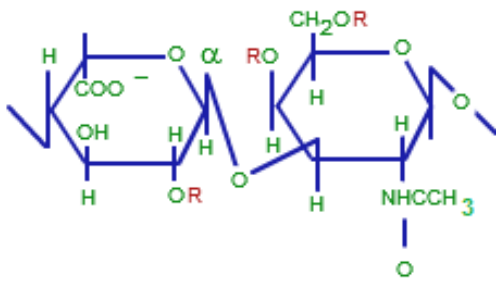
Lisa Nivison-Smith and Anthony Weiss
Regenerative Medicine and Tissue Engineering - Cells and Biomaterials 2011

Proteoglycans / Glycosaminoglycans

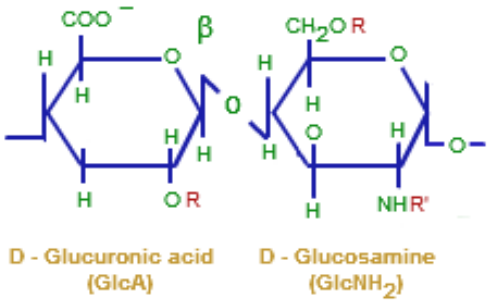




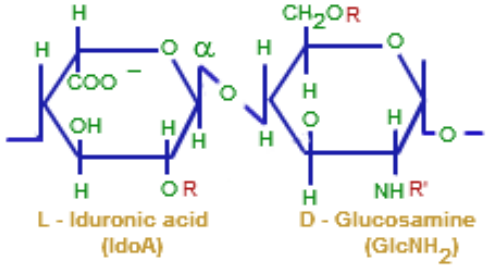
Chonodroitin Sulfate



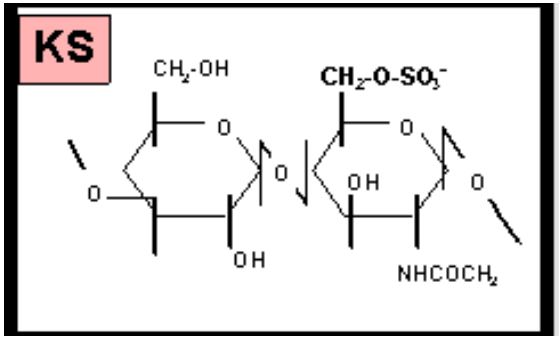
Dermatan Sulfate

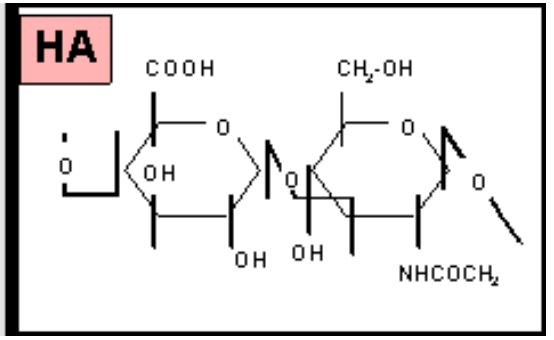


Heparan Sulfate

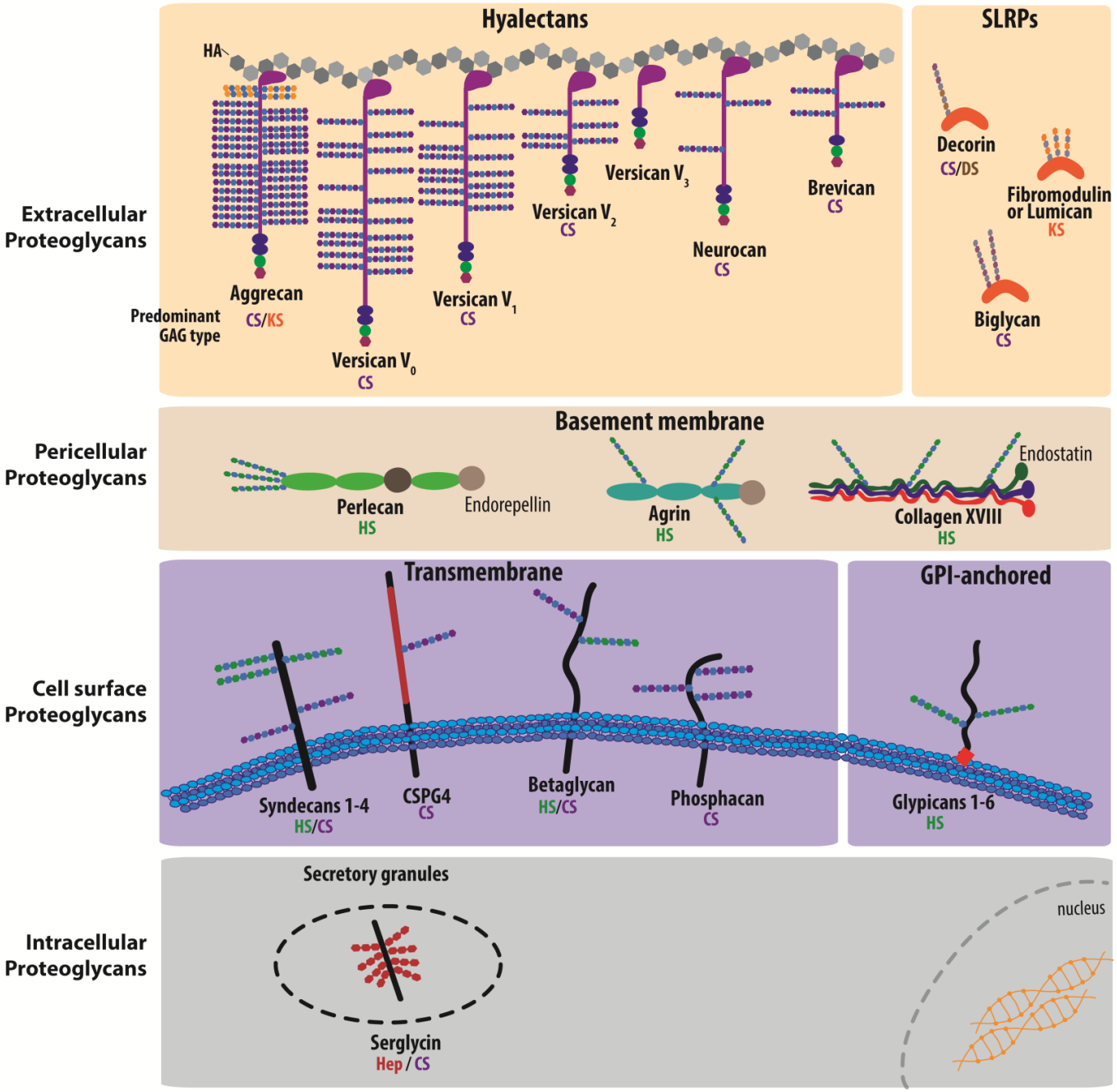


Heparin

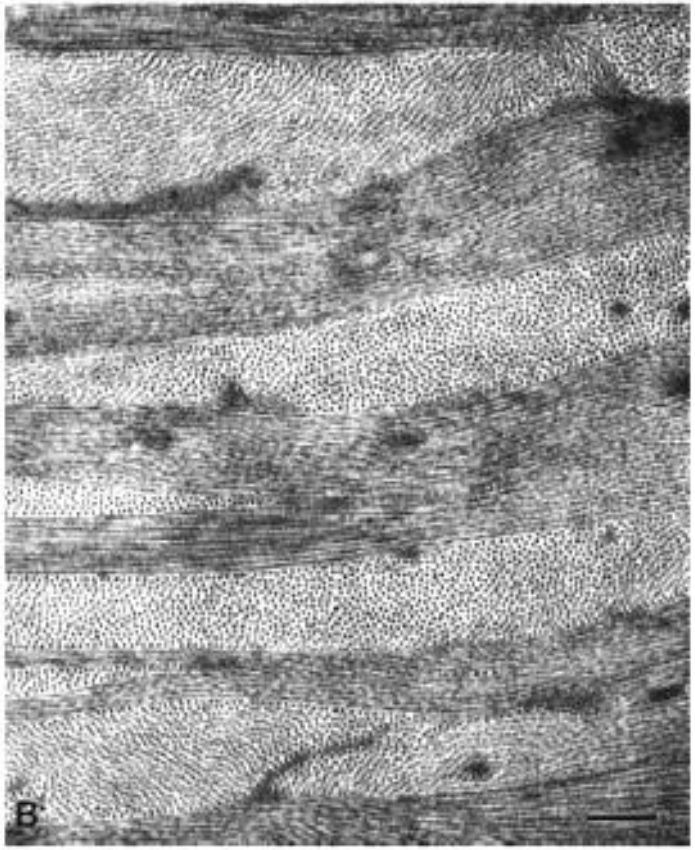


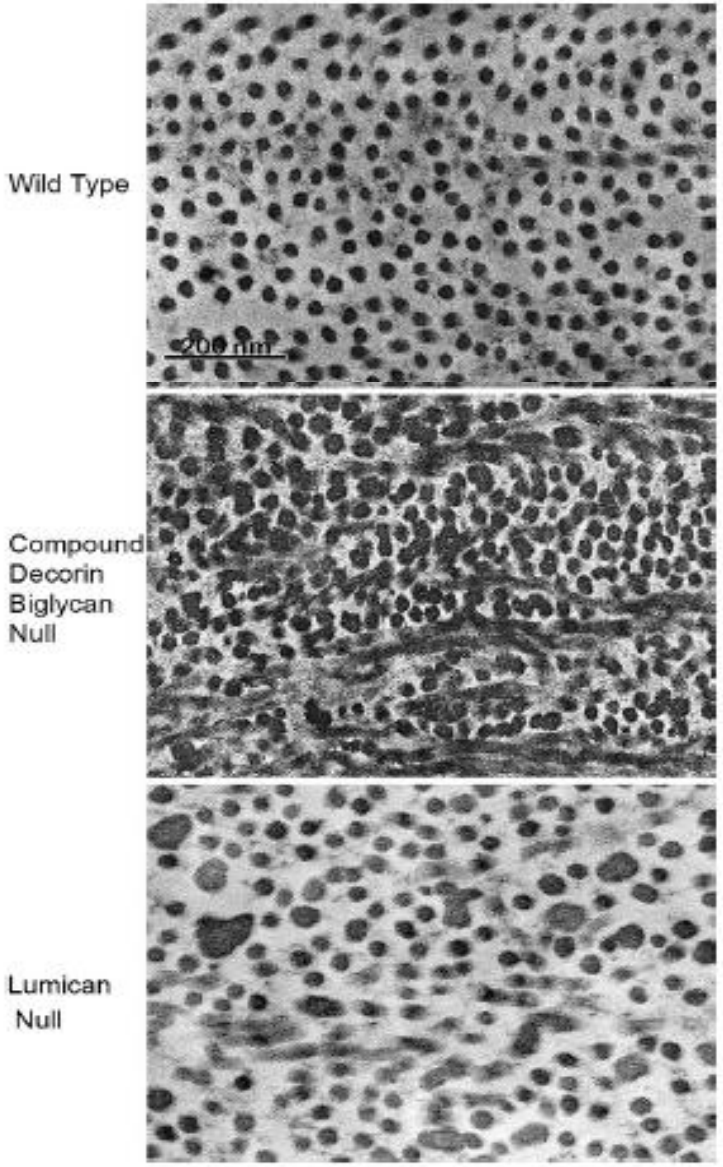


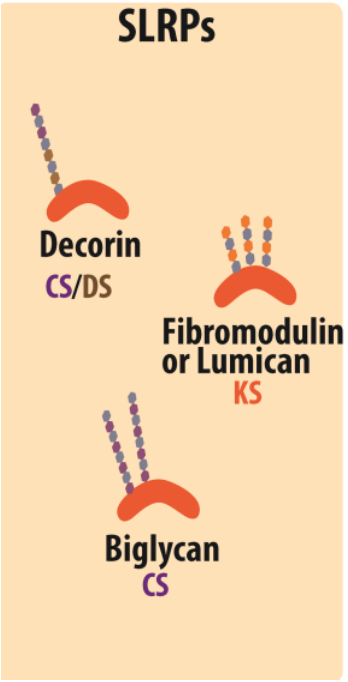
Classification of proteoglycans

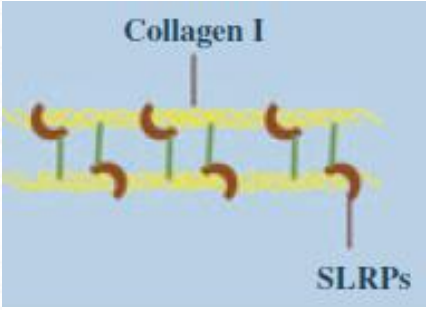


SLRPs: role in collagen fibrillogenesis









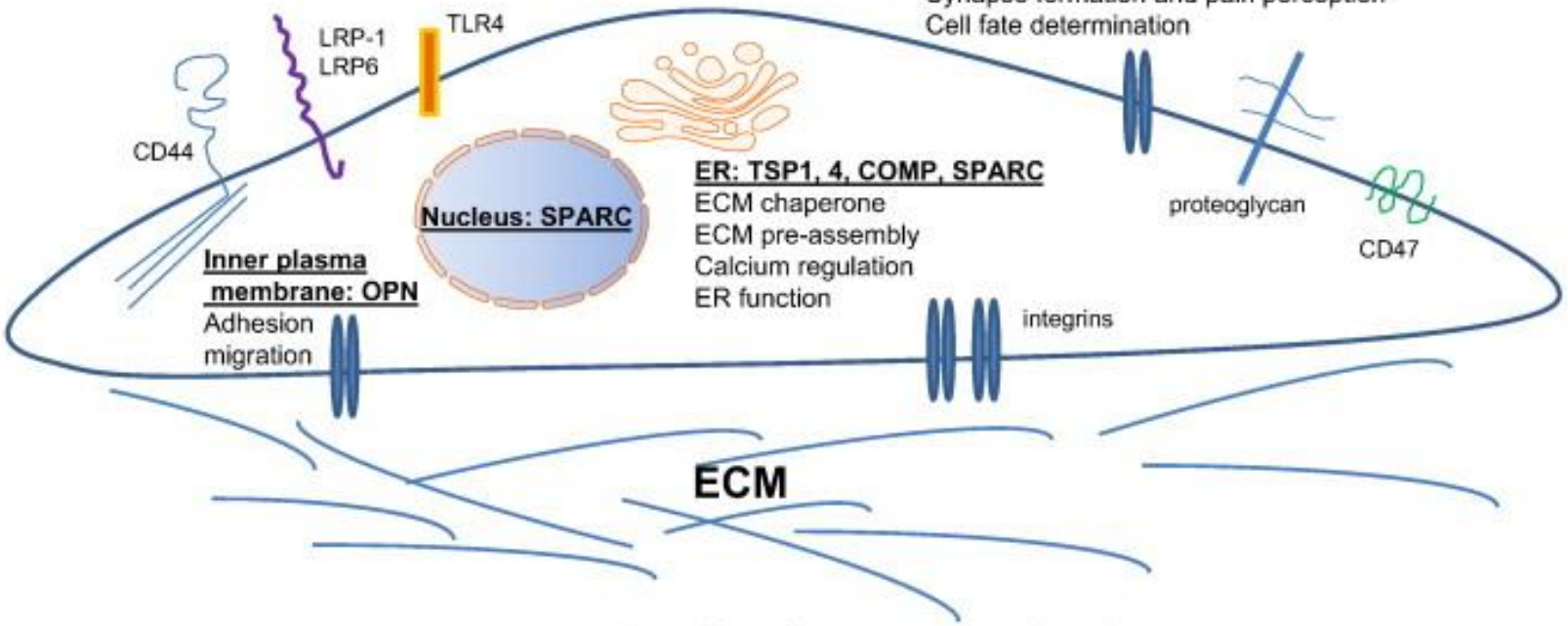
John R. Hassell and David E. Birk Experimental Eye Research 91 (2010) 326-335

Achilleas Theocharis et al.
FEBS Journal 277 (2010) 3904-23

Matricellular Proteins regulate cell function through interactions with diverse receptors and macromolecules in multiple cellular compartments

Body fluids: TSPs, TNs, SPARC, OPN, CCNs, COMP, periostin, fibulin
Growth factor interactions
Hemostasis
Binding to immune cells (innate and adaptive)
Innate immune functions

Receptor Interactions
Cytoskeletal organization
Activate signaling
Inhibit nitric oxide signaling
Growth factor receptor agonist and antagonist
Cell-cell and cell-ECM de-adhesion (intermediate adhesion)
Cell motility
Cell cycle regulation
Anoikis resistance; senescence
Synapse formation and pain perception
Cell fate determination



Extracellular matrix: TSPs, COMP, fibulins, TNs, OPN, SPARC, hevin, PEDF
Collagen fibril organization
Elastin organization
Fibronectin organization
ECM calcification
Proteoglycan interactions

Joanne E. Murphy-Ullrich, E. Helene Sage, Matrix Biology, Volume 37, 2014, 1–14

Marfan Syndrome

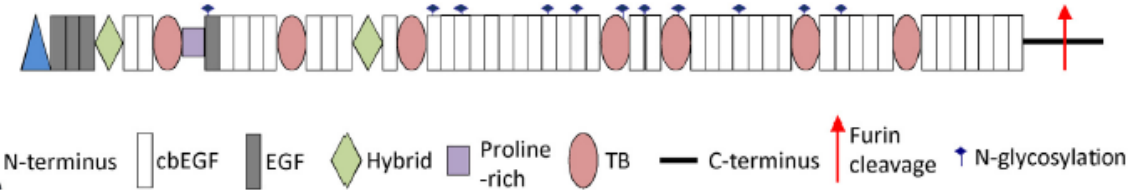
- First described in 1896; named in 1902.
- Common inherited connective tissue disorder
- Incidence: 1 in 3000-5000; approximately 200,000 Americans affected
- M = F; men with shorter life expectancy
- Races affected equally

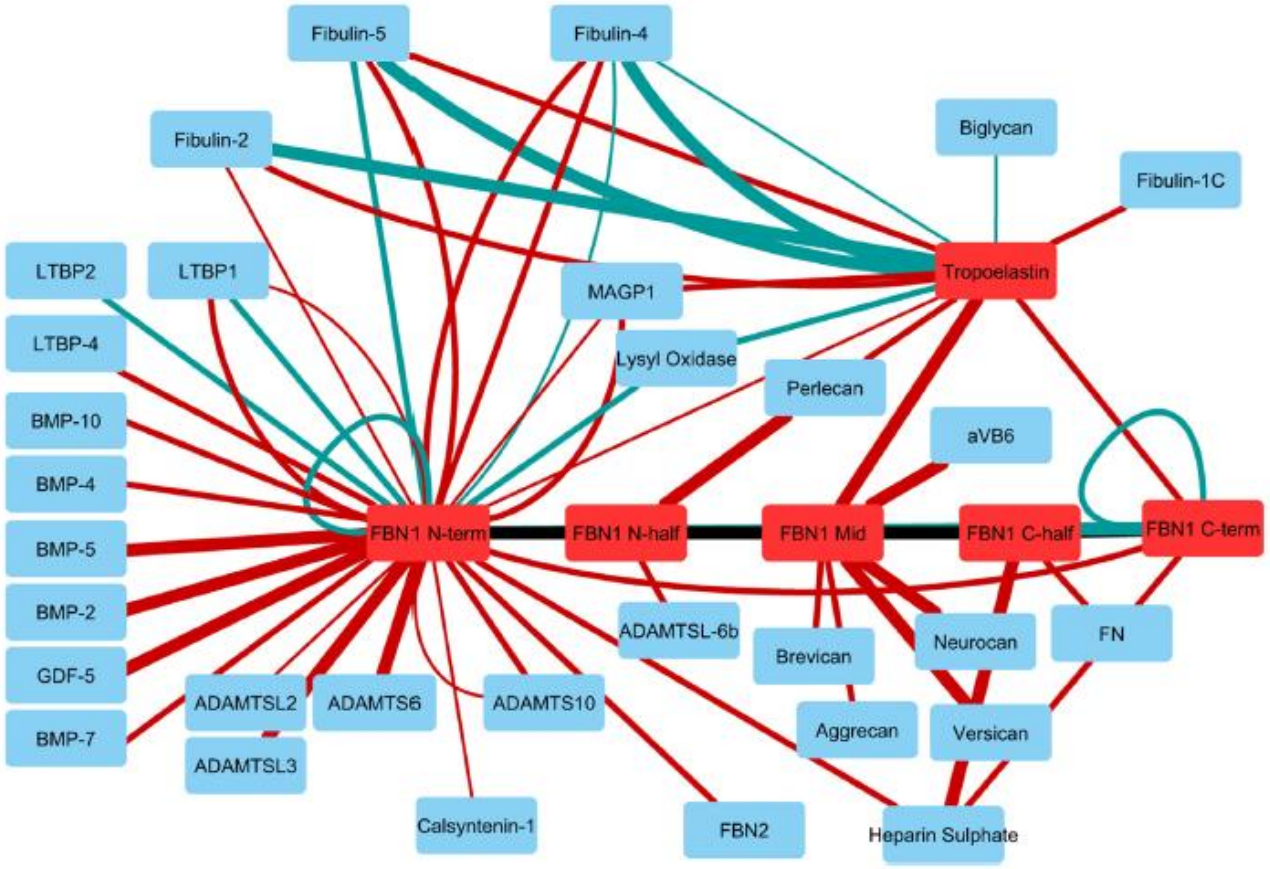
Marfan Syndrome

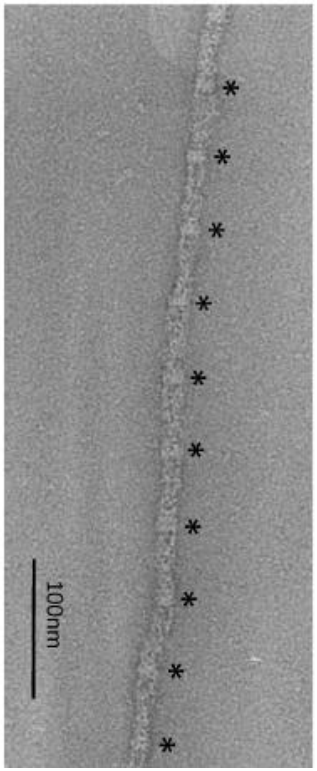
- Autosomal dominant; variable expression
- ~25% spontaneous mutations
- Genes involved in Marfan Syndrome phenotype:
  - Fibrillin-1 (MFS)
    - Microfibril glycoprotein in both elastic and non elastic tissues
    - > 97 different mutations
  - TGFBR (MFS type II or Loeys-Dietz)
    - Works through apoptosis and cell cycle regulation; prevents proper incorporation of fibrillin into tissue
- Other gene mutations may lead to similar phenotypes

Marfan Syndrome: Molecular Mechanism

Fibrillin structure







Marfan Syndrome: Molecular Mechanism

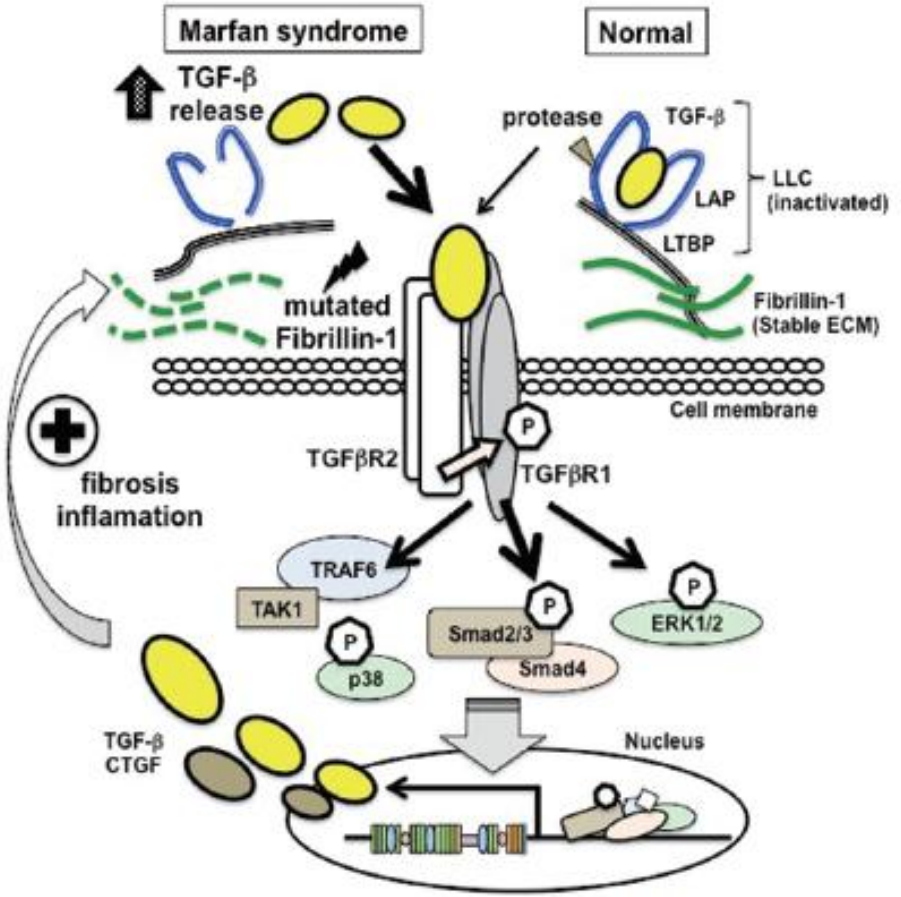


Figure 1. Dysregulation of TGF-β bioavailability in MFS caused by mutations in the FBN1 gene. Latent TGF-β is activated by physical and enzymatic stimuli under normal conditions (right side). Mutated fibrillin-1 in MFS leads to failed ECM sequestration of TGF-β and subsequent activation of TGF-β signaling cascades (left side), which play critical roles in the pathogenesis of MFS. CTGF indicates connective tissue growth factor; ECM, extracellular matrix; LLC, large latent complexes; LAP, latency-associated peptide; and LTBP, latent TGF-β binding protein.

Collagen/proteoglycan deposition
SMCs apoptosis
Elastin degradation
Inflammation

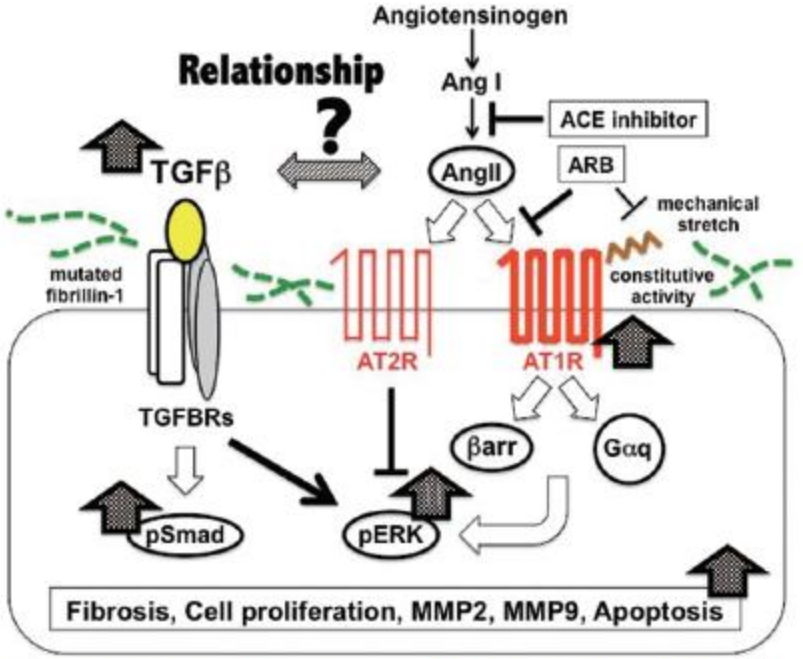
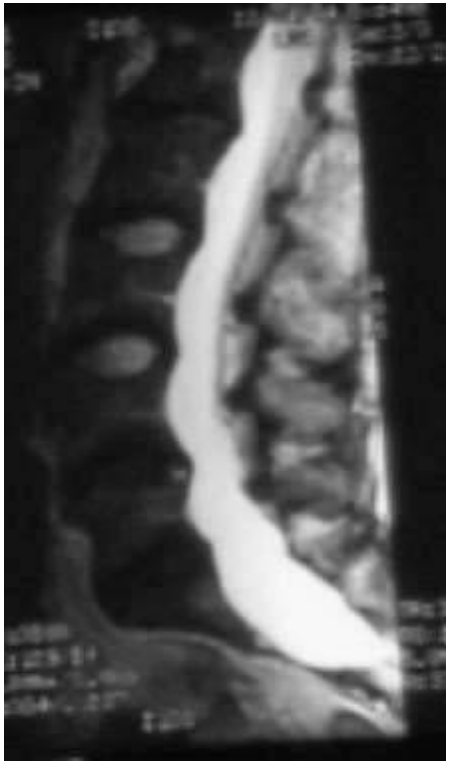


Figure 2. Involvement of non-canonical TGF-β signaling and angiotensin II receptor signaling in MFS. Multiple signals are activated in MFS (dotted arrows), and ERK signaling is activated by both TGFBR and AT1R signaling cascades. ARBs, such as losartan, can inhibit both angiotensin II-dependent and -independent AT1R activation and subsequent ERK activation, offering a promising drug for MFS. ACE indicates angiotensin-converting enzyme; Ang, angiotensin; ARB, Angiotensin II receptor blocker; AT1R, Angiotensin II type 1 receptor; AT2R, Angiotensin II type 2 receptor; βarr, β-arrestin; Gαq, a G-protein α-subunit; and MMP, matrix metalloproteinase.

Marfan Syndrome

Clinical Features

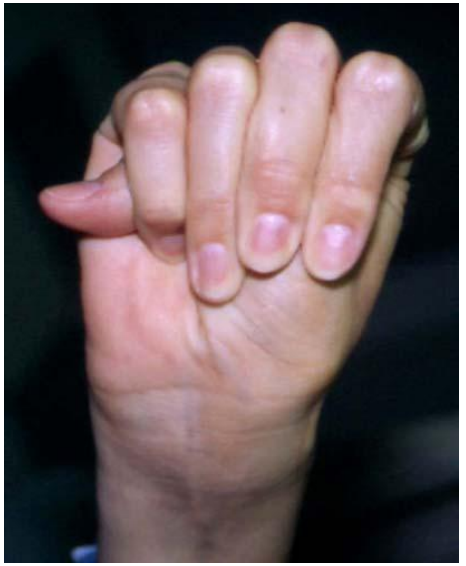
- HEENT:
  - Eye: superior lens dislocation (ectopia lentis)
  - Oropharynx: high palate and crowded dentition
- Cardiac:
  - Mitral valve prolapse
  - Aortic root dilation
- Pulmonary: Spontaneous pneumothorax
- Neurologic: Dural ectasia
- Skin: Stretch marks

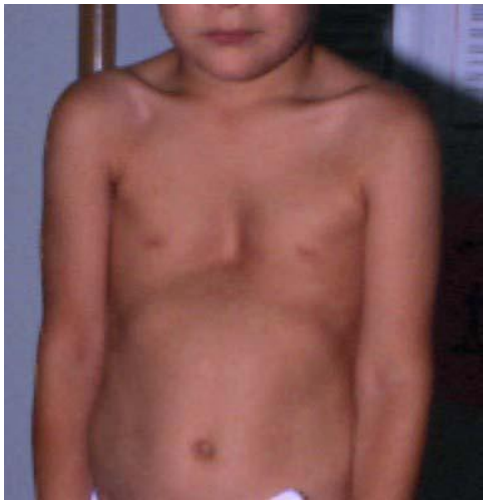


Marfan Syndrome

Clinical Features

- Musculoskeletal:
  - Tall stature (dolichostenomelia)
  - Long digits (arachnodactyly)
  - Thumb sign (distal phalanx protrudes beyond border of clenched fist)
  - Wrist sign (thumb and fifth digit overlap when around the wrist)
  - Sternal deformity (prominent pectus)
  - Scoliosis > 20 degrees
  - Joint hypermobility
  - Arm span exceeding height (ratio >1.05)
  - Reduced elbow extension (<170 degrees)
  - Medial displacement of medial malleolus





Marfan Syndrome
Treatment

- Beta blockade

  Standard of care for adult patients (no data on children)

  Based on studies of propranolol versus placebo

    Slower rate of aortic dilatation with beta blockade

    Survival at 10 yrs not significantly improved

- Calcium channel blockers?
- ARBs

  Recent animal study models of FBN1 mutants demonstrated decreased rate of aortic dilatation

  Mechanism is via TGFBR

  One randomized trial of 17 patients is complete: larger study is now ongoing

Marfan Syndrome: Treatment

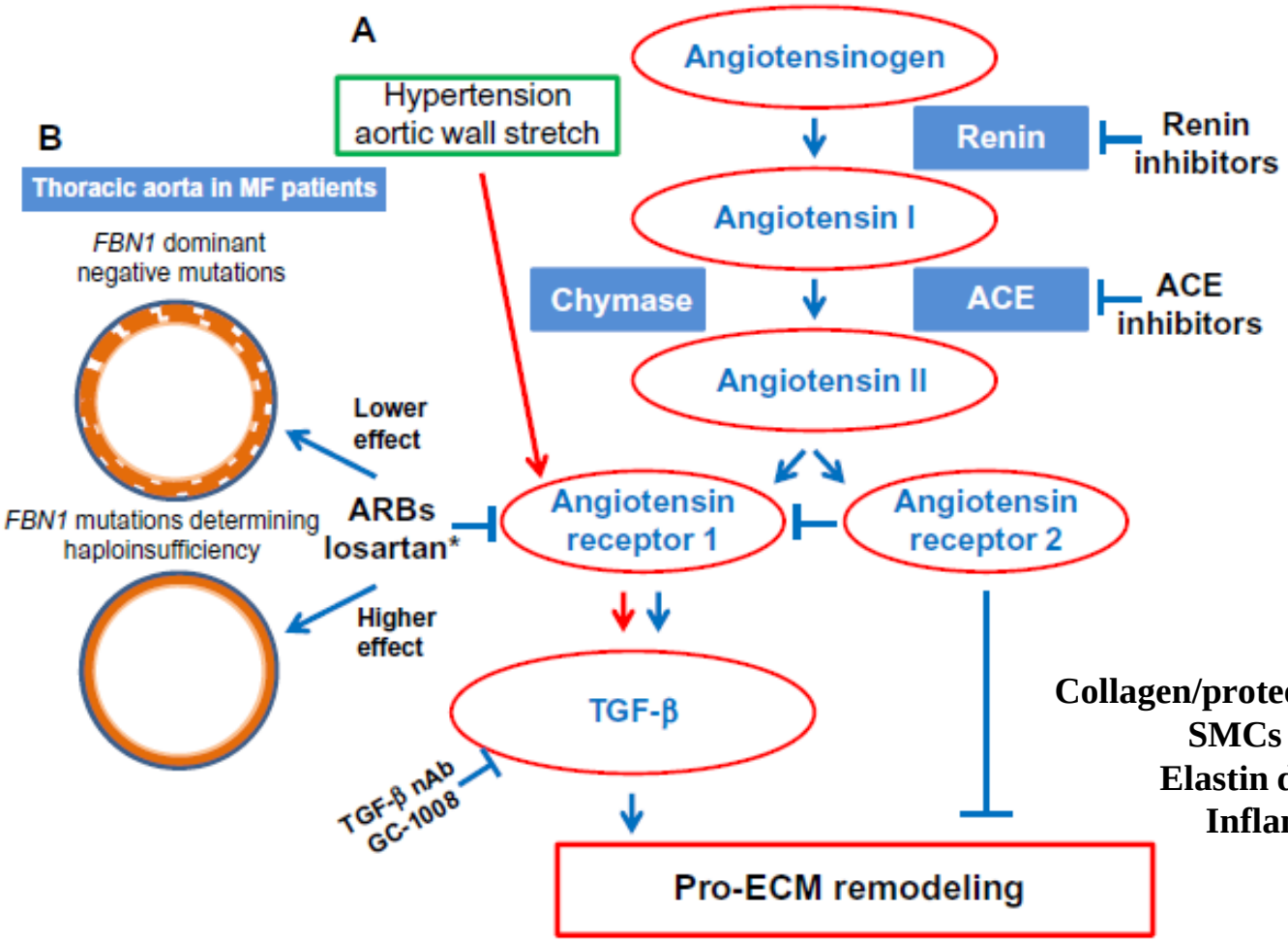


Figure 2 Effects of drug therapies on thoracic aortic wall of MF patients.

Notes: (**A**) Biological targets and therapies upstream of TGF-β in Marfan syndrome. Renin converts angiotensinogen to angiotensin I, which is further converted to angiotensin II by ACE, as well as tissue enzymes including chymase, thus bypassing the inhibition of ACE inhibitors. Angiotensin II then binds to either type 1 or type 2 angiotensin receptors. (**B**) Schematic representation of thoracic aortic wall in patients with Marfan syndrome with *FBN1* dominant negative mutations or haploinsufficiency, as well as the possible explanation of the better effect of losartan in patients with haploinsufficiency. Hypertension and wall stretching represent trigger factors for upregulation of type 1 angiotensin receptor, which in turn increases TGF-β production. *Administration of Losartan decreases TGF-β production and increases proinflammatory response, myofibroblast differentiation, and reactive oxygen species.

Osteogenesis Imperfecta

- The most prevalent heritable bone fragility disorder (incidence 1: 15.000).
- COL1A1 and COL1A2 are the most frequent causative mutations (85-90% of cases), but recently, mutations on 15 other genes have been identified, either with autosomal dominant or autosomal recessive inheritance.
- The most frequent abnormality is a mutation in a glycine residue in one of the two collagen genes that causes

i) Quantitative defects (haploinsufficiency of the gene leading to production of structurally normal collagen ~ 50% of normal amount). OI type I: mid form of disease.

ii) Qualitative defects (replace of glycine by another aminoacid resulting in the production of abnormal collagen molecule). OI type II: Moderate, severe, or lethal form of disease.

Clinical Types of Osteogenesis Imperfecta

Type 1

- The mildest and most common form
- Body produces normal quality collagen, but just not enough of it
- Typically experience bone fractures due to mild traumas
- The teeth may also be affected, resulting in dental cracks and cavities

Type 2

- The most severe form
- Fatal
- Body either produces poor-quality collagen or not enough of it
- Can produce bone deformities
- May have narrowed chests, broken or misshapen ribs, and underdeveloped lungs
- Die either in the womb or shortly after birth

Type 3

- Severe form
- Body produces enough collagen, but it is of poor quality
- A baby's bones can even begin to break before birth
- Bone deformities are common and may get worse as your child gets older.

Type 4

- Most variable form
- Symptoms range from mild to severe
- As with type 3, the body produces enough collagen, but the quality is poor
- Typically born with bowed legs, although the bowing tends to lessen with age

Clinical Types of Osteogenesis Imperfecta

Long Term Effects

- **Type 1**

Can live a normal lifespan with relatively few problems

- **Type 2**

Type 2 is fatal. Infants with type 2 may die in the womb, or shortly after birth from respiratory problems

- **Type 3**

Children with type 3 may have severe bone deformities and often require a wheelchair to get around. People with type 3 usually have shorter lifespans than anyone with type 1 or 4

- **Type 4**

Children with type 4 may need crutches to walk. The lifespan of people with type 4 is normal or close to normal

Osteogenesis Imperfecta Clinical Types

Defective gene	Clinical OI type[b]
COL1A1	I, II, III, IV
COL1A2	I, II, III, IV
CRTAP	III, IV
P3H1	III
PPIB	III
FKBP10	III, IV
SERPINH1	III, IV
PLOD2	III, IV
BMP1	I, III, IV
SPARC	IV
TMEM38B	IV
SEC24D	III, IV
P4HB	III
IFITM5	V
SERPINF1	III, IV
WNT1	IV
SP7	III
CREB3L1	II

Table 1. Classification of osteogenesis imperfecta (OI) based on the cellular localization (color-coded) of the defective protein. It is important to note that mutations in proteins located in the ER and Golgi ultimately cause type I collagen defects in the bone matrix. AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.

Localization	Protein	Function	Gene	Inheritance	Clinical severity
Matrix	α1(I)	Matrix structural component	*COL1A1*	AD	Mild to lethal OI depending on the mutation
Matrix	α2(I)	Matrix structural component	*COL1A2*	AD	Moderate to lethal depending on the mutation
Matrix	PEDF	Collagen-binding protein/pigment epithelium derived factor	*SERPINF1*	AR	Moderate to severe OI – postnatal onset
Matrix	BMP1	Extracellular protease	*BMP1*	AR	Moderate to severe OI
Matrix	WNT1	Secreted signaling molecule	*WNT1*	AR	Moderate to severe OI – CNS defects
Matrix	SPARC	Matrix-associated protein	*SPARC*	AR	Moderate to severe OI
Plasma membrane	BRIL	Bone-restricted interferon-induced transmembrane-like protein	*IFITM5*	AD	Variable severity – hyperplastic callus formation, calcification of interosseous membrane
Plasma membrane	LRP5	WNT signaling co-receptor	*LRP5*	AR	Osteoporosis-pseudoglioma syndrome – ocular defects
ER-Golgi	TRIC-B	Cation channel	*TMEM38B*	AR	Moderate to severe OI
ER-Golgi	S2P	Membrane-bound transcription factor site-2 protease	*MBTPS2*	XLR	Moderate to severe OI – chest deformities
ER-Golgi	OASIS	Cyclic AMP responsive element binding protein 3-like protein 1	*CREB3L1*	AR	Severe OI
ER-Golgi	HSP47	Type I procollagen chaperone	*SERPINH1*	AR	Severe OI
ER	FKBP65	Type I procollagen chaperone	*FKBP10*	AR	Moderate to severe OI
ER	LH2	Collagen telo-peptide lysyl hydroxylase	*PLOD2*	AR	Moderate to severe OI – joints contractures
ER	CYCLOPHILIN B	Peptidylprolyl Isomerase B	*PPIB*	AR	Moderate to severe OI
ER	P3H1	Prolyl 3-hydroxylase	*P3H1*	AR	Severe to lethal OI
ER	CRTAP	Adapter protein???	*CRTAP*	AR	Severe to lethal OI
Nucleus	SP7/Osterix	Transcription factor	*SP7*	AR	Mild to moderate OI

Osteogenesis Imperfecta: Molecular Mechanism

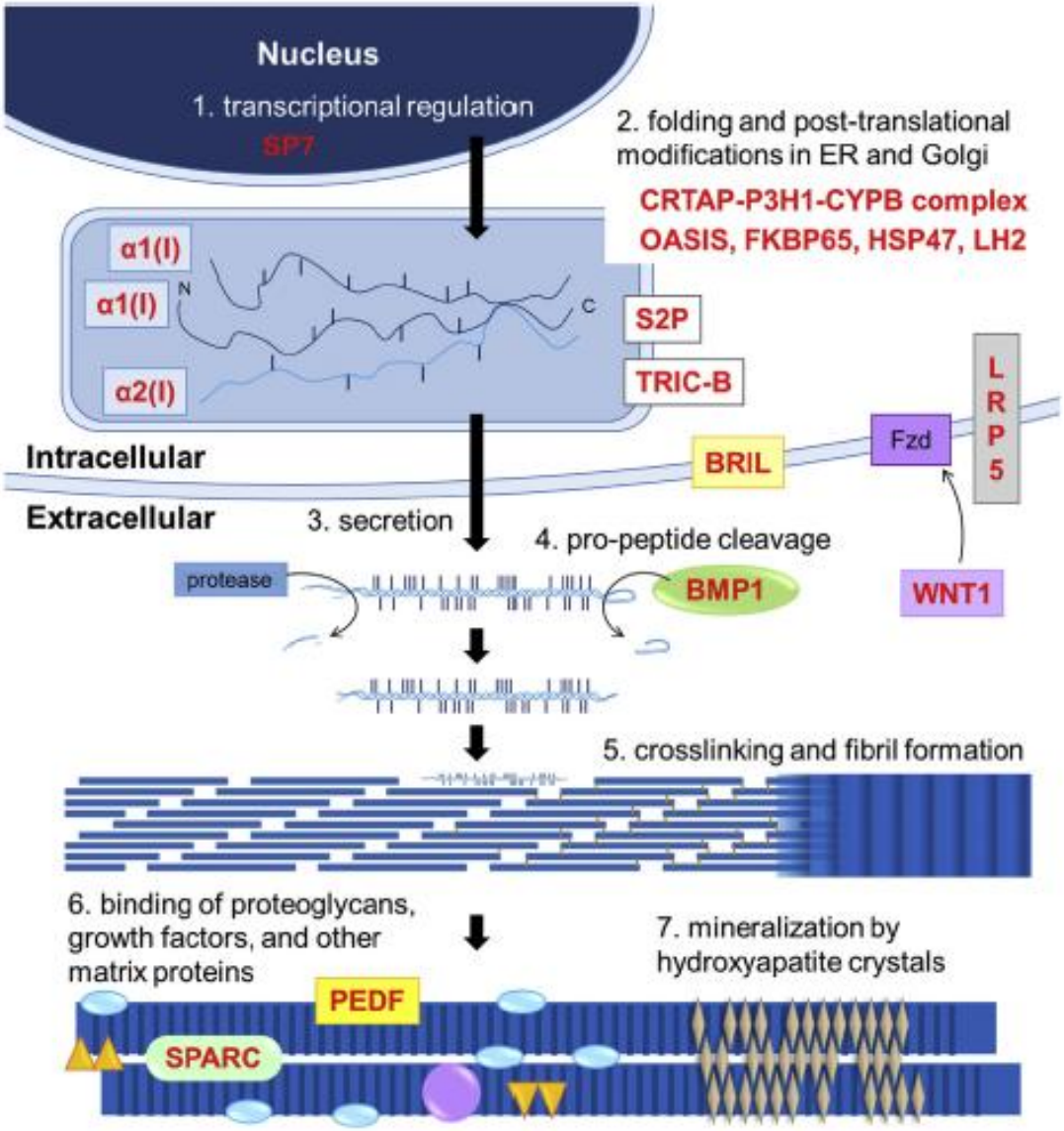


Fig. 3. Schematic diagram illustrating essential processes of type I collagen synthesis, its assembly in the matrix, interaction with other matrix components, and mineralization. Some of the proteins that regulate these processes and that are mutated in various types of OI are also indicated. Alterations of one or more of these key steps in the formation of ECM represent major pathogenetic mechanisms in OI.

Symptoms of Osteogenesis Imperfecta

Symptoms

- The symptoms of brittle bone disease vary according to the type of the disease
- Everyone who suffers from brittle bone disease has fragile bones to varying degrees.

- bone deformities
- multiple broken bones
- loose joints
- short stature
- weak teeth
- triangular-shaped face
- blue sclera (bluish color in the white of the eye)
- bowed legs and arms
- kyphosis (an abnormal outward curve of the upper spine)
- scoliosis (an abnormal lateral curve of the spine)
- early hearing loss
- respiratory problems
- heart defects

Treatment of Osteogenesis Imperfecta

Although there is no cure for brittle bone disease, there are supportive therapies such as:

- physical and occupational therapy to increase mobility and muscle strength to help reduce risk of fractures
- bisphosphonate medications to increase bone formation
- medication to reduce any pain
- low-impact exercise to help build bone
- surgery to place rods in the bones to strengthen them
- reconstructive surgery to correct bone deformities
- mental-health counseling to help with body-image issues

Ehlers-Danlos Syndrome

- A group of inherited disorders of connective tissue caused by qualitative and/or quantitative abnormalities in collagen production
- Collagen is present in nearly every tissue and organ system in the body
- EDS associated with many widespread complications and symptoms; tissues often involved are skin, joints, and blood vessel walls
- There are 6 major types that vary in their specific cause and presentation (dependent on the form of collagen affected)
- Recorded prevalence of 1 in 2,500 (often misdiagnosed)
- Most cases inherited in autosomal dominant pattern

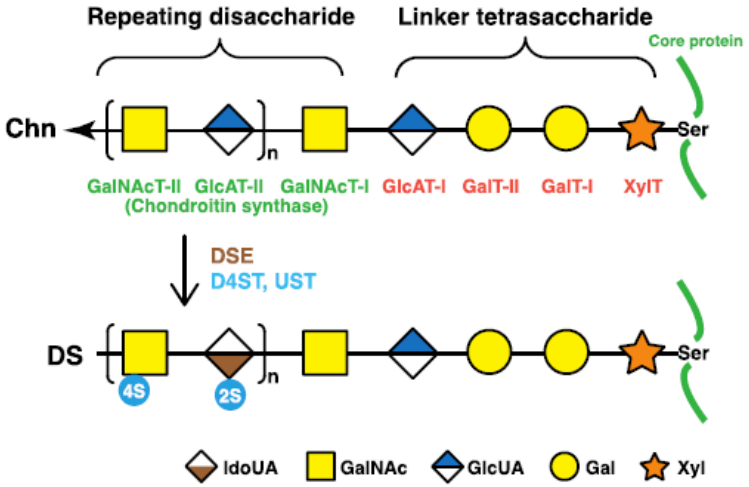
Major Subtypes of Ehlers-Danlos Syndrome

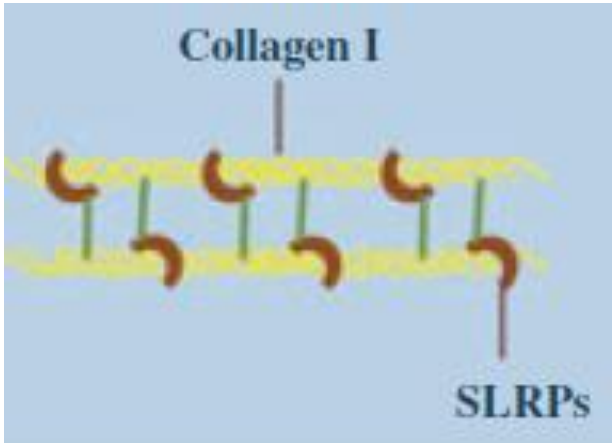
Table 1. Major Subtypes of Ehlers-Danlos Syndromes[a]

Major Subtype	Major Diagnostic Criteria (and Other Clinical Features)	Inheritance	Genetic Mutation	Prevalence
Classic	Significant skin hyperextensibility and velvety skin. Significant tissue fragility and widened atrophic scars; and/or Significant joint hypermobility.	Autosomal dominant	Type V collagen genes *COL5A1* *COL5A2*	1 in 20 000
Hypermobile	Significant joint hypermobility. Moderate skin hyperextensibility and/or velvety skin. (No significant tissue fragility or wound healing abnormalities.)	Autosomal dominant	Unknown for most cases	1 in 5000 to 20 000; >90% are female
Vascular	Fragility or spontaneous rupture of vasculature or visceral organs. Significant bruising. Thin, translucent skin. Characteristic facies of prominent eyes, thin face, nose, and lobeless ears. (No significant skin hyperextensibility. Joint hypermobility restricted to minor joints.)	Autosomal dominant	Type III collagen gene *COL3A1*	1 in 50 000 to 100 000
Kyphoscoliotic	Significant joint hypermobility. Severe muscular hypotonia at birth. Progressive kyphoscoliosis. Globe rupture.	Autosomal recessive	Collagen lysyl hydroxylase	Rare
Arthrochalasic	Severe joint hypermobility with recurrent subluxations. Congenital bilateral hip dislocation. (Moderate skin hyperextensibility and tissue fragility.)	Autosomal dominant	Type I collagen genes *COL1A1* and *COL1A2*	Rare
Dermatosparactic	Severe skin fragility. Sagging and redundant skin. (Easy bruising and soft, doughy skin)	Autosomal recessive	Procollagen I N-terminal proteinase (*ADAMST2* gene)	Rare

Minor Subtypes of Ehlers-Danlos Syndrome

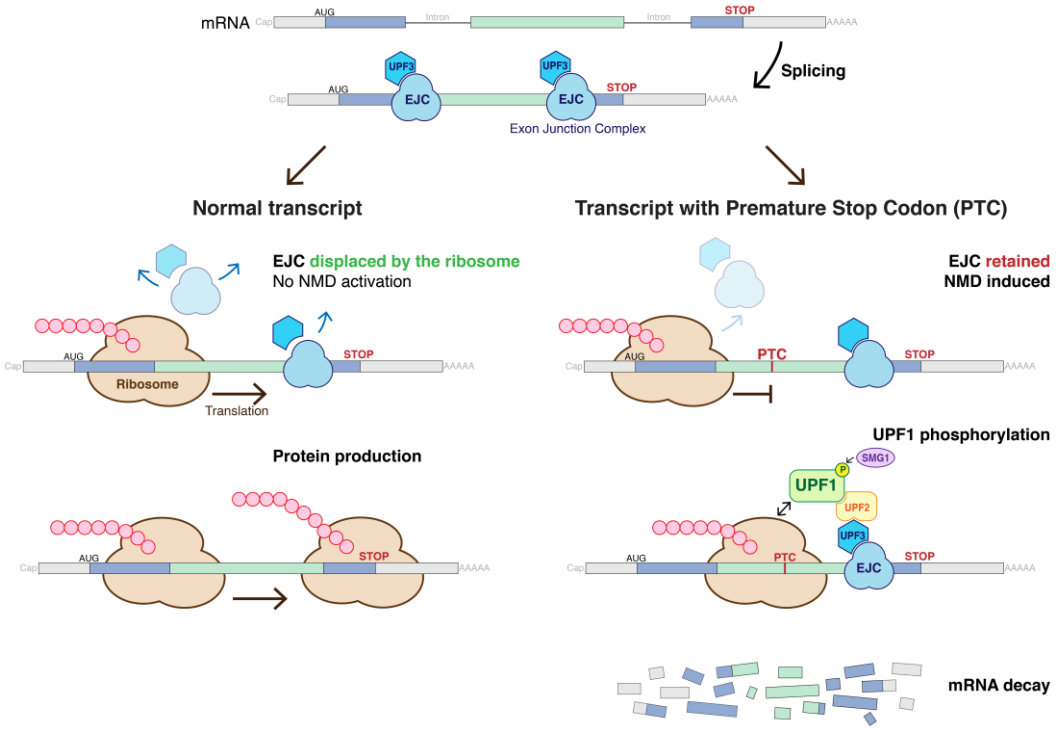
Enzymes and DS-PG Core Proteins	Coding Genes	MIM Number	Human Genetic Disorders	Clinical Features
β4Galactosyltransferase-I (GalT-I)	*B4GALT7*	130070 604327	Ehlers-Danlos syndrome progeroid type 1	Developmental delays, aged appearance, a short stature, craniofacial dysmorphism, and generalized osteopenia.
			Larsen of Reunion Island syndrome	Multiple dislocations, hyperlaxity, dwarfism, and distinctive facial features.
β3Galactosyltransferase-II (GalT-II)	*B3GALT6*	615349 615291	Ehlers-Danlos syndrome progeroid type 2	Sparse hair, wrinkled skin, defective wound healing with atrophic scars, osteopenia, and radial head dislocation.
		271640	Spondyloepimetaphyseal dysplasia with joint laxity type 1	Spatulate fingers with short nails, hip dislocation, elbow contracture, clubfeet, and mild craniofacial dysmorphism including prominent eyes, blue sclera, a long upper lip, and small mandible with a cleft palate.
Dermatan sulfate epimerase	*DSE*	615539 605942	Ehlers-Danlos syndrome musculocontractural type 2	Characteristic facial features, congenital contracture of the thumbs and feet, hypermobility of the finger, elbow, and knee joints, atrophic scarring of the skin, and myopathy.
Dermatan 4-*O*-sulfotransferase	*CHST14*	601776 608429	Ehlers-Danlos syndrome musculocontractural type 1; EDS Kosho type	Craniofacial dysmorphism, multiple congenital contractures including adduction-flexion contracture of the thumbs and clubfeet, malformations of the heart, kidney, intestine, and eye; skin hyperextensibility, bruisability, and fragility with atrophic scars; recurrent joint dislocations, progressive foot or spinal deformities, pneumothorax, large subcutaneous hematomas, and diverticular perforation.
			Adducted thumb-clubfoot syndrome	





Mechanism of Ehlers-Danlos Syndrome

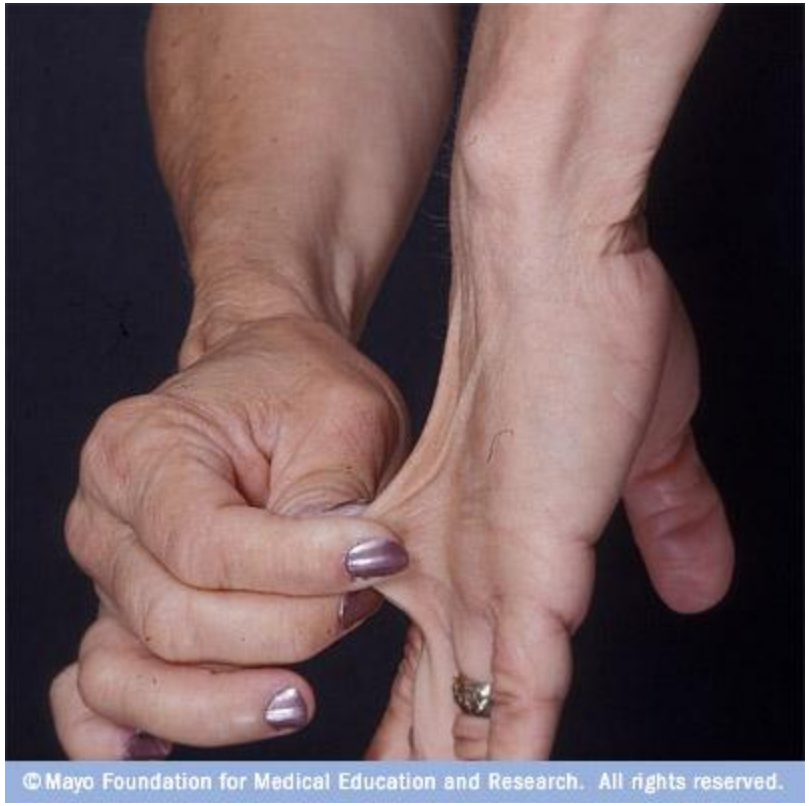
- Reduction of collagen V that has a regulatory role in collagen type I fibrillogenesis. Collagen V is embedded within collagen fibrils regulating fibril assembly and diameter.
- Most common mutations results in point nonsense mutations that employ a point-nonsense-mediated mRNA decay pathway to eliminate mutant mRNA.

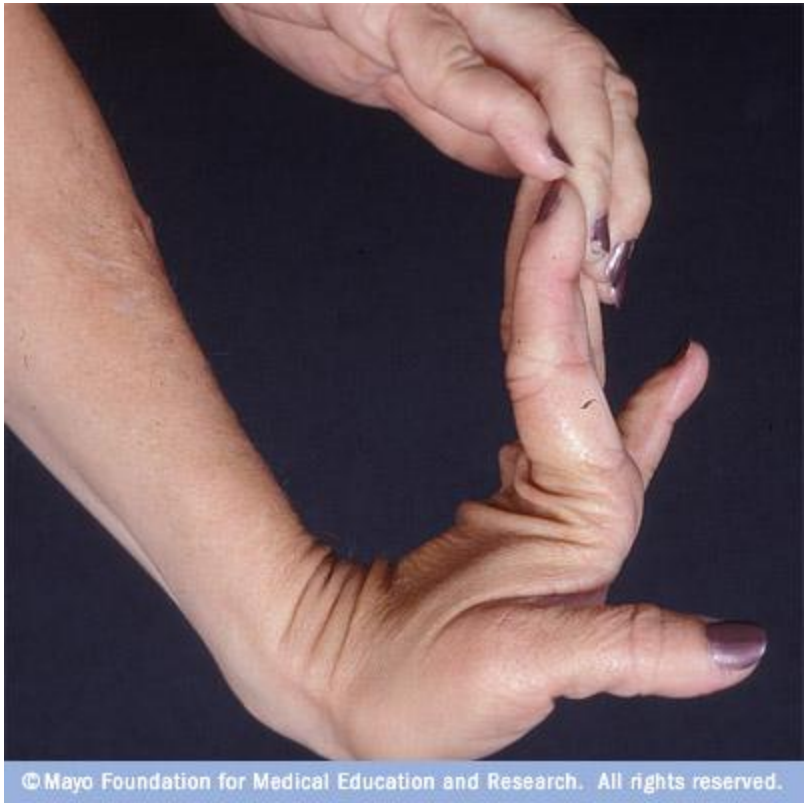


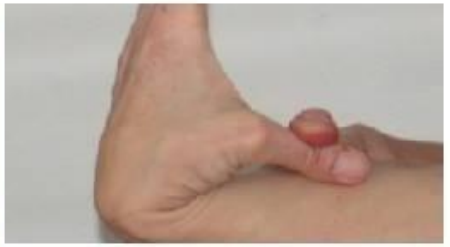
Major Symptoms

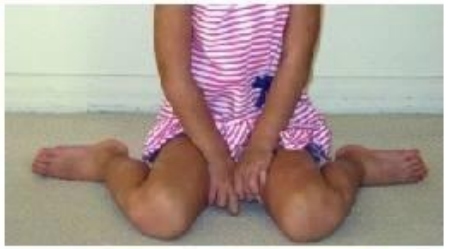
- Stretchy, loose, and/or “velvety” skin
- Flexible joints with hypermobility (causes chronic joint pain, damage and reactive muscle pain)
- Abnormal wound healing
- Joint dislocations and/or partial dislocations (aka subluxations)
- Easy bruising
- Muscle pain and weakness
- Heart and vascular problems such as aneurysms, MVP, aortic root dilatation
- Organ rupture, hernia

Joint and Skin Findings







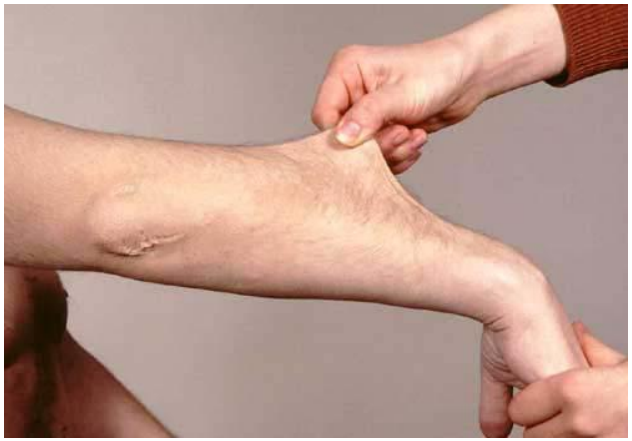


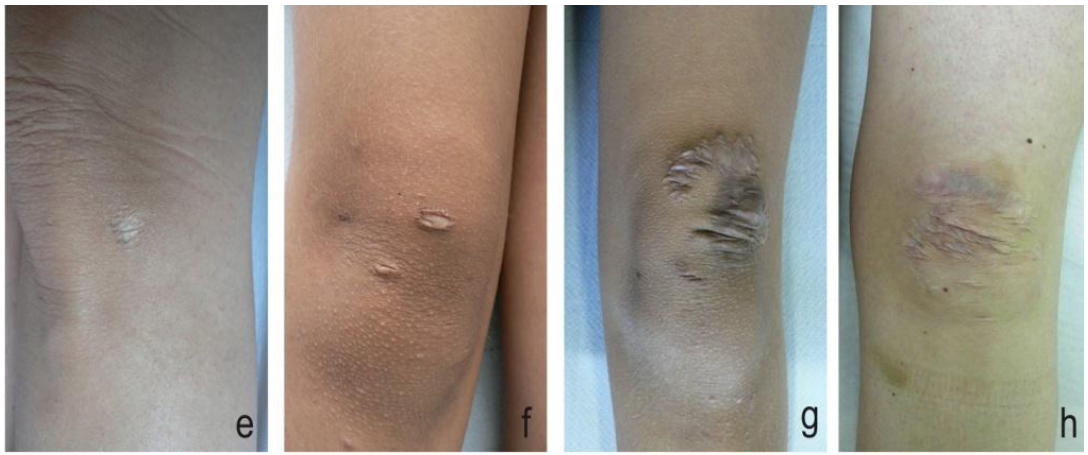
If you can do more than a couple of these AND you have chronic joint pain educate yourself about Joint hypermobility syndrome/Ehlers-Danlos Syndrome

Pay extra attention if you have any of these associated conditions: frequent dislocations, tendonitis/tendonosis, POTS, easy bruising, fragile skin, fatigue, poor healing, TMJ, early onset of osteoarthritis/osteoperosis, IBS or other GI issues, flat feet, Chiari malformation, organ rupture, or mitral valve prolapse,

Classical Type (Types I & II)

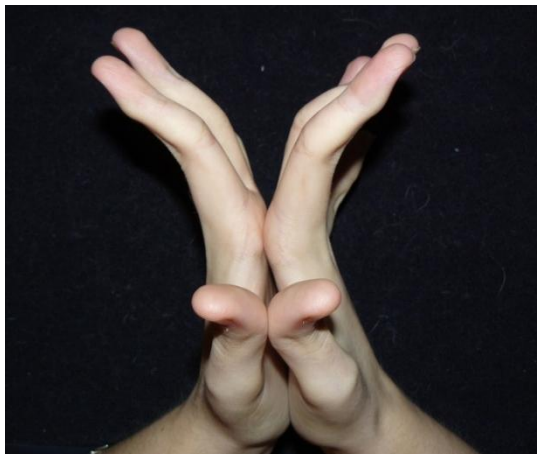
- Generalized hyperextensibility of joints and skin
- Easy bruising, hemarthroses
- Poor wound healing and retention of sutures
- Congenital dislocation of hips
- Scoliosis
- Mitral valve prolapse





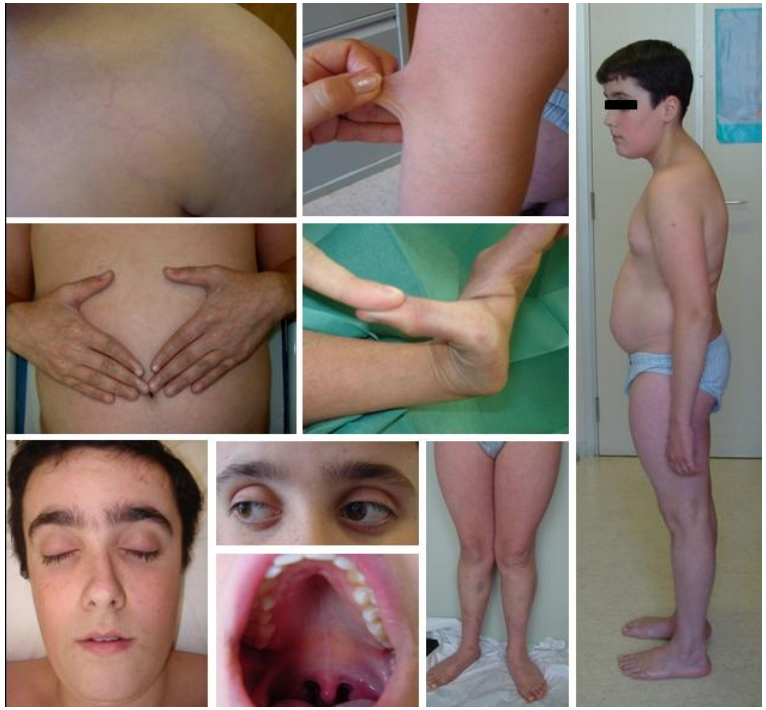
Hypermobility Type (Type III)

- Most common type (reported in up to 1 in 5,000, probably MUCH higher)
- Exact cause unknown; no genetic test available
- Autosomal dominant inheritance
- Cardinal feature: Joint hyper-extensibility
- Chronic degenerative joint disease with advanced, premature osteoarthritis
- Less skin involvement
- Mitral valve prolapse

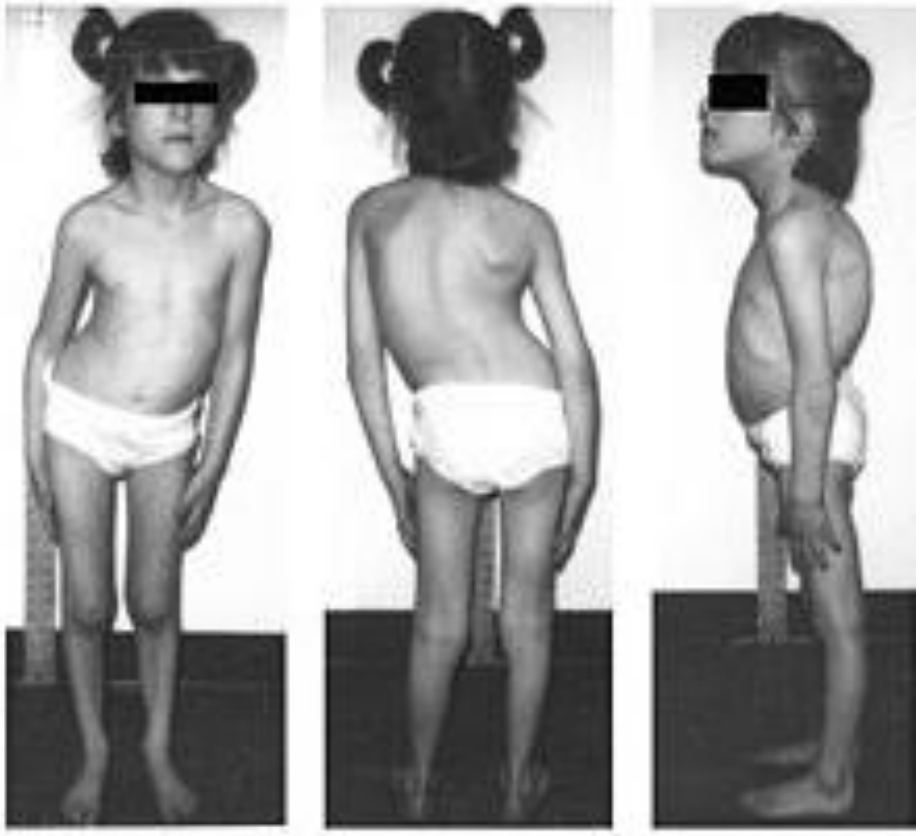


Vascular Type (Type IV)

- Most serious type (1 in 250,000)
- Prone to ruptured/dissected arteries and aneurysms, intestinal and uterine rupture
- Easy bruising
- Visible veins beneath thin, translucent skin
- Characteristic facies: protruding eyes, thin nose/lips, sunken cheeks, small chin
- Joint involvement variable
- Relative deficiency in type III collagen



Kyphoscoliosis Type (Type VI)
Arthrochalasia Type (Type VIIA/VIIB)
Dermatosparaxis Type (Type VIIC)



Kyphoscoliosis Type

Treatment

- No specific cure available
- Goal: Manage symptoms and prevent complications
- Important EDS screening:
  - Echocardiogram
  - DEXA scan
  - CNS imaging (including vascular scans)
- Patient education and genetic counseling
- Rehabilitation and Maintenance – PT/OT, aquatic therapy
- Postural training and body awareness
- Chronic pain management
- Orthopedic surgery (in skilled hands)