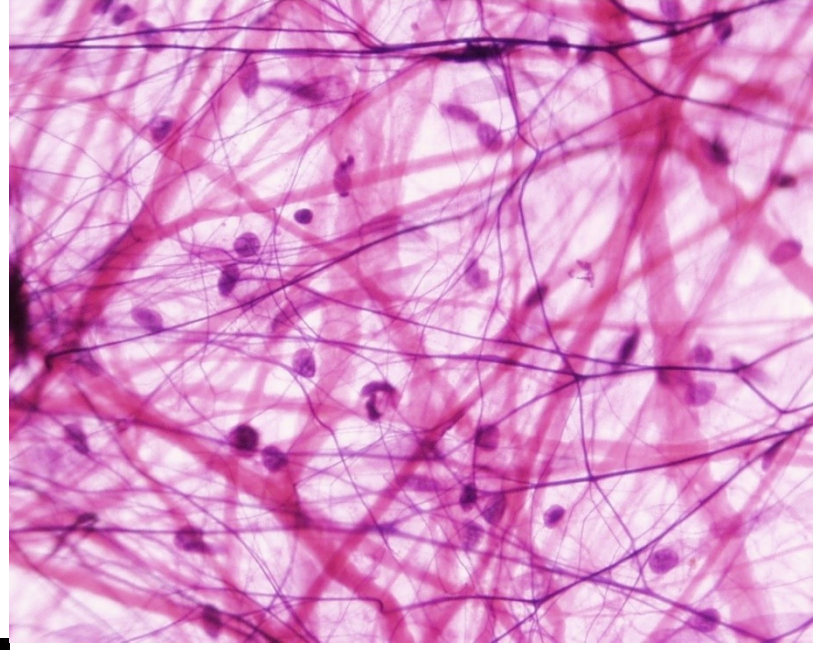
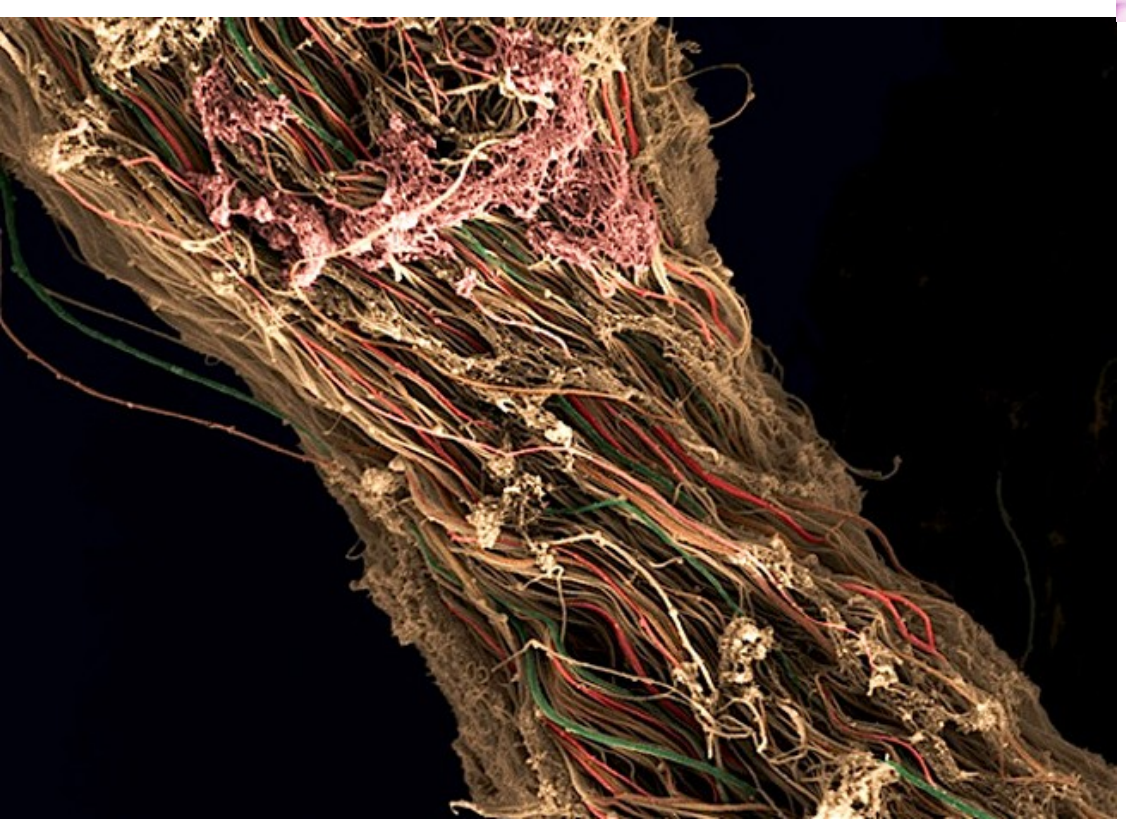
MUNI MED
Department of Histology and Embryology



Connective tissue I 2024



Connective tissue proper

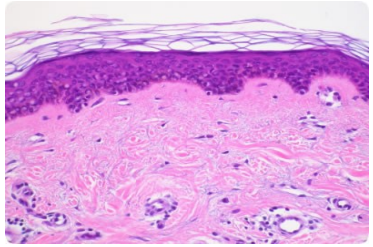
Petr Vaňhara

pvanhara@med.muni.cz

CONTEMPORARY TISSUE CLASSIFICATION

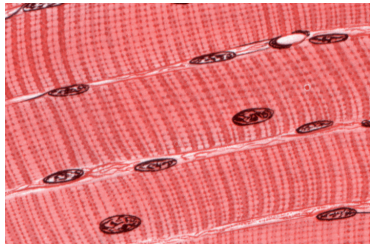
Tissue classification is based on **morphology** **and** **function**:

Epithelial tissue



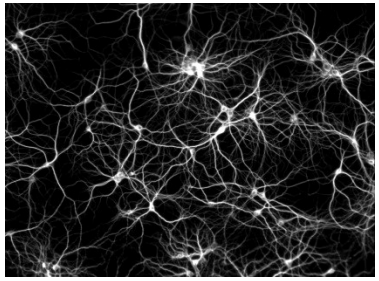
Continual, avascular layers of cells with different function, oriented to open space, with specific junctions and minimum of ECM and intercellular space.
Derivates of all three germ layers

Muscle tissue



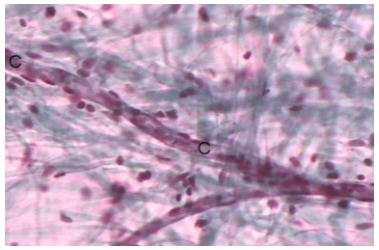
Myofibrils → contraction
Mesoderm – skeletal muscle, myocard, mesenchyme – smooth muscles

Nerve tissue



Neurons and neuroglia
Reception and transmission of electric signals
Ectoderm

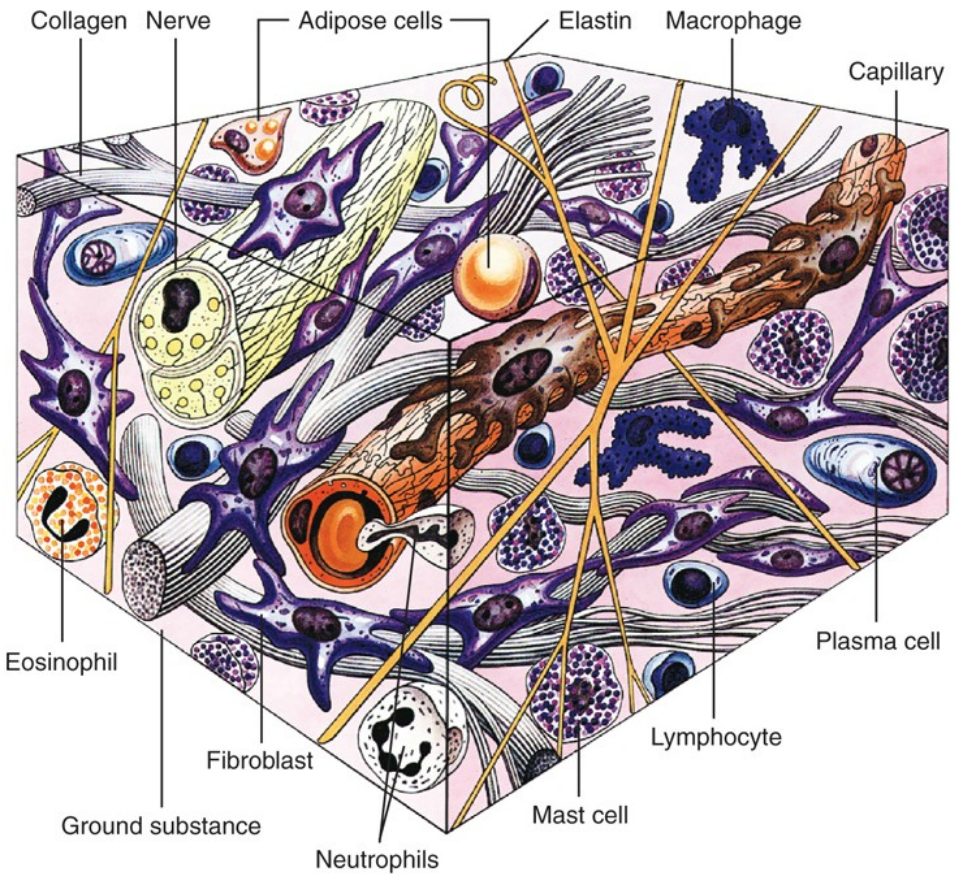
Connective tissue



Dominant extracellular matrix
Connective tissue, cartilage, bone…
Mesenchyme

Various functions of connective tissues depend on its mechanical and biological properties

- surrounds other tissues and provides structural support
- compartmentalization
- physical-chemical environment
- nutrition
- innervation
- immunological support
- storage of energy
- cell signaling and tissue regeneration



From Williams PL, ed: Gray's anatomy: the anatomical basis of clinical practice, *ed 38, Edinburgh, 1995, Churchill Livingstone.*

GENERAL COMPOSITION OF CONNECTIVE TISSUE

All tissues are composed of **cells** and **extracellular matrix**
In connective tissue, the **ECM is dominant**

Cells

Permanent and **temporary cell populations**

- fibroblasts/myofibroblasts
- immune cells
- phagocytes
- adipocytes
- adult stem cells
- specialized cells of cartilage

(chondroblasts/chondrocytes)

- specialized cells of bone
- (osteoblasts/osteocytes/osteoclasts)

ECM

Fibrous component

- collagen fibers (prototypically col. I, II)
- reticular
- elastic

Amorphous component (ground substance)

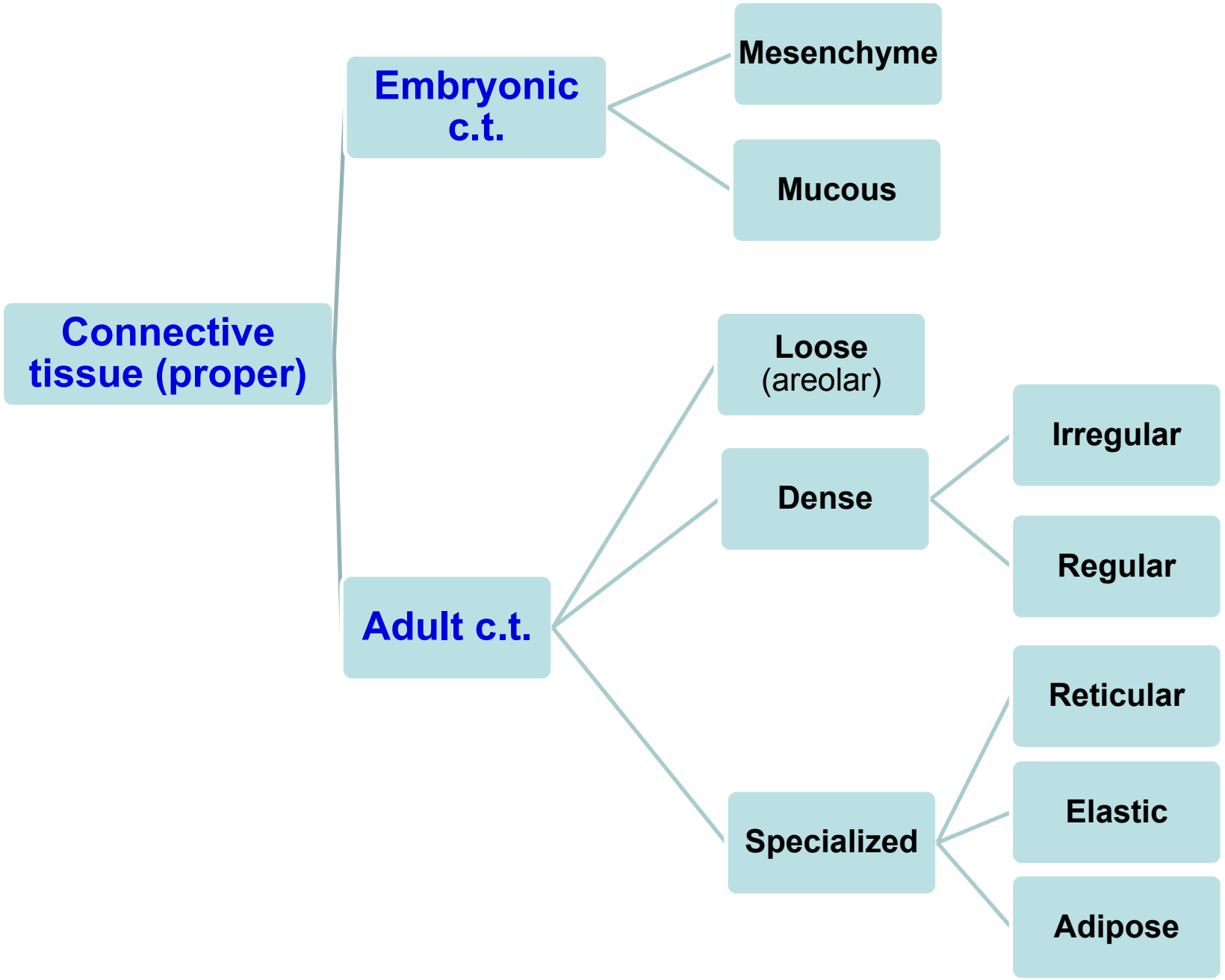
Complex matrix consisting of

- glycosaminoglycans
- glycoproteins
- proteoglycans

Specific composition and properties is dependent on the tissue type

(connective × ligament × cartilage × bone)

GENERAL CLASSIFICATION OF CONNECTIVE TISSUE



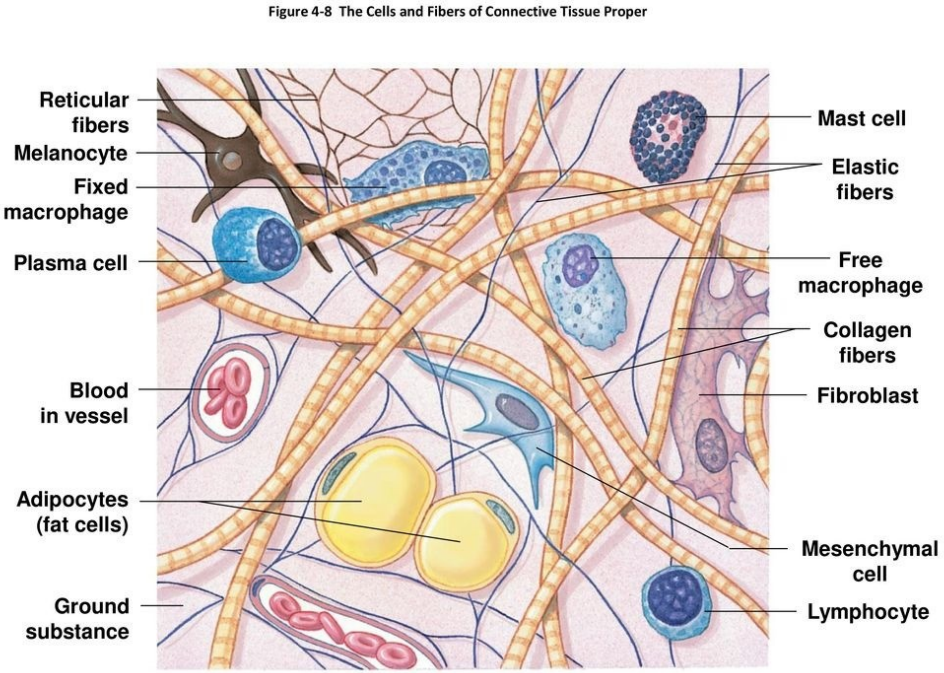
Cells of c.t. proper

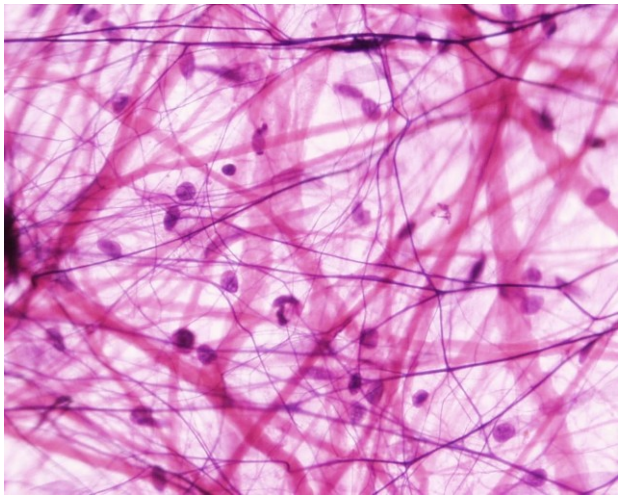
Permanent

- Fibroblasts/fibrocytes/myofibroblasts
- Adipocytes
- Adult stem cells

Transiet (migratory)

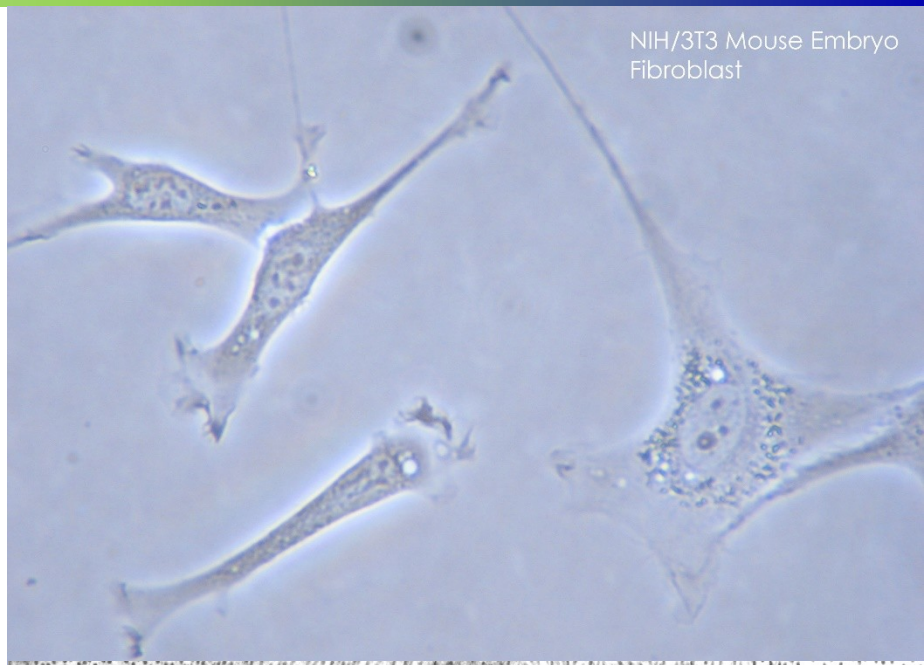
- Macrophages of c.t. /histiocytes)
- Mast cells
- Plasma cells
- Lymphocytes, granulocytes
- …

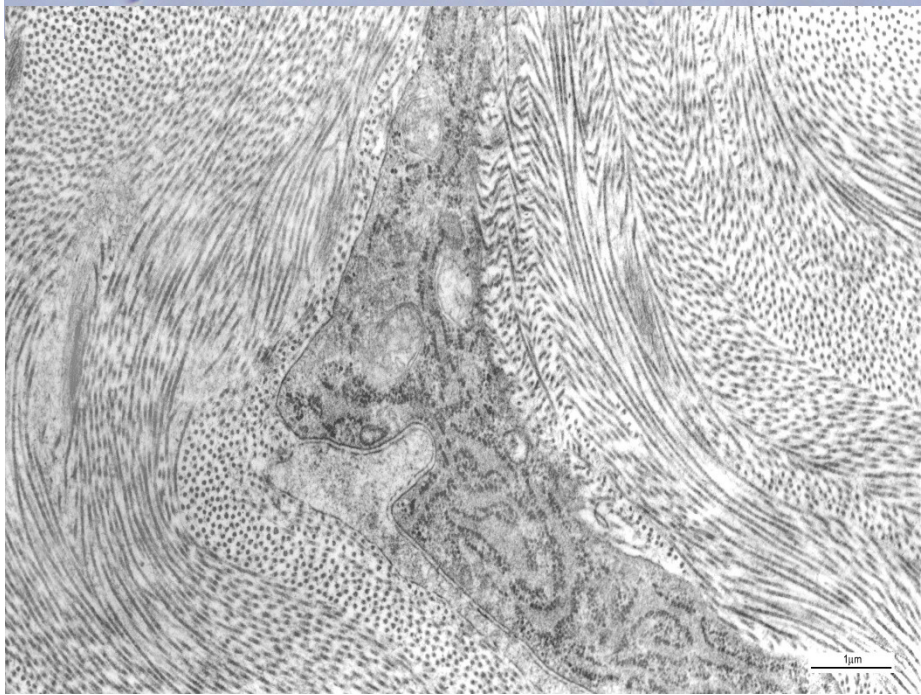




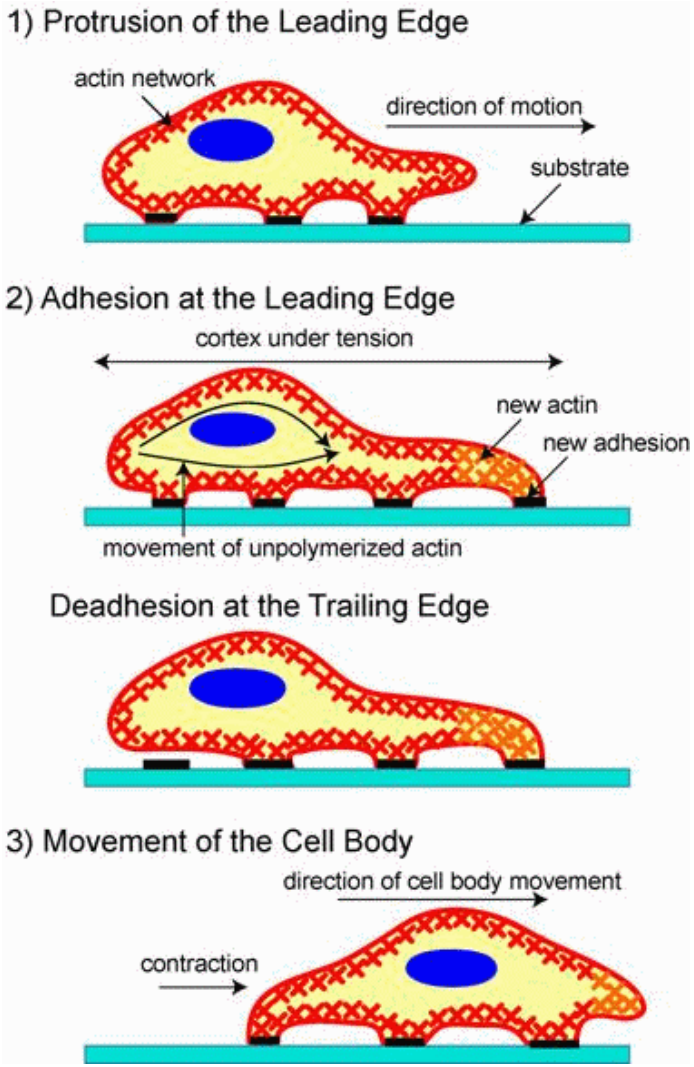
Fibroblasts

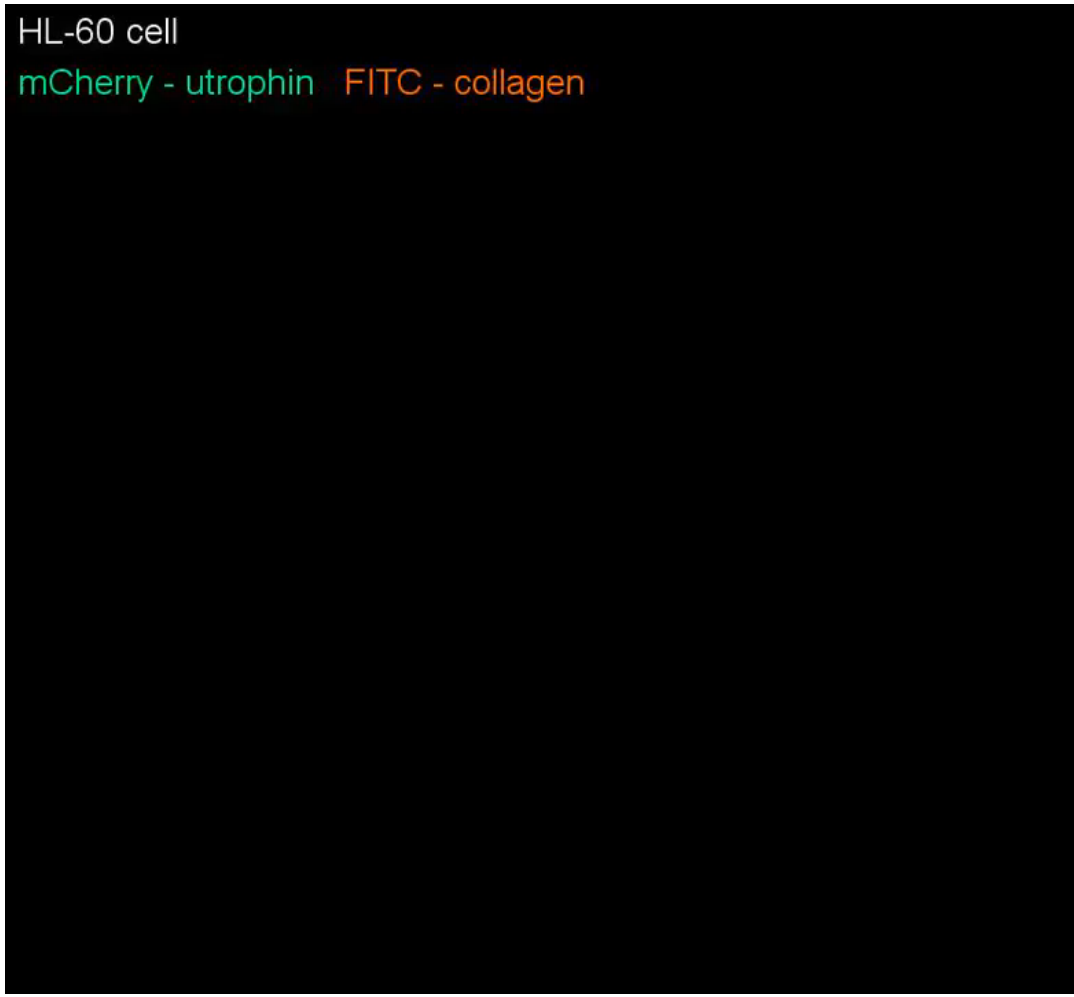
- Principal c.t. cells
- ECM producers
- Originate from mesenchyme and resides in the c.t. permanently
- Lack typical epithelial polarity
- Migration
- Fibrocyte ↔ fibroblast
- Myofibroblasts
- Different tissues contain fibroblasts with different biological properties



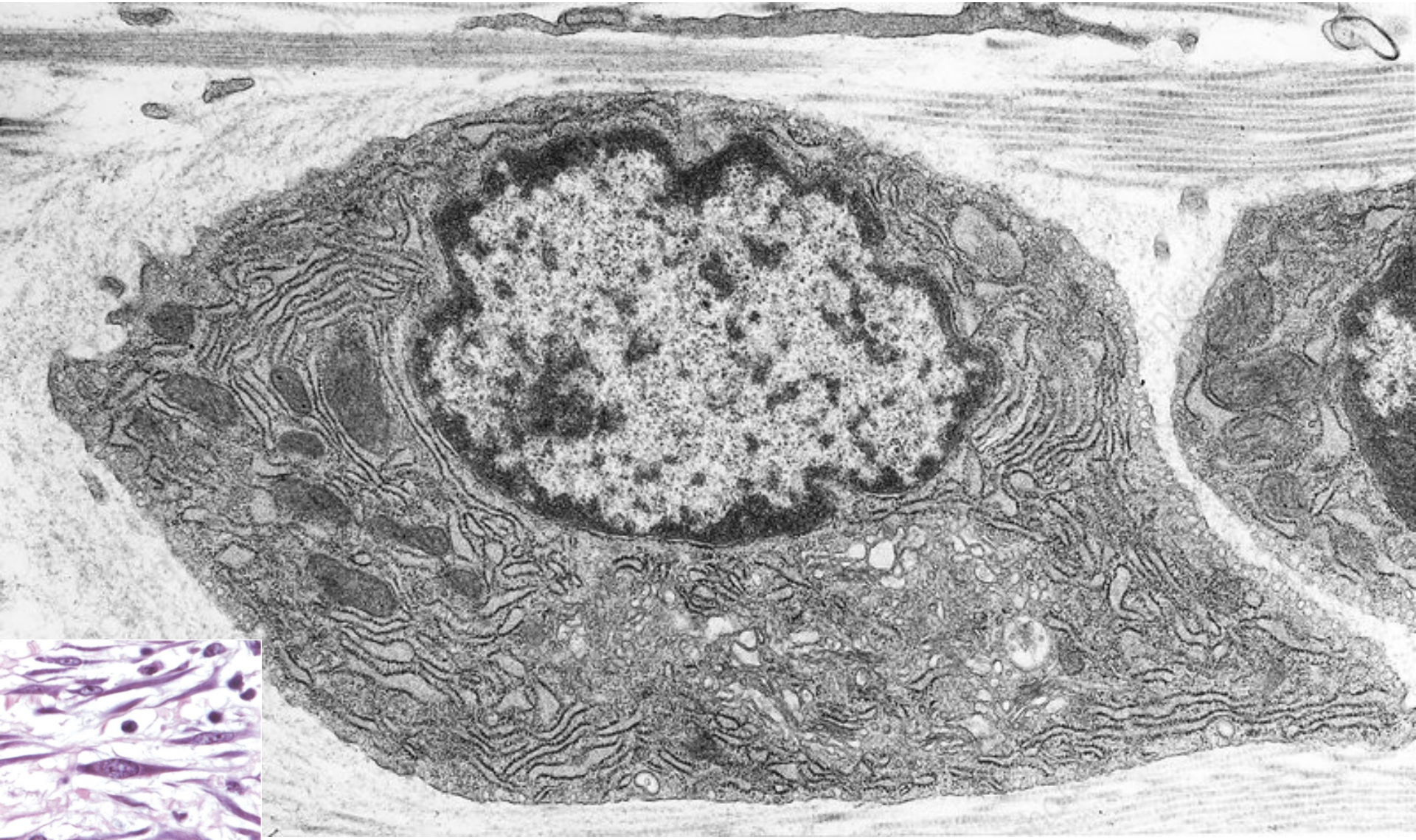


Migration of fibroblasts





CELLS OF CONNECTIVE TISSUE PROPER

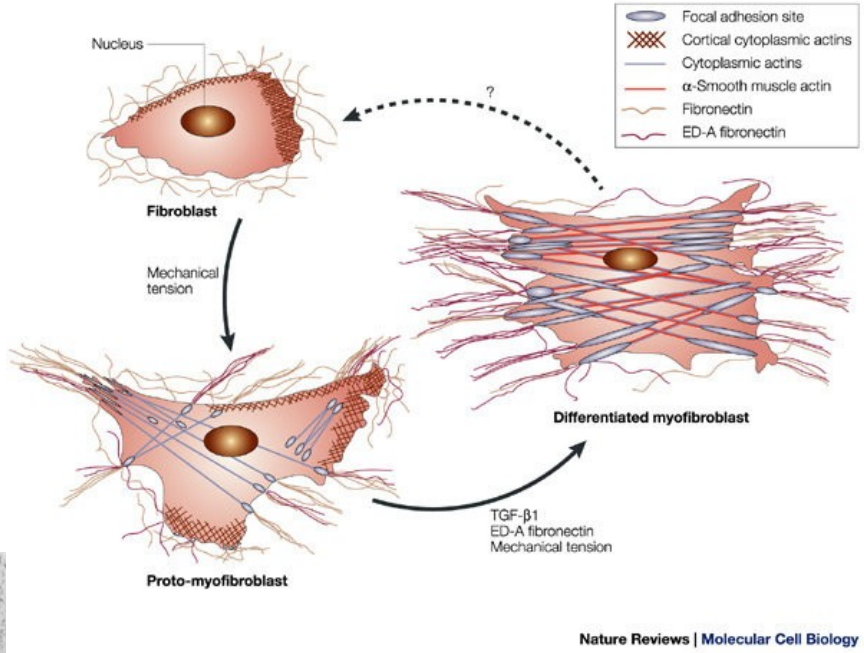


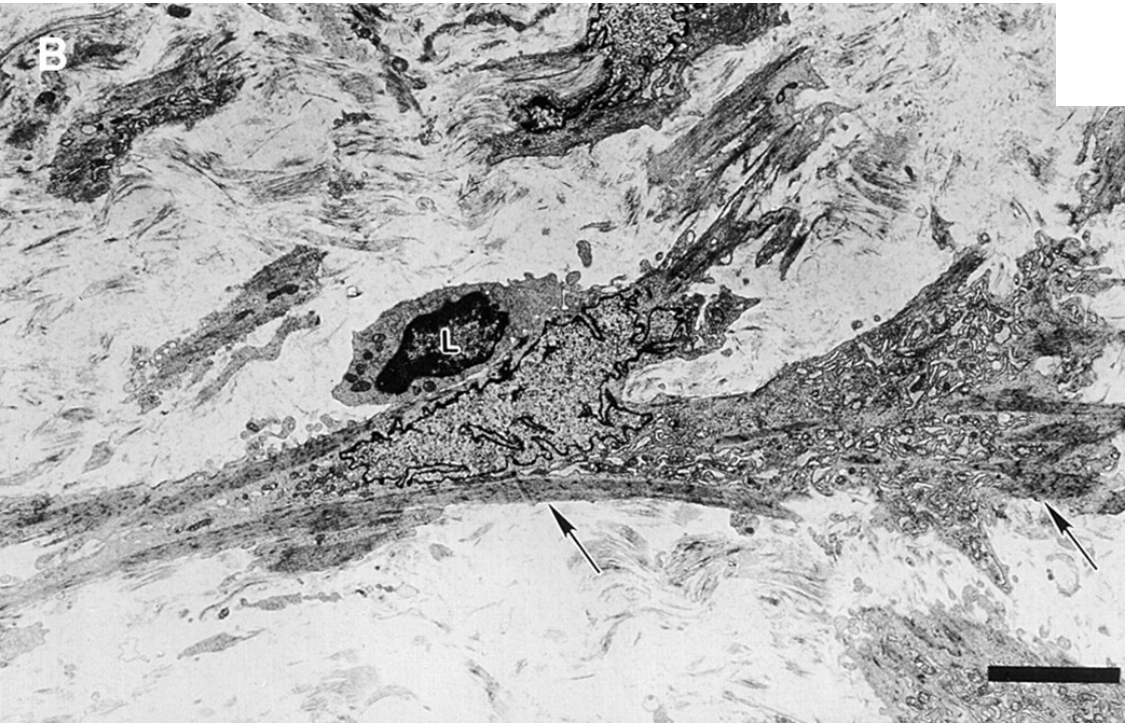
https://www.sciencephoto.com/media/1232046/view/fibroblast-tem

DOI: 10.1038/nrm809

Myofibroblasts

- Features of fibroblasts and smooth muscle cells
- Contractile cellular structures composed of actin microfilaments and myosin
- Wound closure and healing

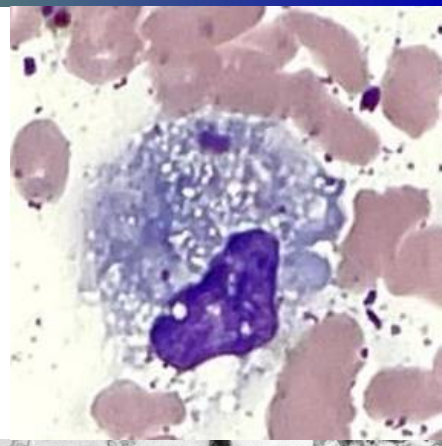


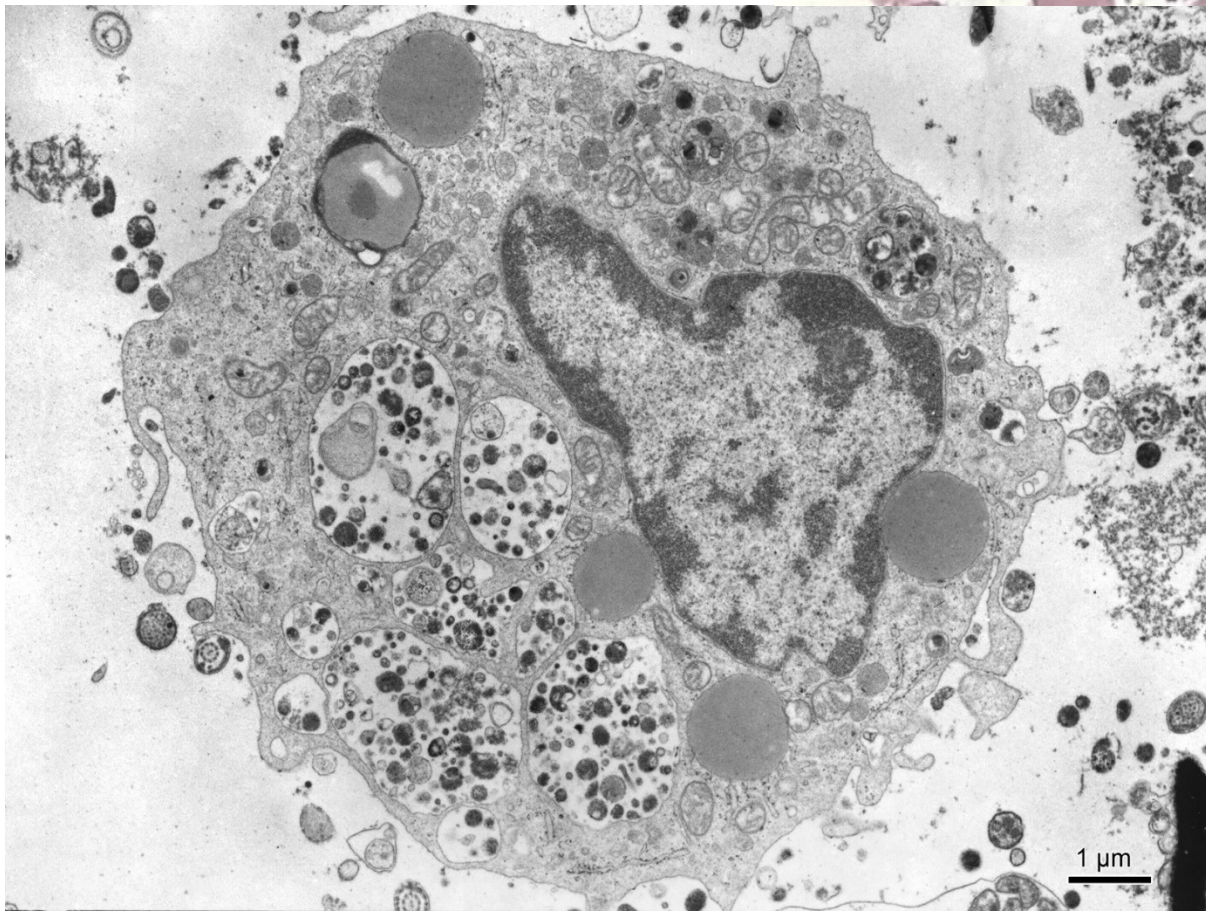


10.1164/ajrccm.161.5.9903102

Macrophages

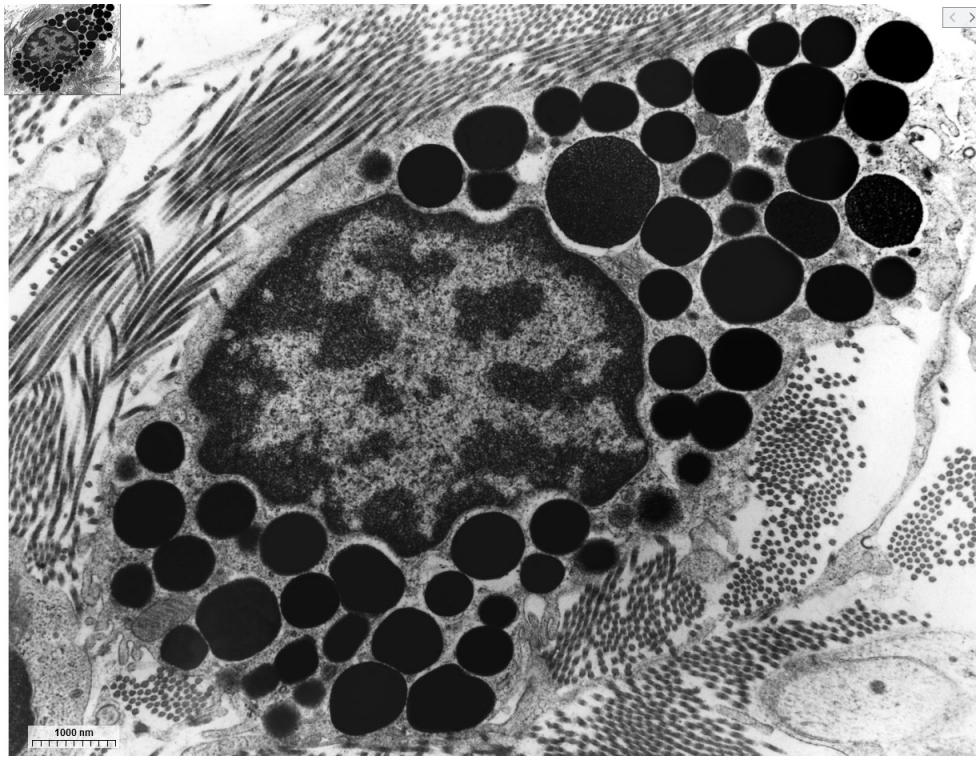
- Histiocytes
- Derived from circulating monocytes (monocyte-macrophage mononuclear system)
- Phagocytosis
- Immunomodulation





Mast cells

- Large, oval, 20-30μm
- Similar to other leukocytes with granules, but it is tissue resident
- Granules
  - heparin
  - histamine
  - serine proteases (inflammation regulators)
  - eosinophil and neutrophil chemoattractants
  - leukotriens
- Perivascular and mucosal mast cells



T. Clark Brelje and Robert L. Sorenson, Minneapolis, Minnesota, USA.

- Mediators of immediate hypersensitivity reaction

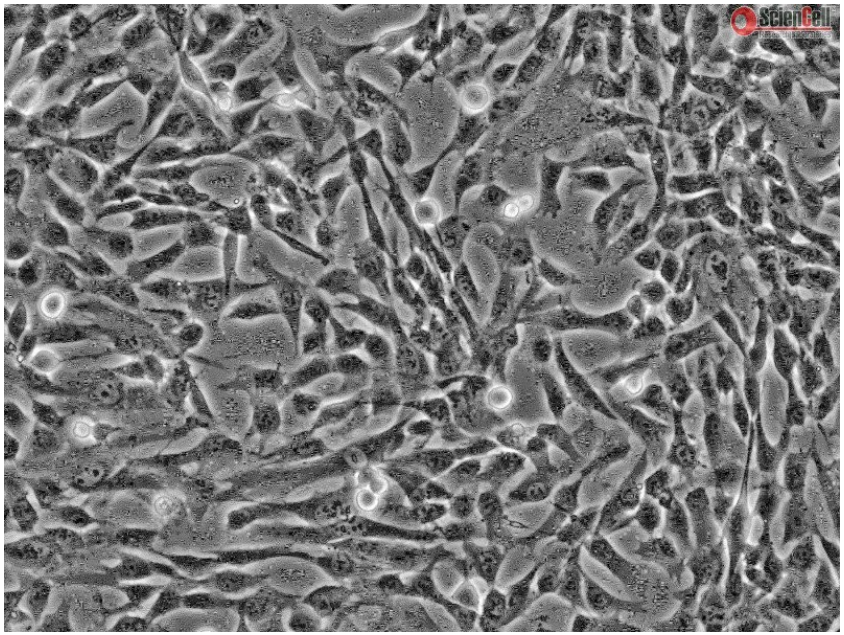
Plasma cells

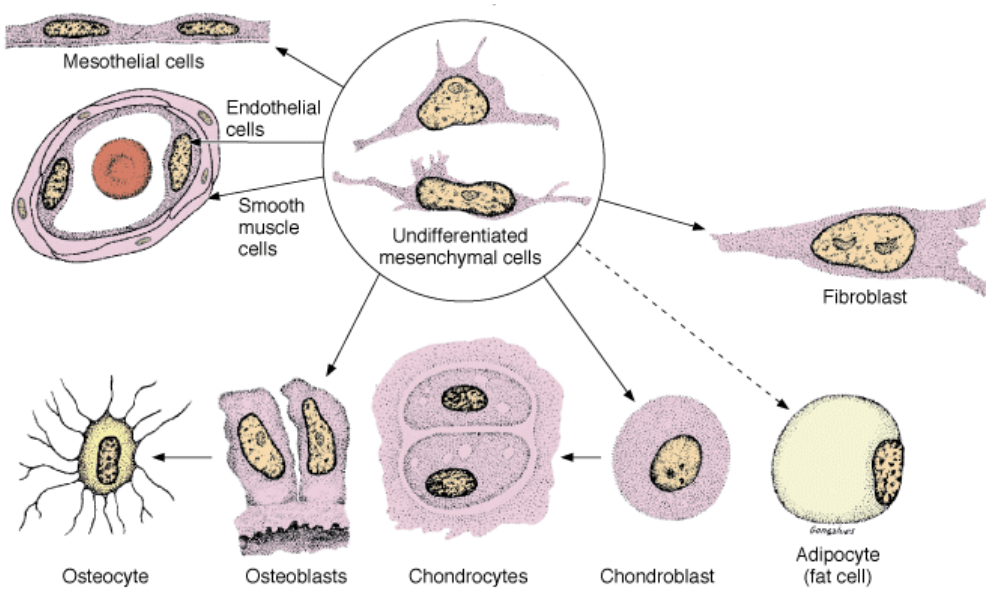
- Large, ovoid cells
- derived from B-lymphocytes
- Basophilic cytoplasm – RER
- Clockface nucleus (alternating heterochromatin and euchromatin)
- Produce antibodies (immunoglobulins)
- Short lifespan (10-20 days)

https://www1.udel.edu/biology/Wags/histopage/histopage.htm

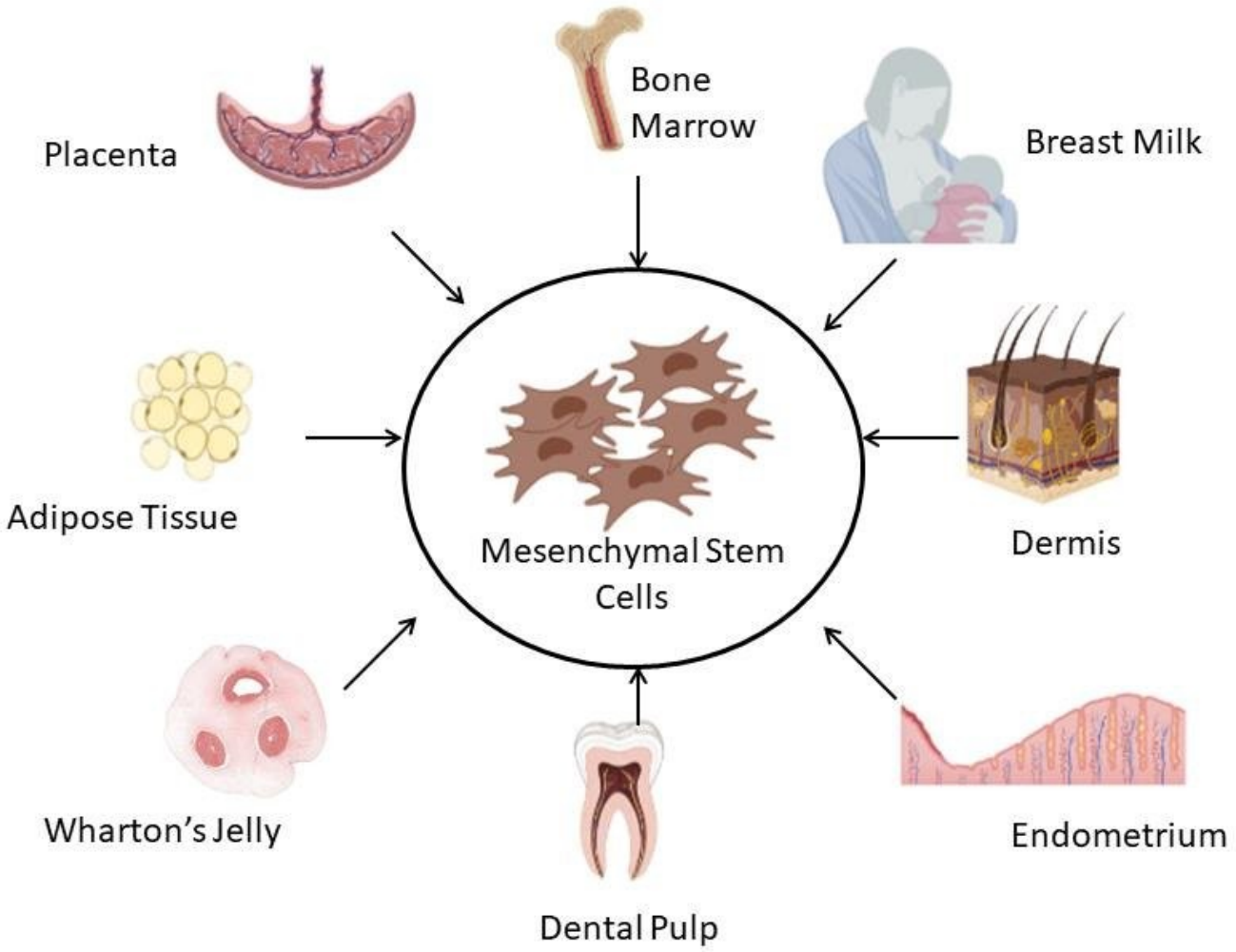
Mesenchymal stem (stromal) cells

- Mesenchymal origin
- Adult tissues
- Differentiate to many cells of CT



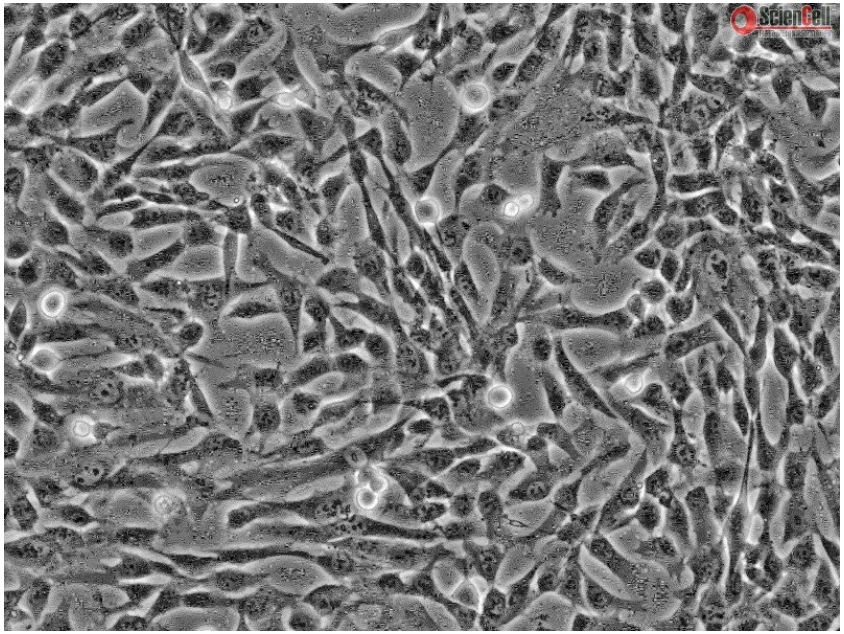


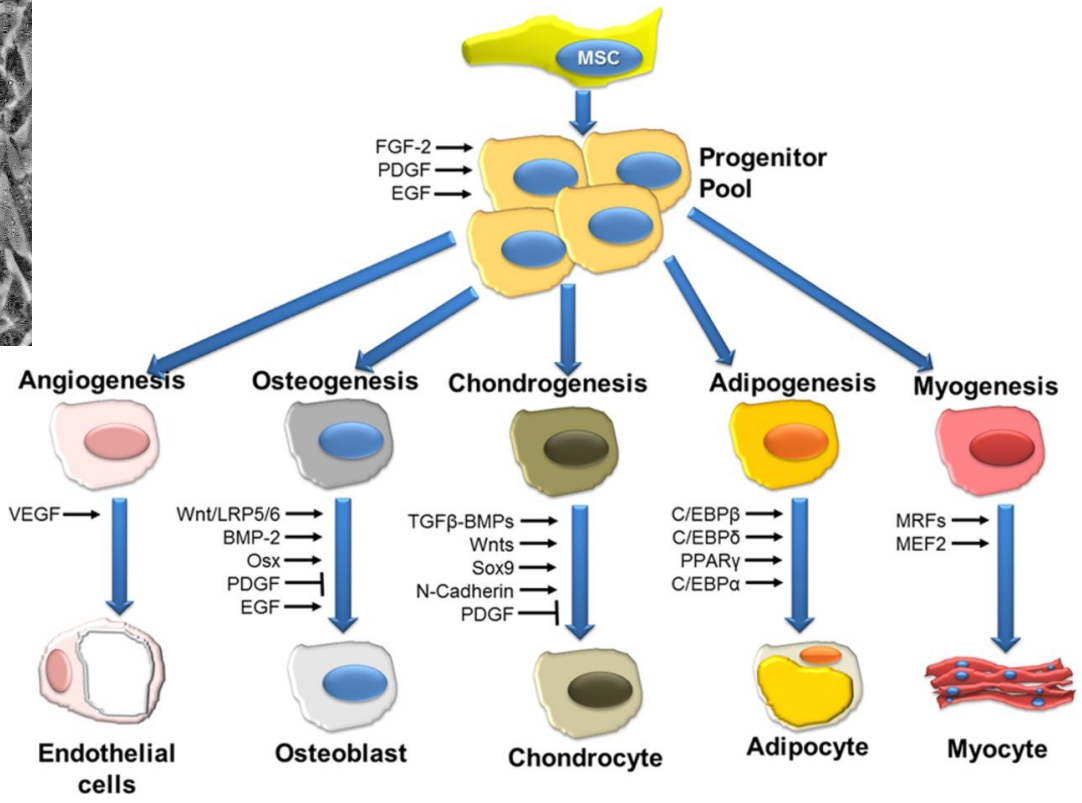
Mesenchymal stem (stromal) cells



- **Mesenchymal stem cells are different in different tissues**

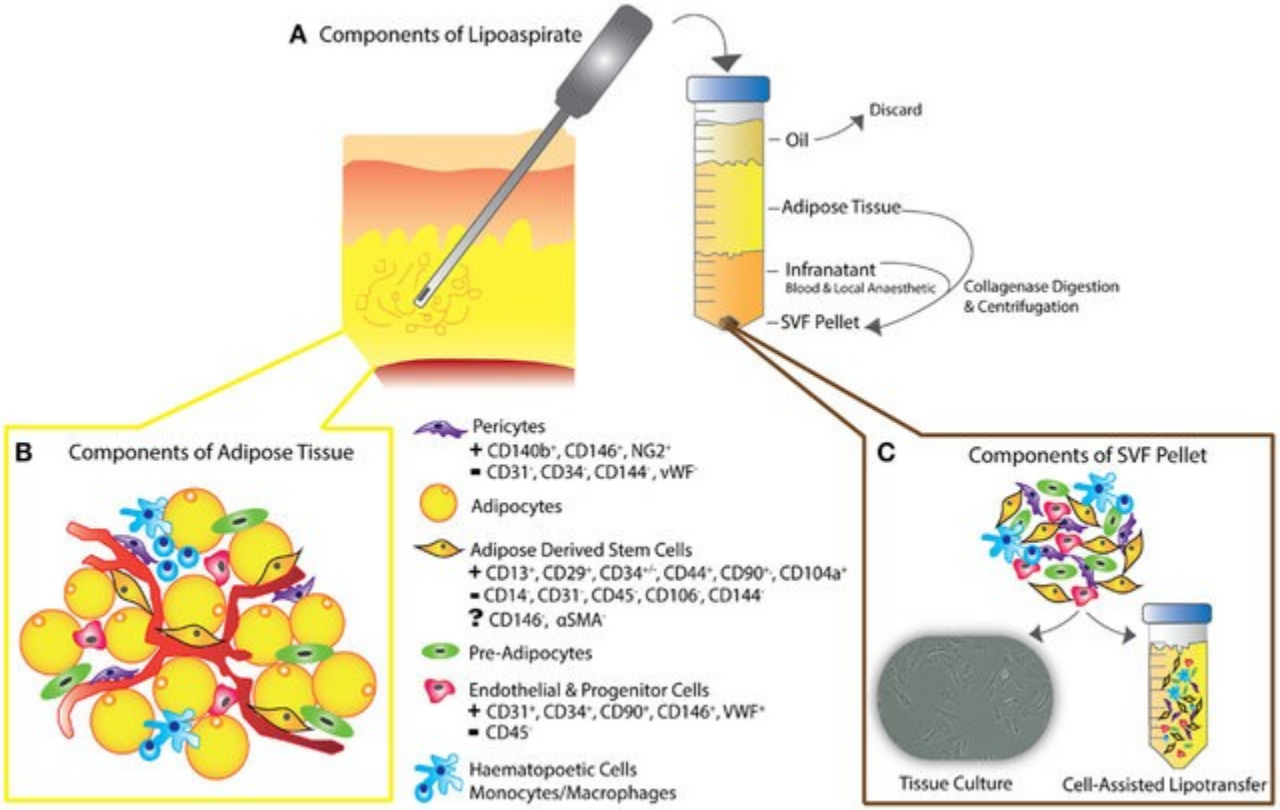
Mesenchymal stem (stromal) cells





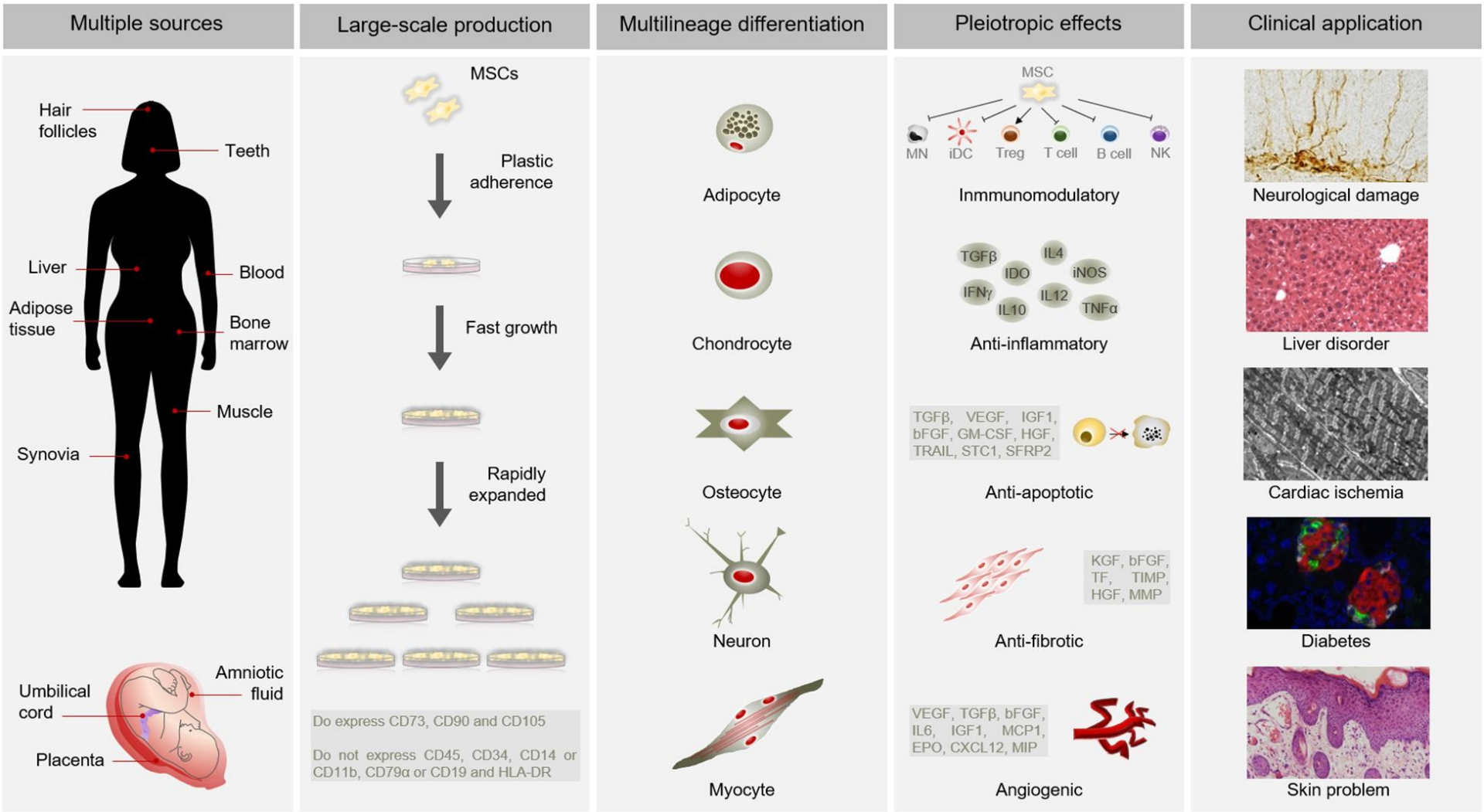
- Mesenchymal stem cells are important tools for tissue engineering and understanding tissue biology

MESENCHYMAL STEM CELLS – CLINICAL CONTEXT



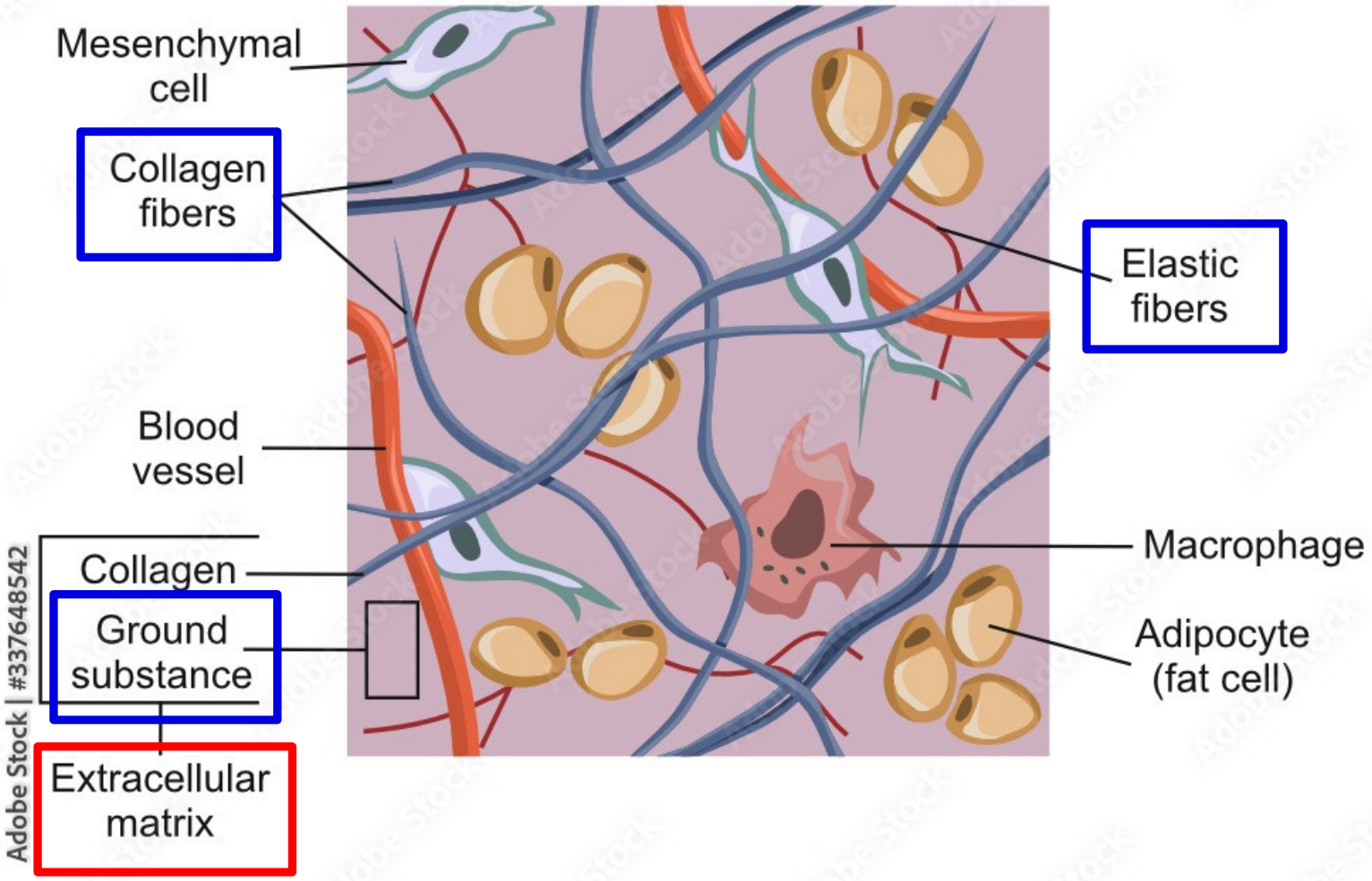
DOI: 10.3389/fsurg.2015.00001

POTENTIAL APPLICATIONS OF MESENCHYMAL STEM CELLS



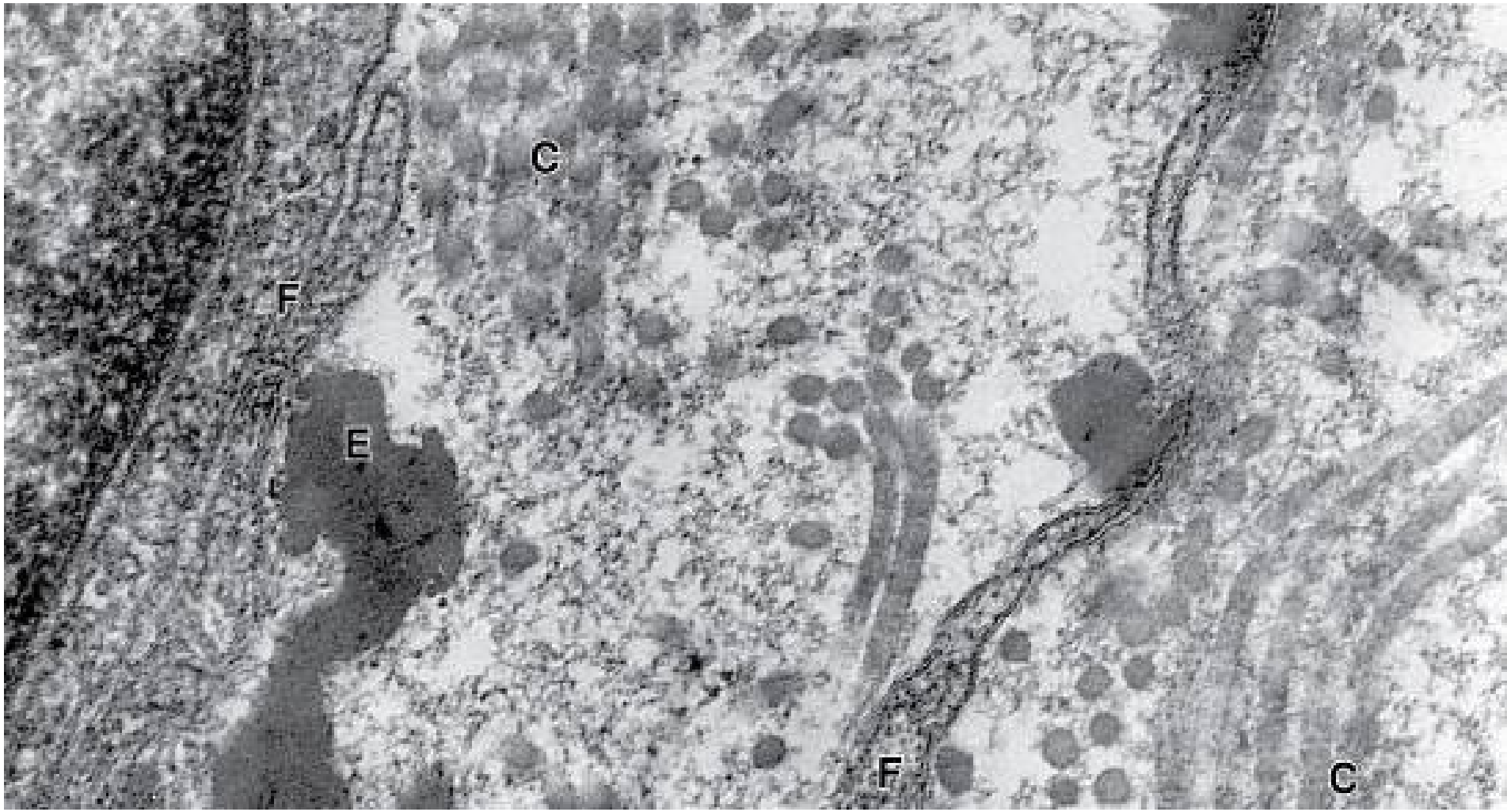
https://doi.org/10.3389/fbioe.2020.00043

ECM = fibers + ground substance



ECM OF CONNECTIVE TISSUE PROPER

Composition of ECM determines biochemical and biophysical properties of c.t.



ECM of connective tissue is produced by fibroblasts (or chondrocytes, osteoblasts).
However, specific ECM can be produced by virtually any cell of our body (eg. epithelial and muscle cells producing basal lamina).

Extracellular matrix

Fibrous component

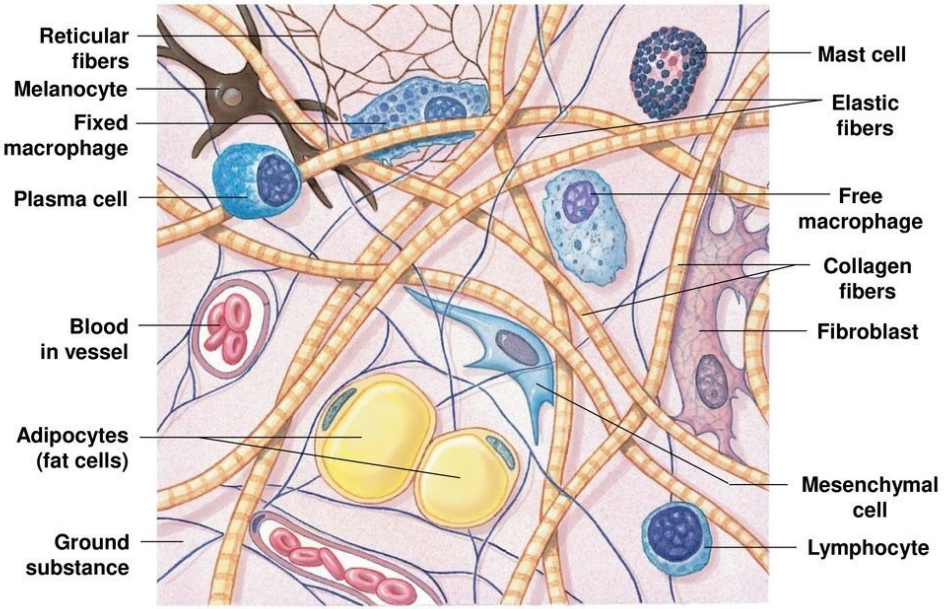
- Collagen fibers (e.g. col. I, II)
- Reticular
- Elastic

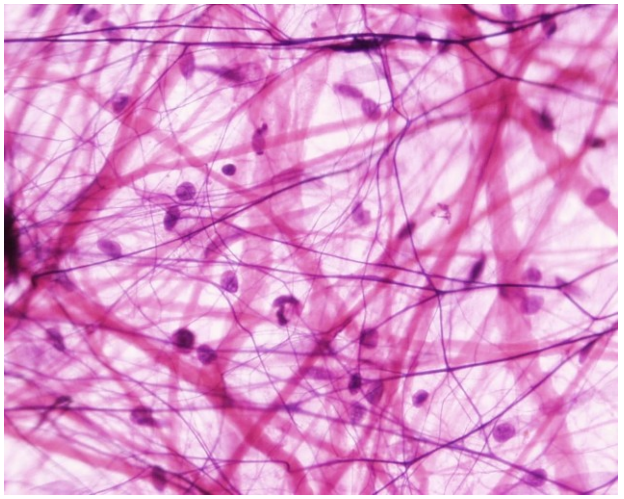
Amorphous component (ground substance)

Complex matrix consisting of

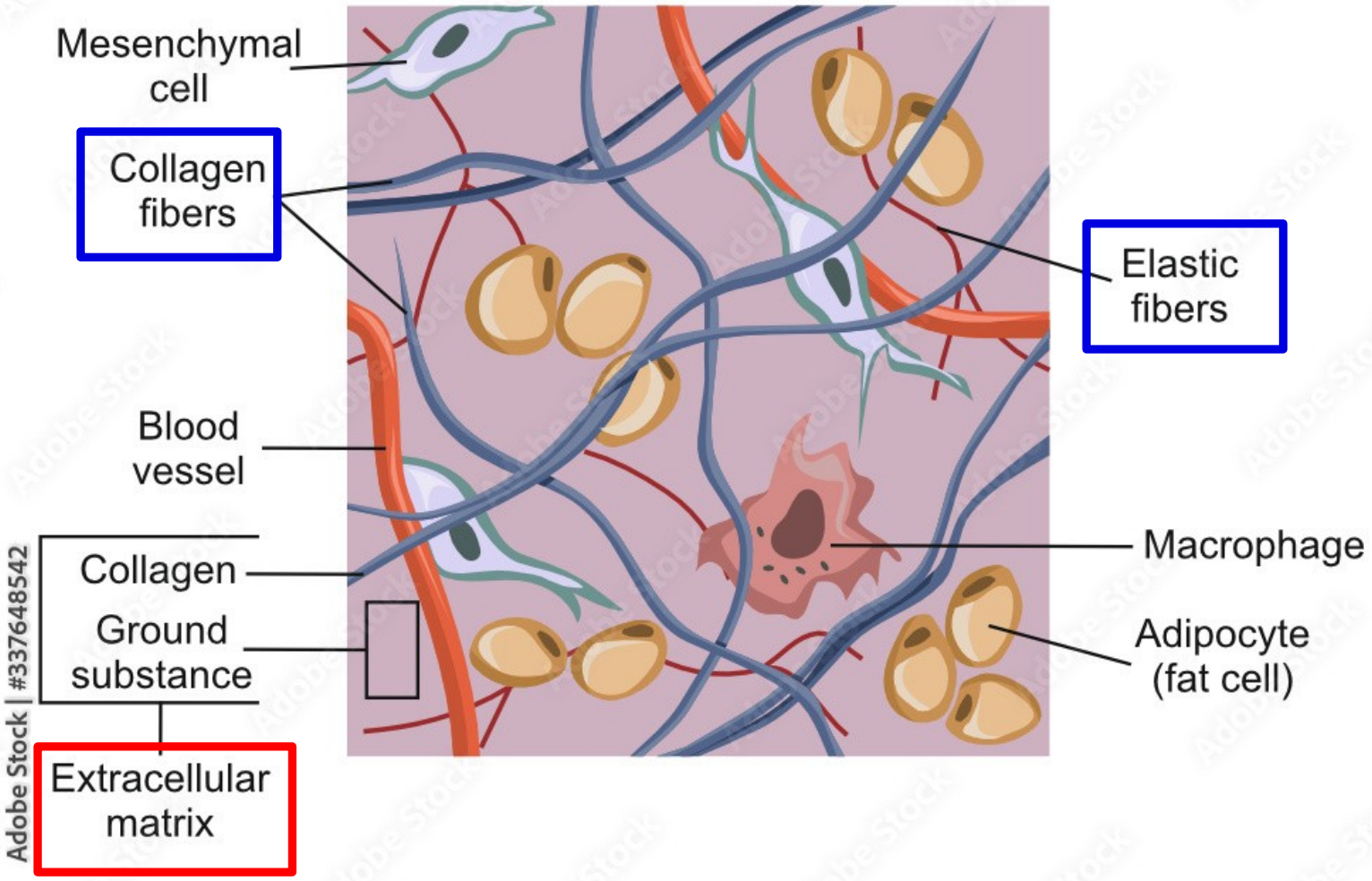
- Glycosaminoglycans
- Glycoproteins
- Proteoglycans

Figure 4-8 The Cells and Fibers of Connective Tissue Proper



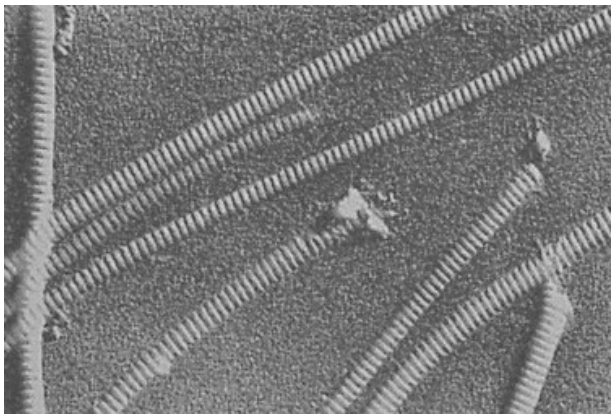


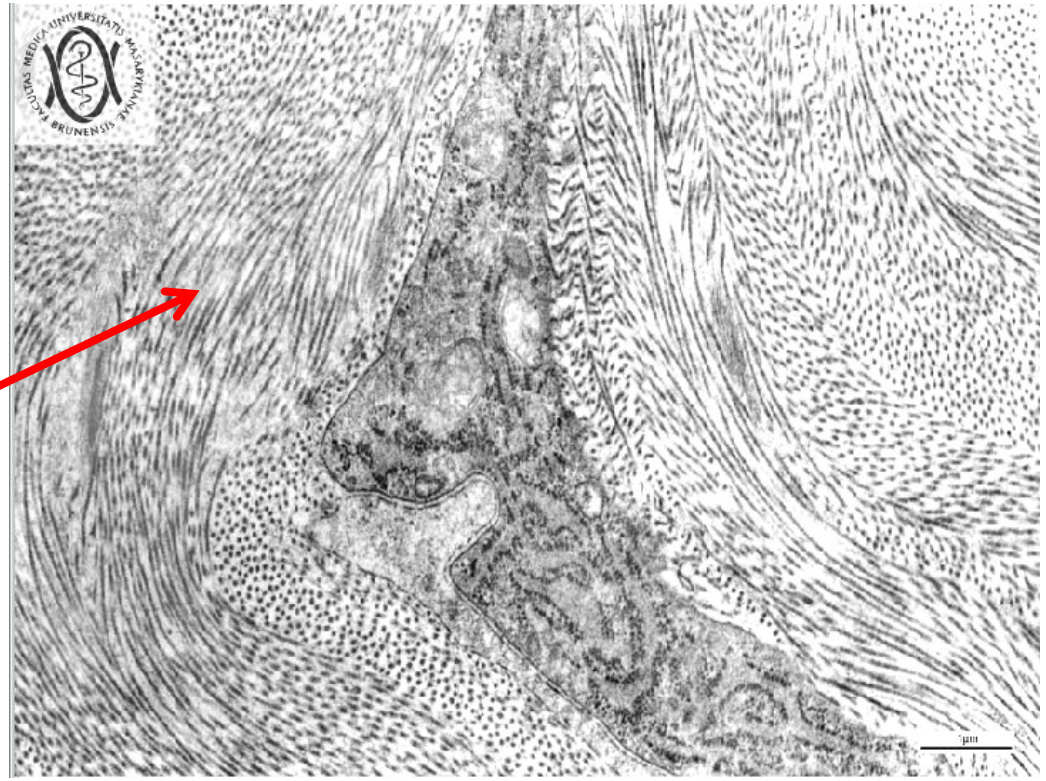
Fibers


Mesenchymal cell
Collagen fibers
Elastic fibers
Blood vessel
Collagen
Ground substance
Macrophage
Adipocyte (fat cell)
Extracellular matrix
Adobe Stock | #337648542

Collagen fibers

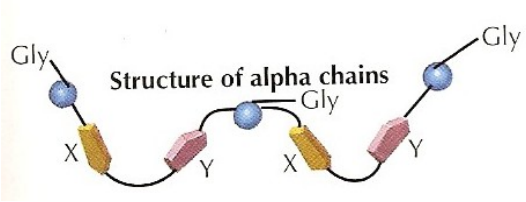
- family of fibrous proteins encoded by >35 genes
- polymer – subunit = procollagen and tropocollagen; triple helix
- different structural and mechanical properties (strength, elasticity, pliability…)
- most abundant protein in human body (30% dry weight)





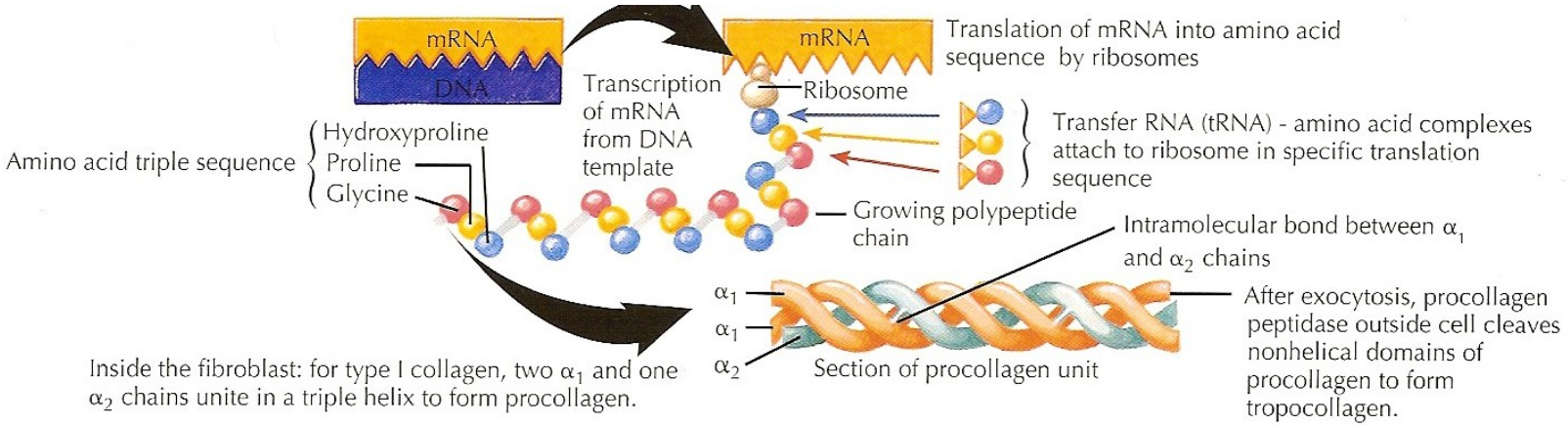
Collagen synthesis

- Polyribosomes bind to RER and synthetize peptide chains α1 a α2 (~250 AA, 28kDa)



- In RER peptide chains are modified (hydroxylation of proline and lysine – co-factor vitamin C)

Chains assemble into triple helix - **procollagen**



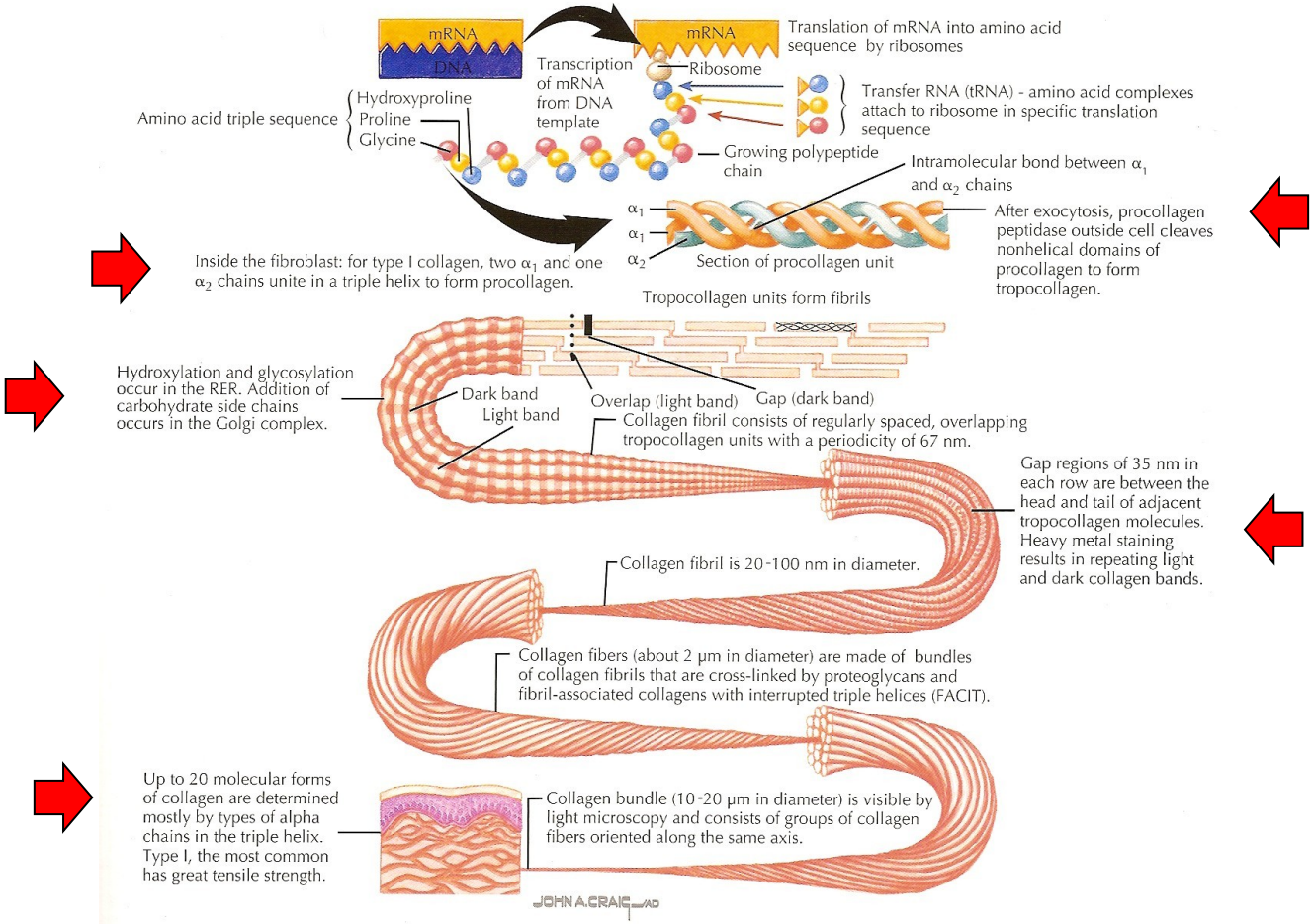
- In GA, procollagen is further modified and secreted from cells

Collagen synthesis

Procollagen is then modified to **tropocollagen** (by procollagenpeptidase)

Tropocollagen is organized to higher fibrillar structures in ECM (fibrils, fibers)

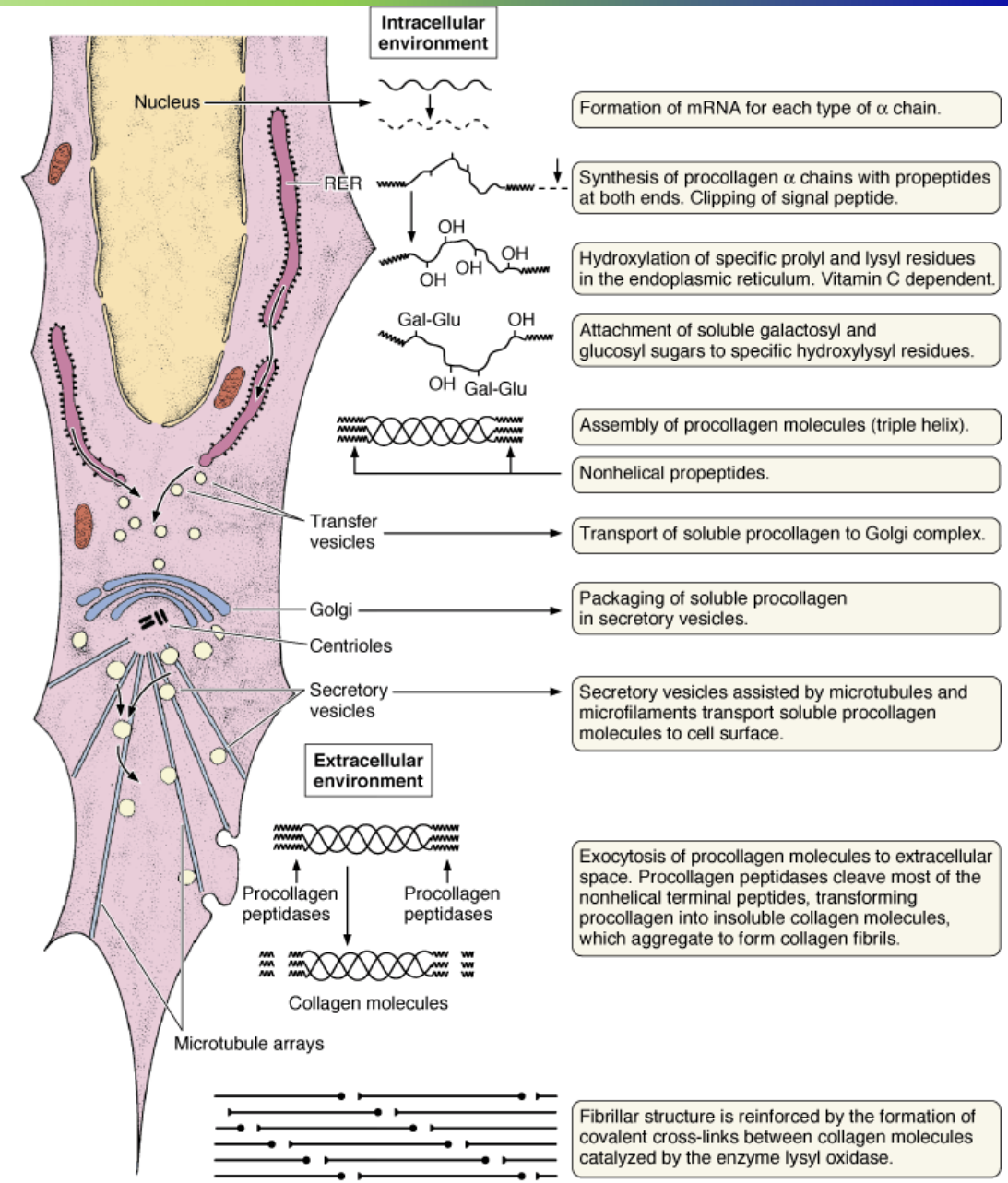
Individual collagen molecules are connected (lysyloxidases)



further study: **https://www.ncbi.nlm.nih.gov/books/NBK507709/**

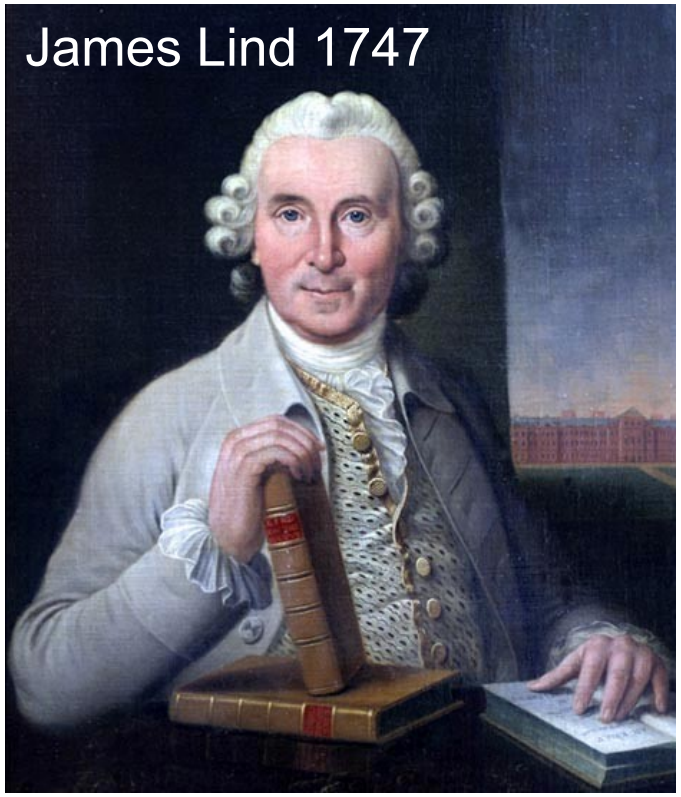
EXTRACELLULAR MATRIX – FIBROUS COMPONENT

Collagen synthesis

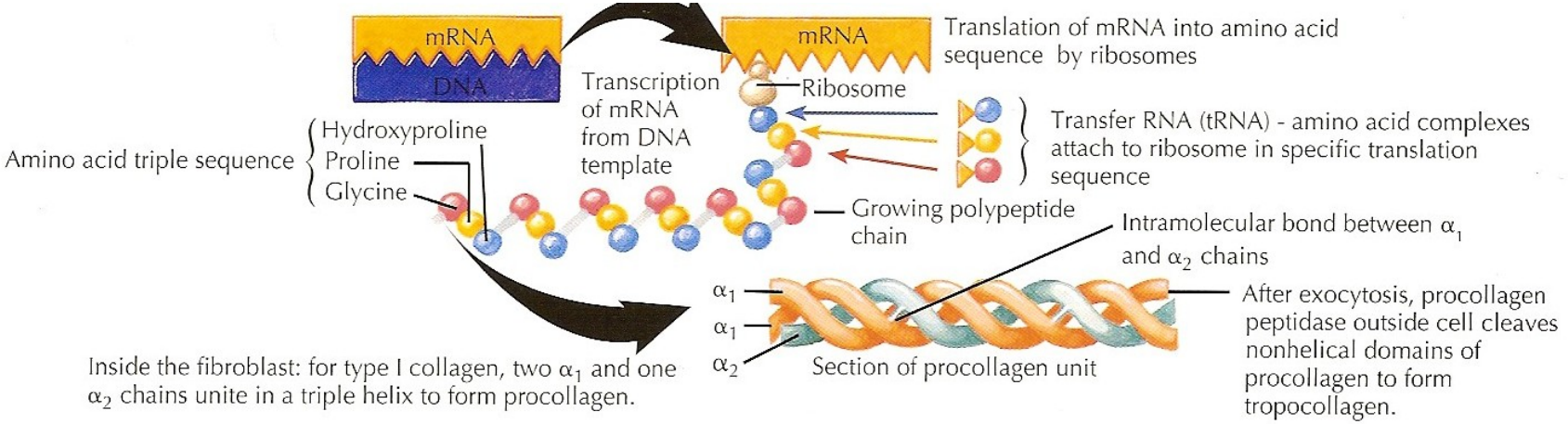


Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

CLINICAL CONTEXT



Autor: BIOPHOTO ASSOCIATES/SCIENCE PHOTO LIBRARY



COLLAGEN FAMILY

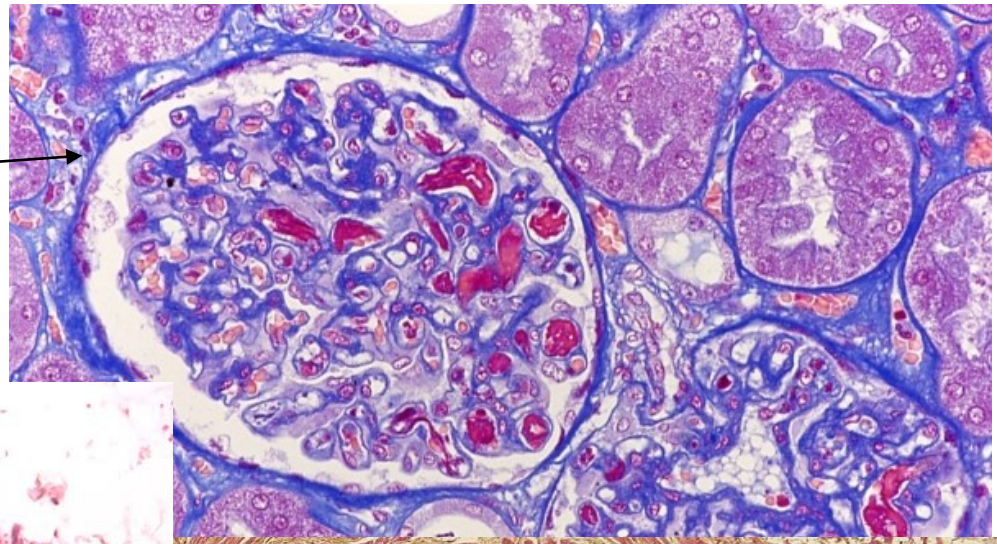
Type	Localization	Structure	Main function
I	Bone, tendons, meniscus, dentin, dermis, capsules of organs, loose CT 90% of type I	Fibrils (75nm) – fibers (1-20μm)	Resilience in pull
II	Hyaline and elastic cartilage	Fibrils (20nm)	Resilience in pressure
III	Skin, veins, smooth muscles, uterus, liver, spleen, kidney, lung	Like I, high content of proteoglycans and glycoprotiens, reticular network	Shape formation
IV	Basal lamina of epithelium and endtohelium, basal membranes	No fibrils or fibers	Mechanical support
V	Lamina of muscle cells and adipocytes, fetal membranes	Like IV	
VI	Interstitial tissue, chondrocytes – adhesion		Connecting dermis and epidermis
VII	Basal membrane of epithelium		
VIII	Some endothelia (Cornea)		
IX, X	Growth plate, hypertrophic and mineralized cartilage		Growth of bones, mineralization

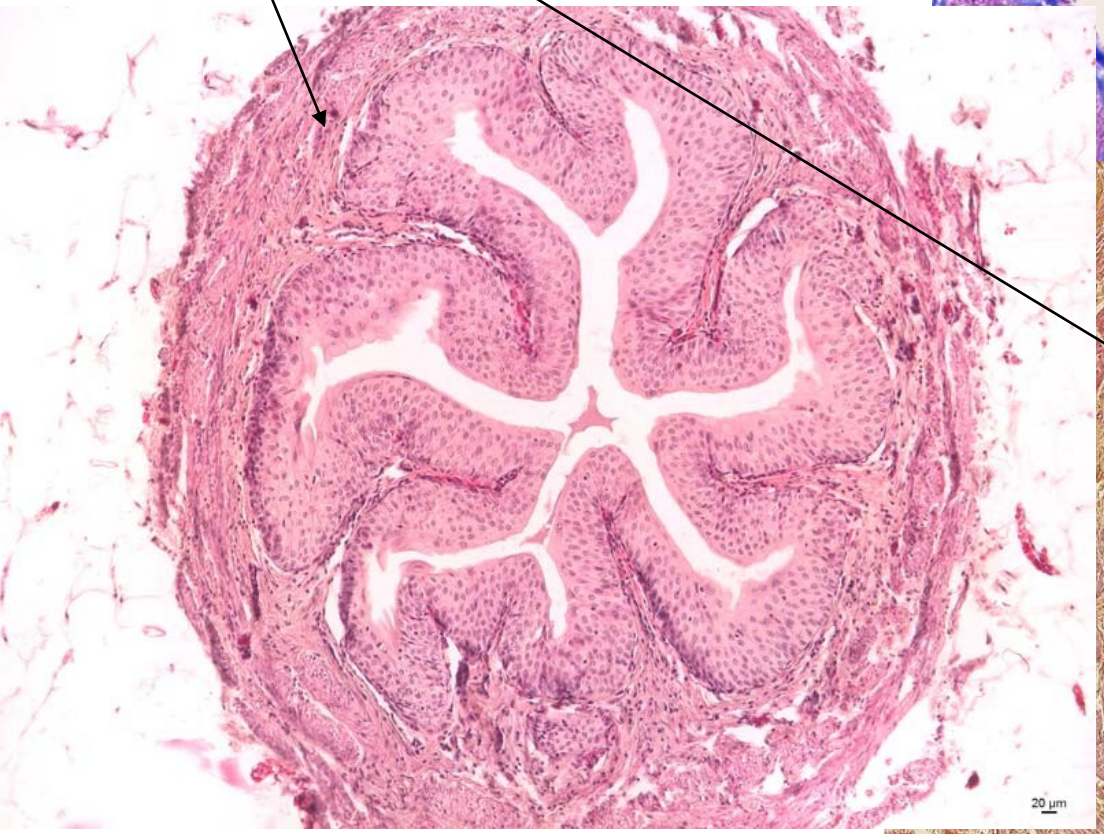
COLLAGEN IN LIGHT MICROSCOPE

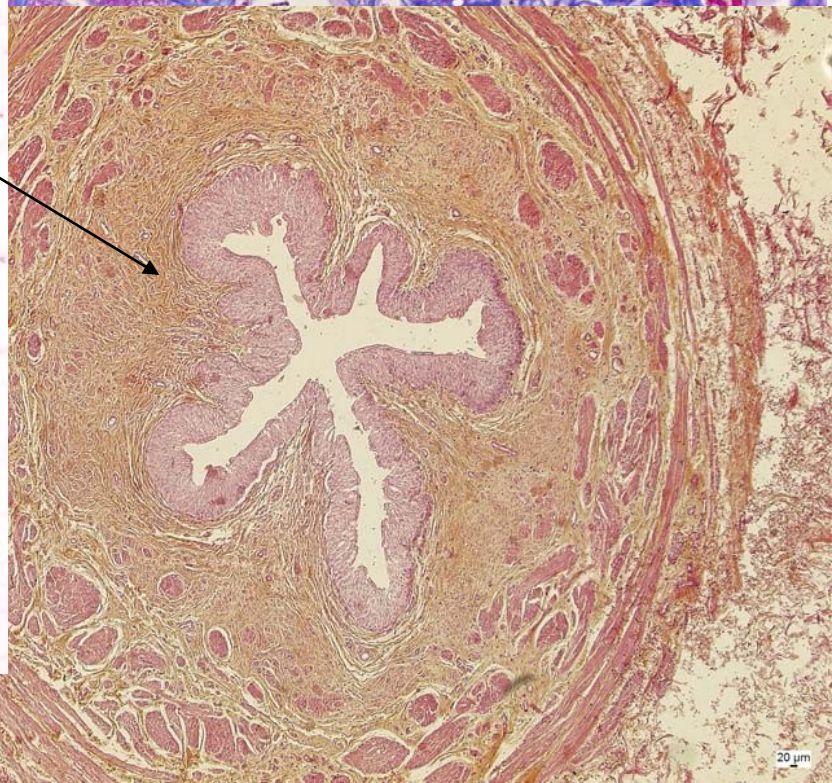
AZAN

HE

HES







COLLAGEN IN ART

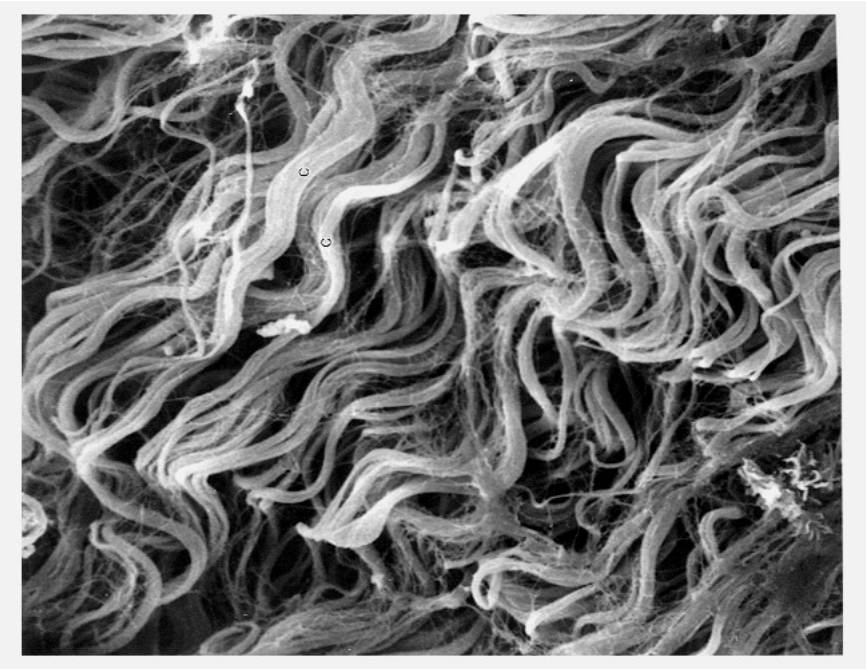
Julian Voss-Andreae
"Unraveling Collagen"

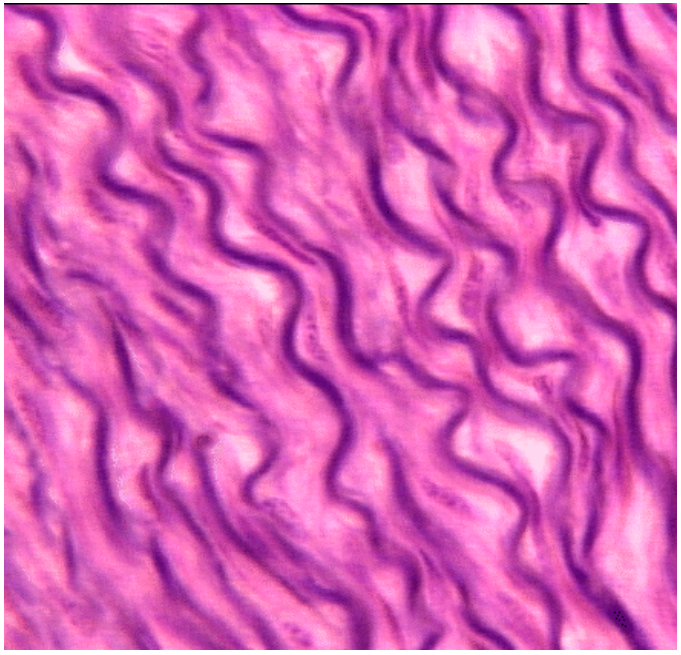
2005

Orange Memorial Park
Sculpture Garden, City of
South San Francisco, CA

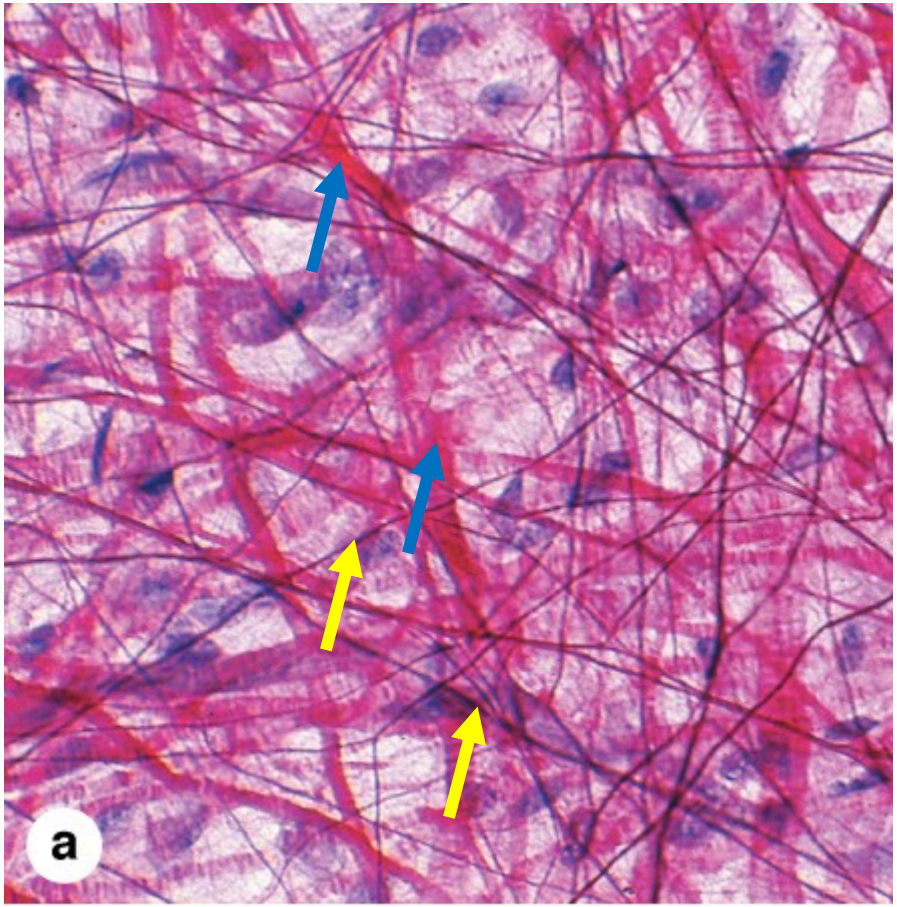
Elastic fibers

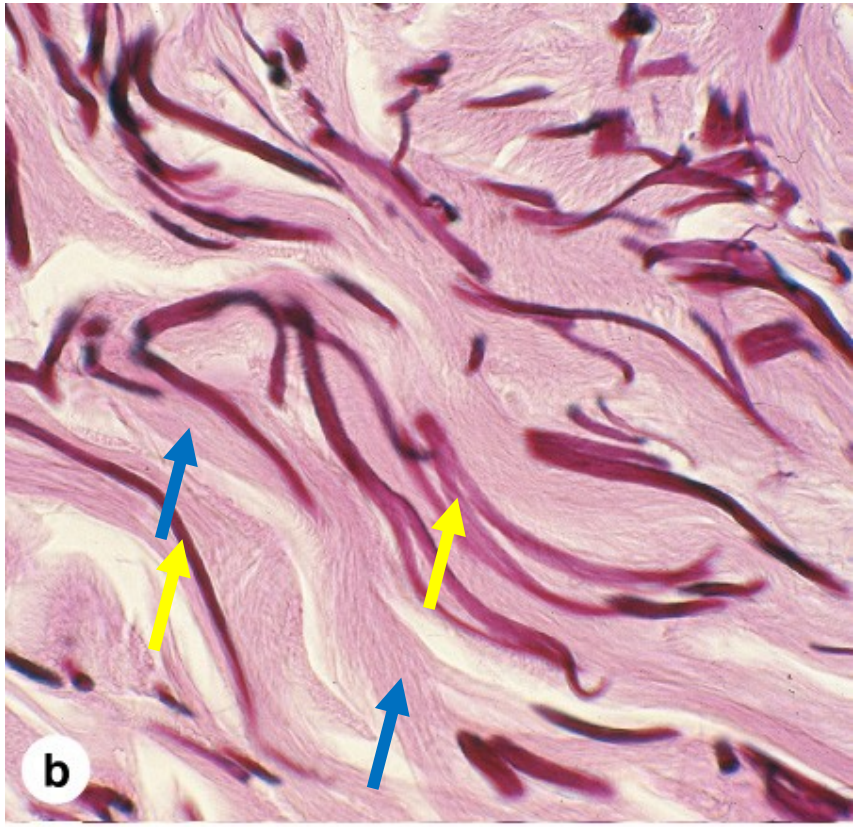
- less abundant than collagen
- polymer – **tropoelastin**
- minimal tensile resistance, loss of elasticity if overstretched
- reduction of hysteresis = allow return back to original state after mechanic change
- staining – orcein, aldehyde fuchsin





Elastic fibers

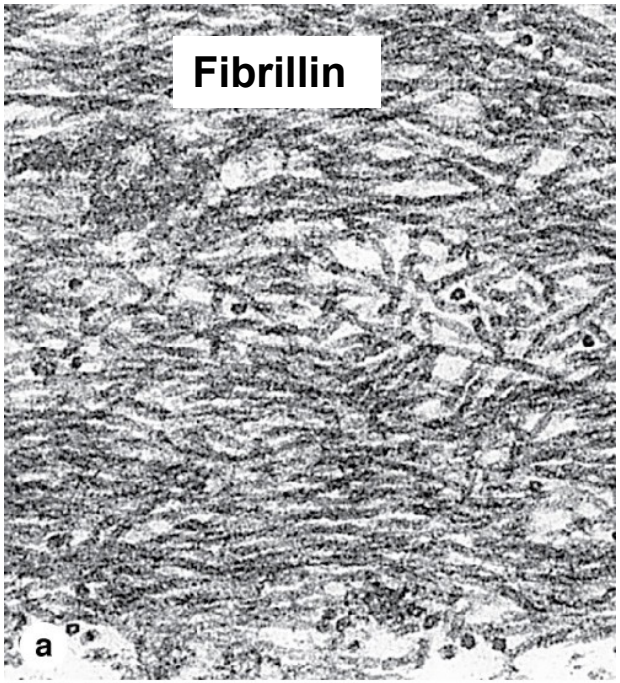


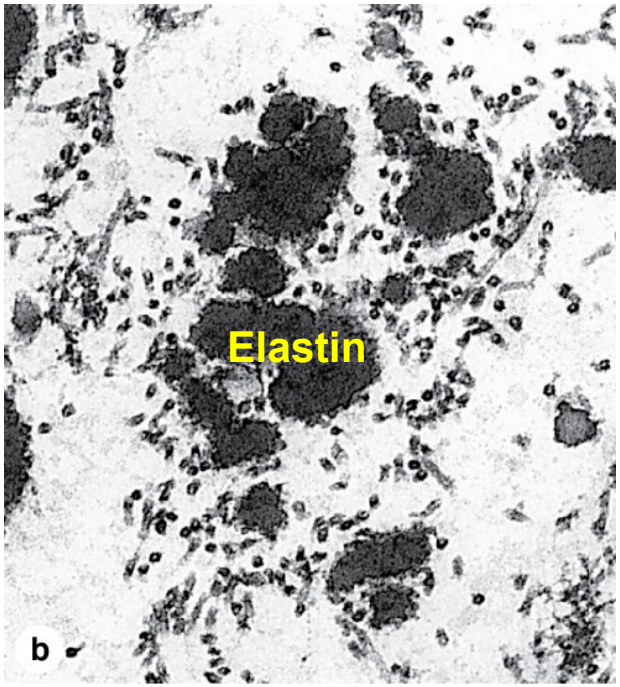


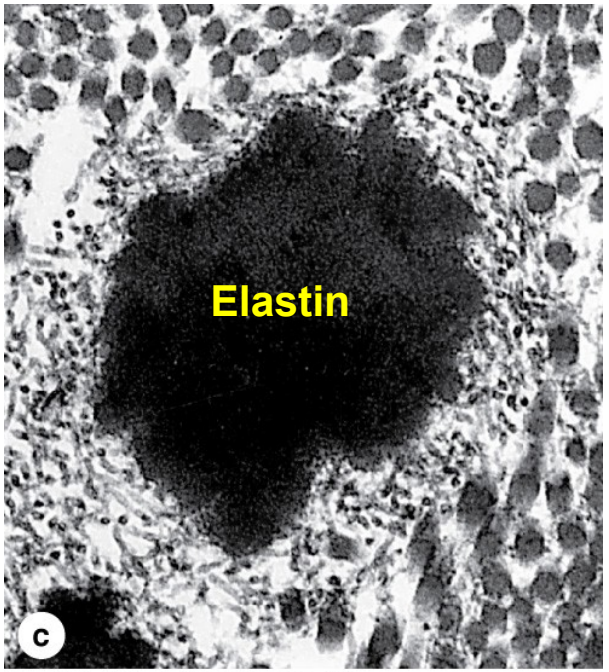
Elastin

Collagen

Elastic fibers



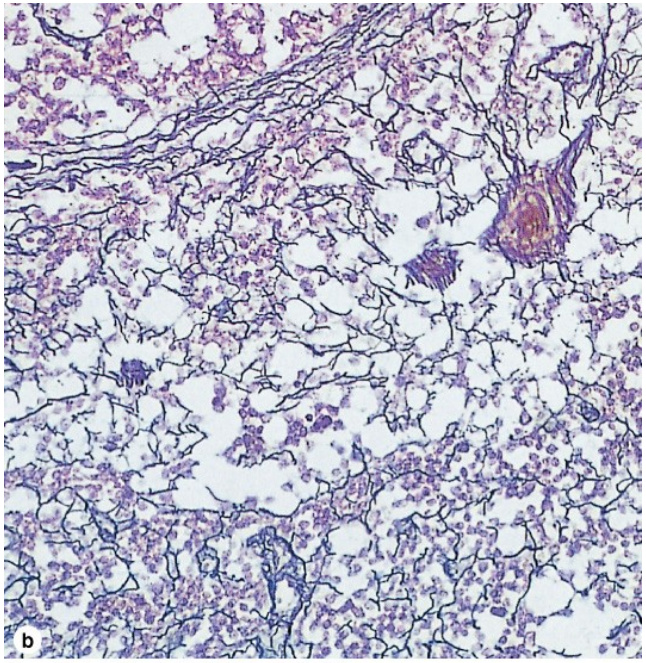




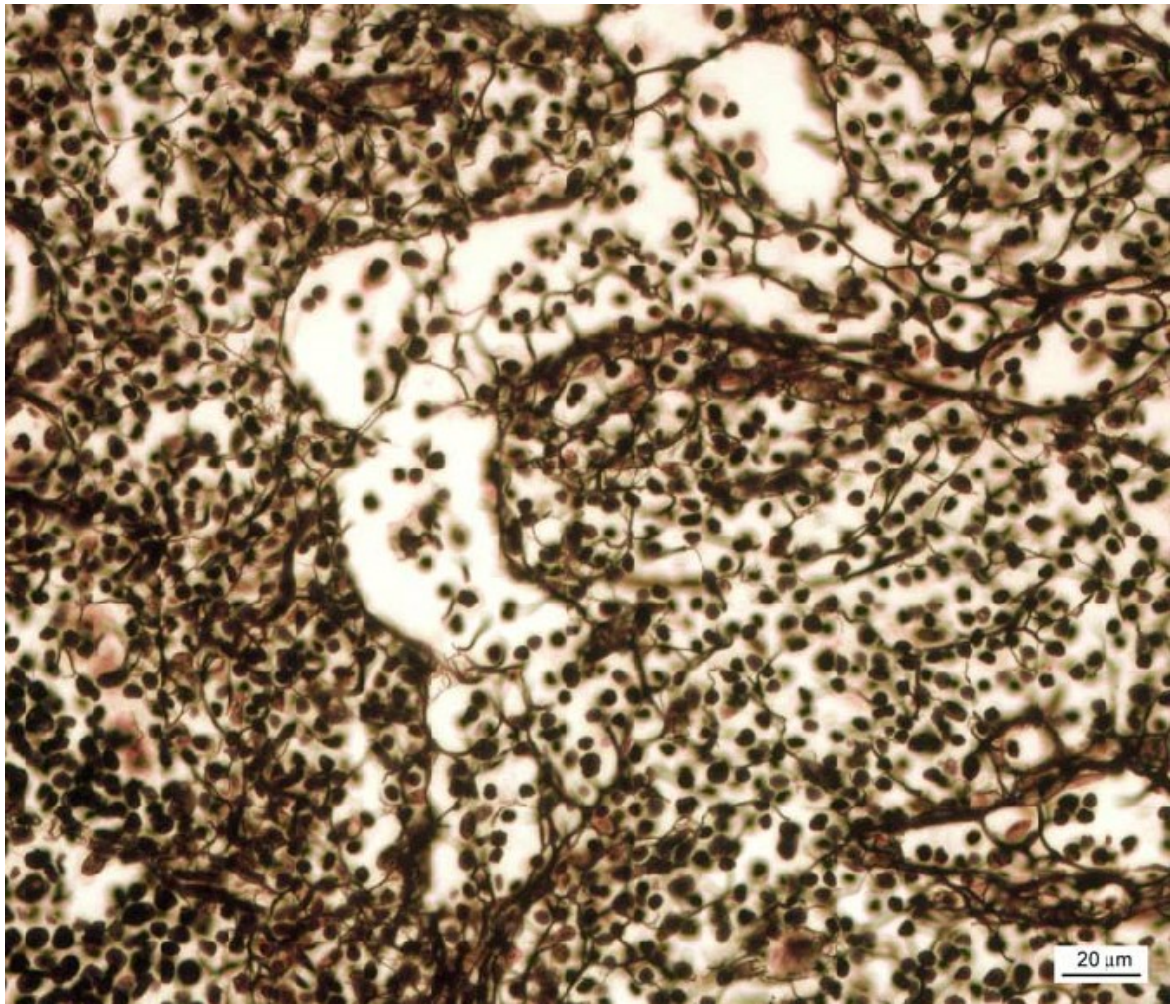
- Similarly to collagen, elastin precursors are secreted and polymerize
- Deposition of elastin aggregate along fibers of protein fibrillin
- Amount of fibrillin (nonelastic) and elastin (elastic) determines elasticity of CT

Reticular fibers

- collagen 3D meshwork
- bone marrow, spleen, lymphatic nodules
- microenvironment for e.g. hematopoietic stem cells and progenitors

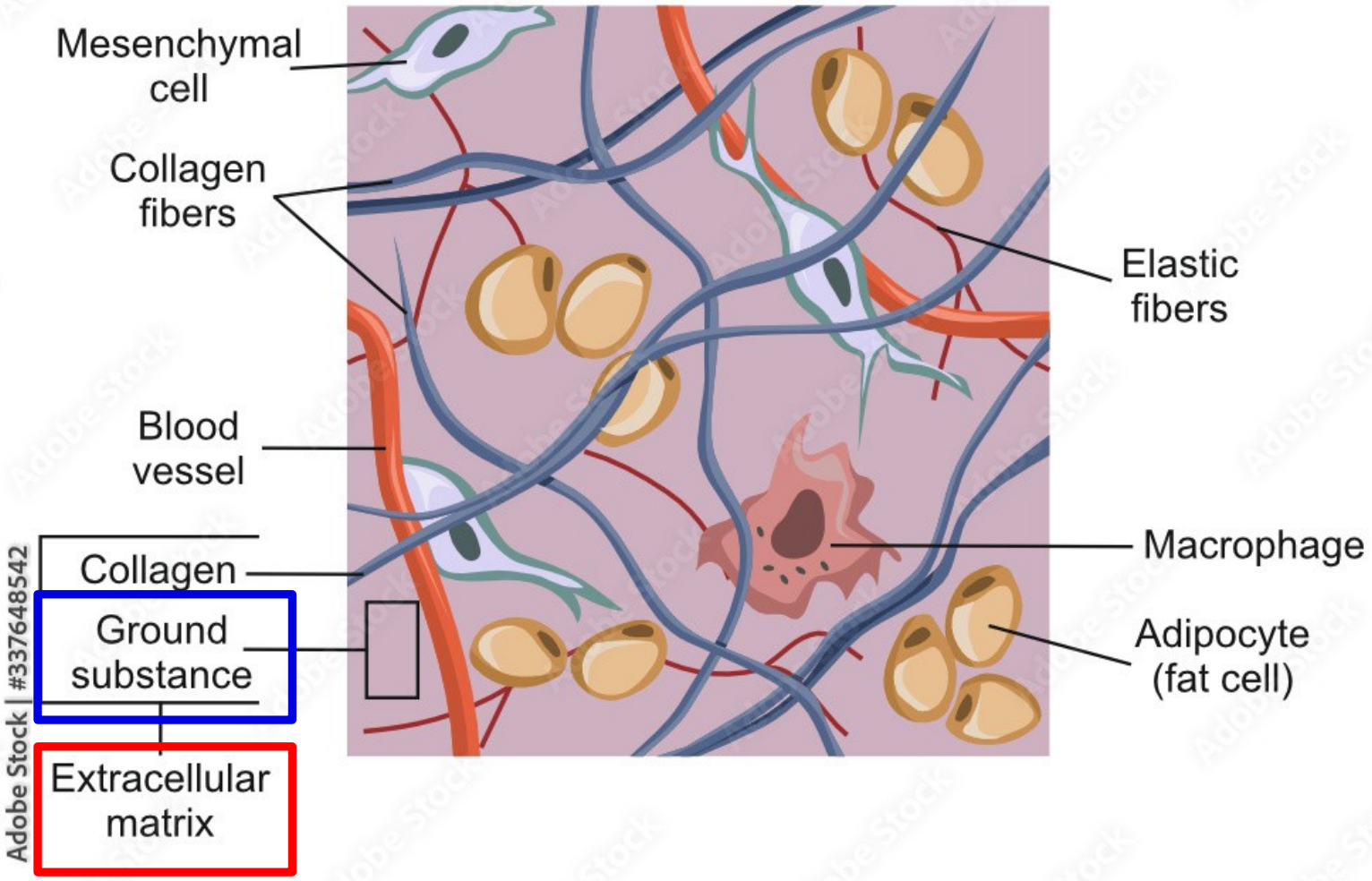


Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com



RETICULAR CONNECTIVE TISSUE

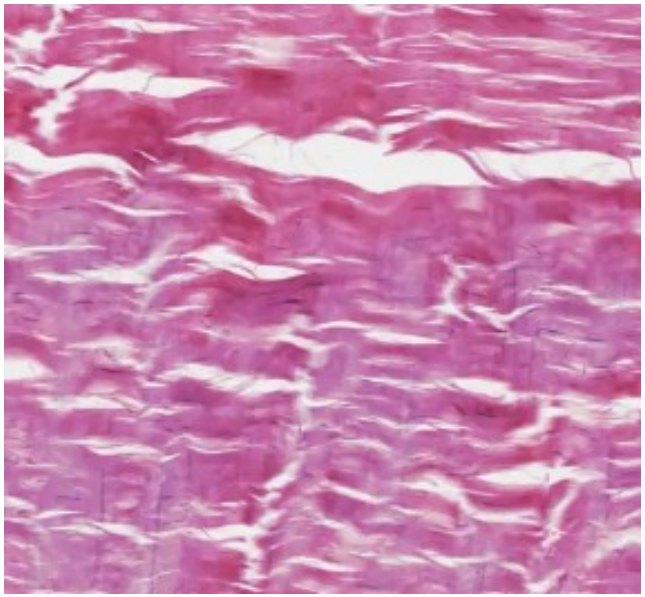
Ground substance

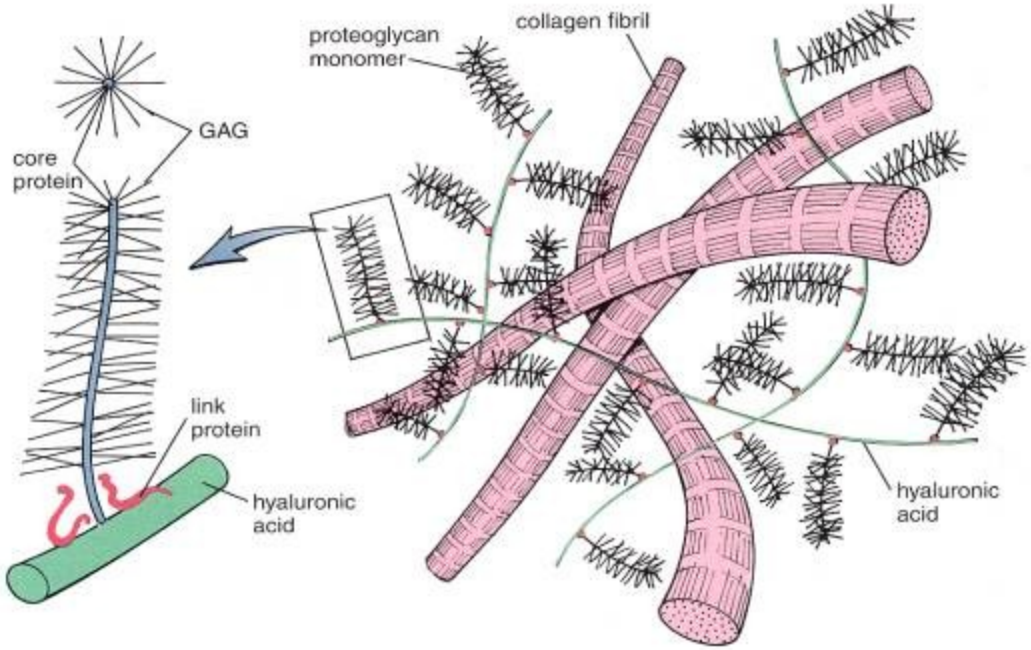


Ground substance

- Amorphous extracellular matrix
- Colorless, transparent, homogenous substance consisting of:

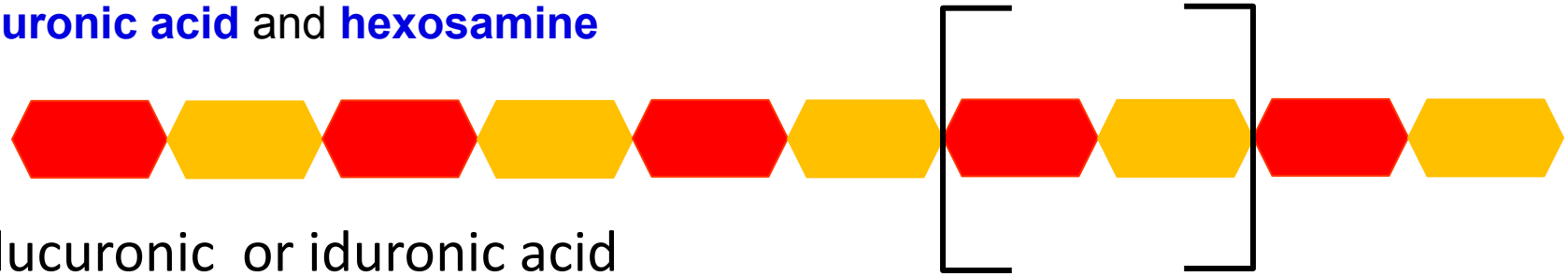
  glycosaminglycans, **proteoglycans** and **structural glycoproteins**



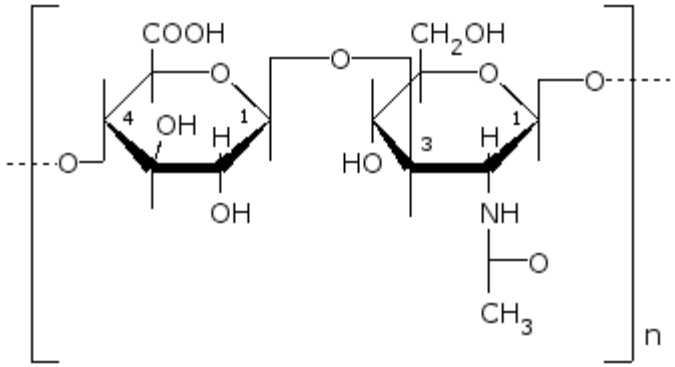


Glycosaminoglycans (GAGs)

- linear polysaccharides composed of two disaccharide subunits
– **uronic acid** and **hexosamine**



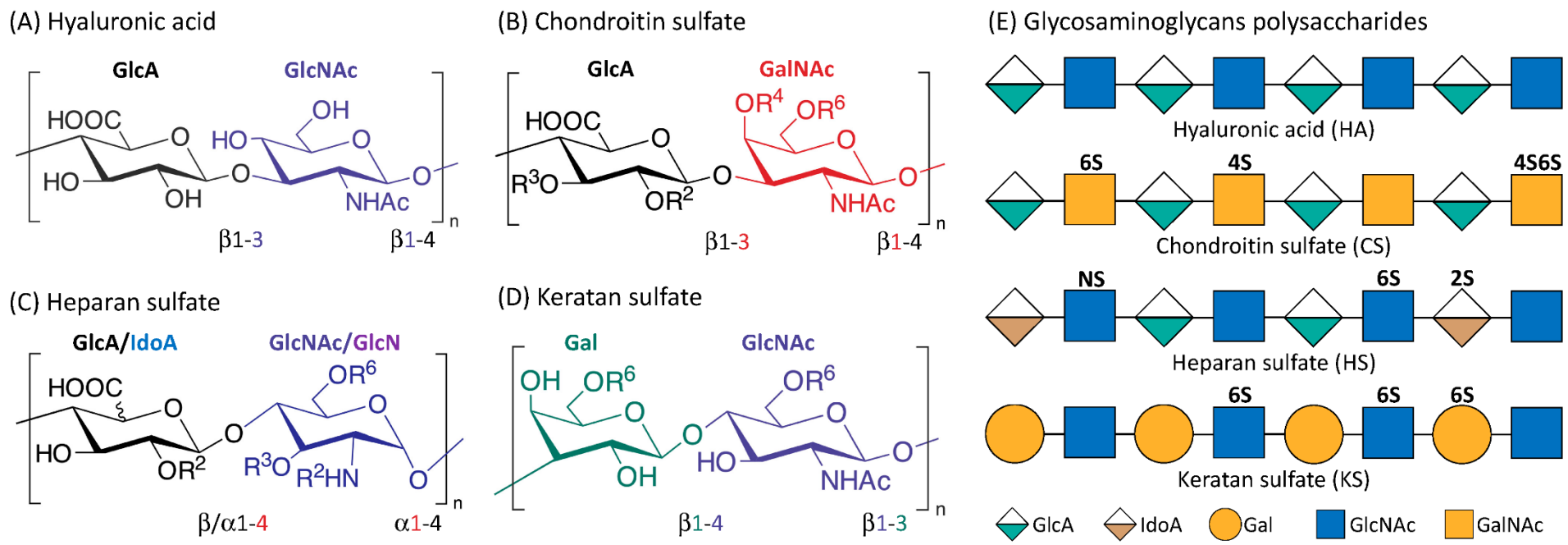
glucuronic or iduronic acid



glucosamin or galactosamin

Glycosaminoglycans (GAGs)

- linear polysaccharides composed of two disaccharide subunits
– **uronic acid** and **hexosamine**



https://doi.org/10.3390/cancers15010266

Glycosaminoglycans (GAGs)

bind to proteins (except for hyaluronic acid)

Glycosaminoglycan	Localization
Hyaluronic acid	Umbilical cord, synovial fluid, fluid of corpus vitreum, cartilage
Chondroitinsulfate	Cartilage, bone, cornea, skin, notochord, aorta
Dermatansulfate	Skin, ligaments, adventitia of aorta
Heparansulfate	Aorta, lungs, liver, basal membranes
Keratansulfate	Iris, cartilage, nucleus pulposus, anulus fibrosus

CLINICAL CONTEXT

- glycosaminoglycans = acid mucopolysaccharides (polysaccharides rich in hexosamines)

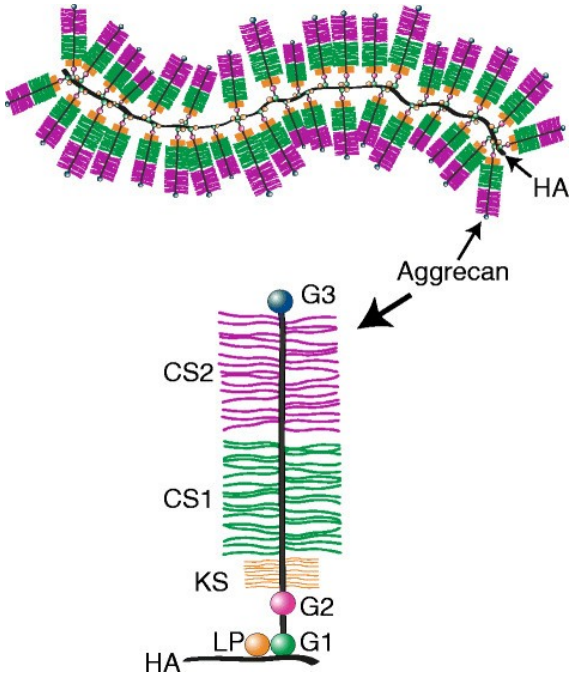
- group of rare genetic diseases – **mucopolysaccharidoses**
  - autosomal recessive disease caused by mutation in genes coding for enzymes of GAG metabolism
  - broad spectrum of problems
  - typical symptoms – craniofacial dysmorphia, cardiomyopathy, splenomegaly, slow growth and psychomotor development

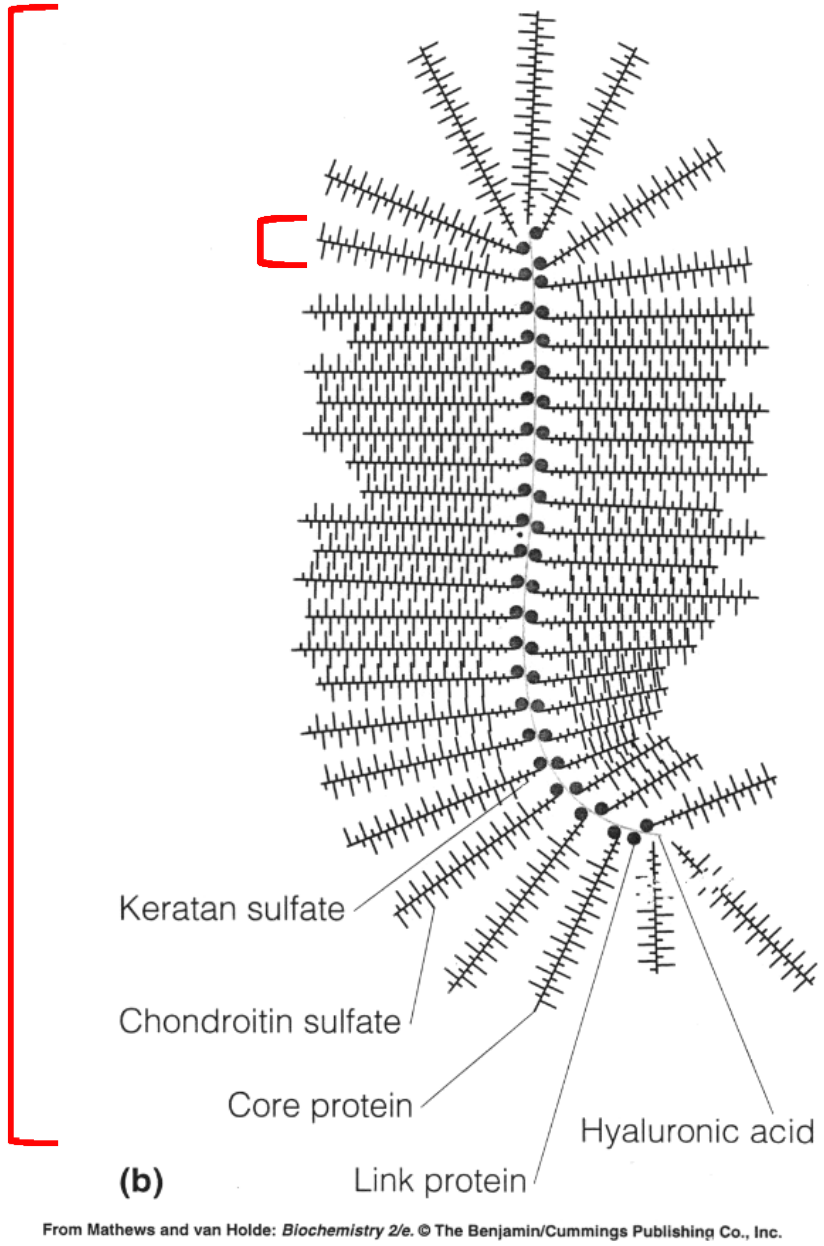
MPS TYPE	EPONYM	ENZYME DEFECT
I	Hurler	α-L-iduronidase
II	Hunter	Iduronate 2-sulfatase
III-A	Sanfilippo type A	Heparan N-sulfatase
III-B	Sanfilippo type B	α-N-acetylglucosaminidase
III-C	Sanfilippo type C	Acetyl-CoA: α glucosaminide N-acetyltransferase
III-D	Sanfilippo type D	N-acetylglucosamine 6-sulfatase
IV-A	Morquio type A	Galactose 6-sulfatase
IV-B	Morquio type B	β-galactosidase
VI	Maroteaux-Lamy	N-acetylgalactosamine 4-sulfatase
VII	Sly	β-glucuronidase

Proteoglycans

- protein core + dominant linear saccharide component
- proteoglycan aggregates
- water-binding, volume dependent of hydratation

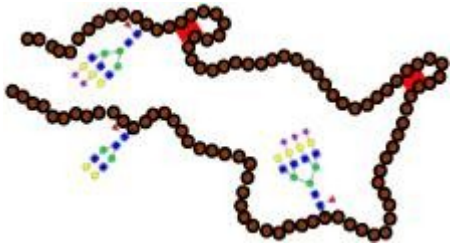
- aggrecan (cartilage)
- syndecan
- fibroglycan





From Mathews and van Holde: *Biochemistry 2/e.* © The Benjamin/Cummings Publishing Co., Inc.

Structural glycoproteins

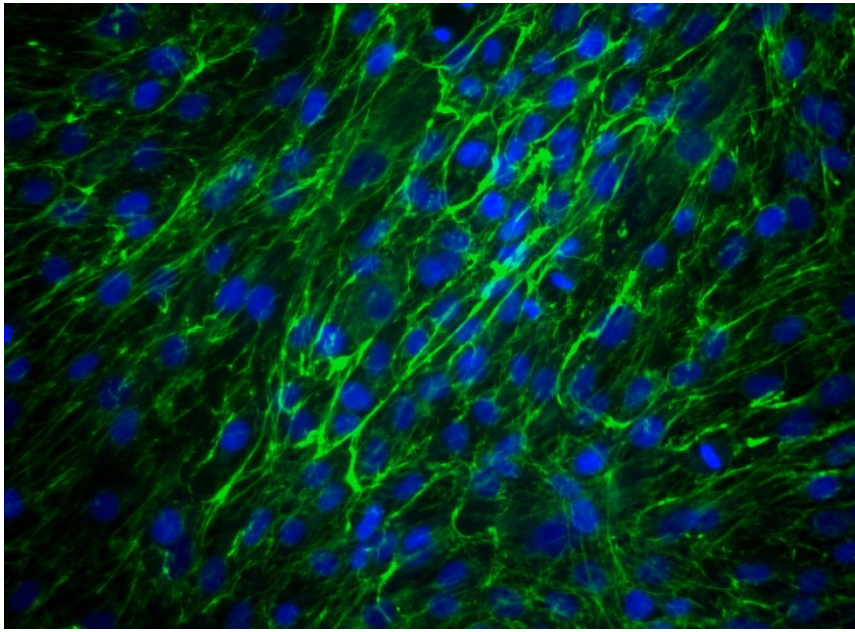


- dominant protein + branched saccharide component
- interaction between cells and ECM

— **fibronectin** – connects collagen fibers and glykosaminoglycans, cell adhesion and migration

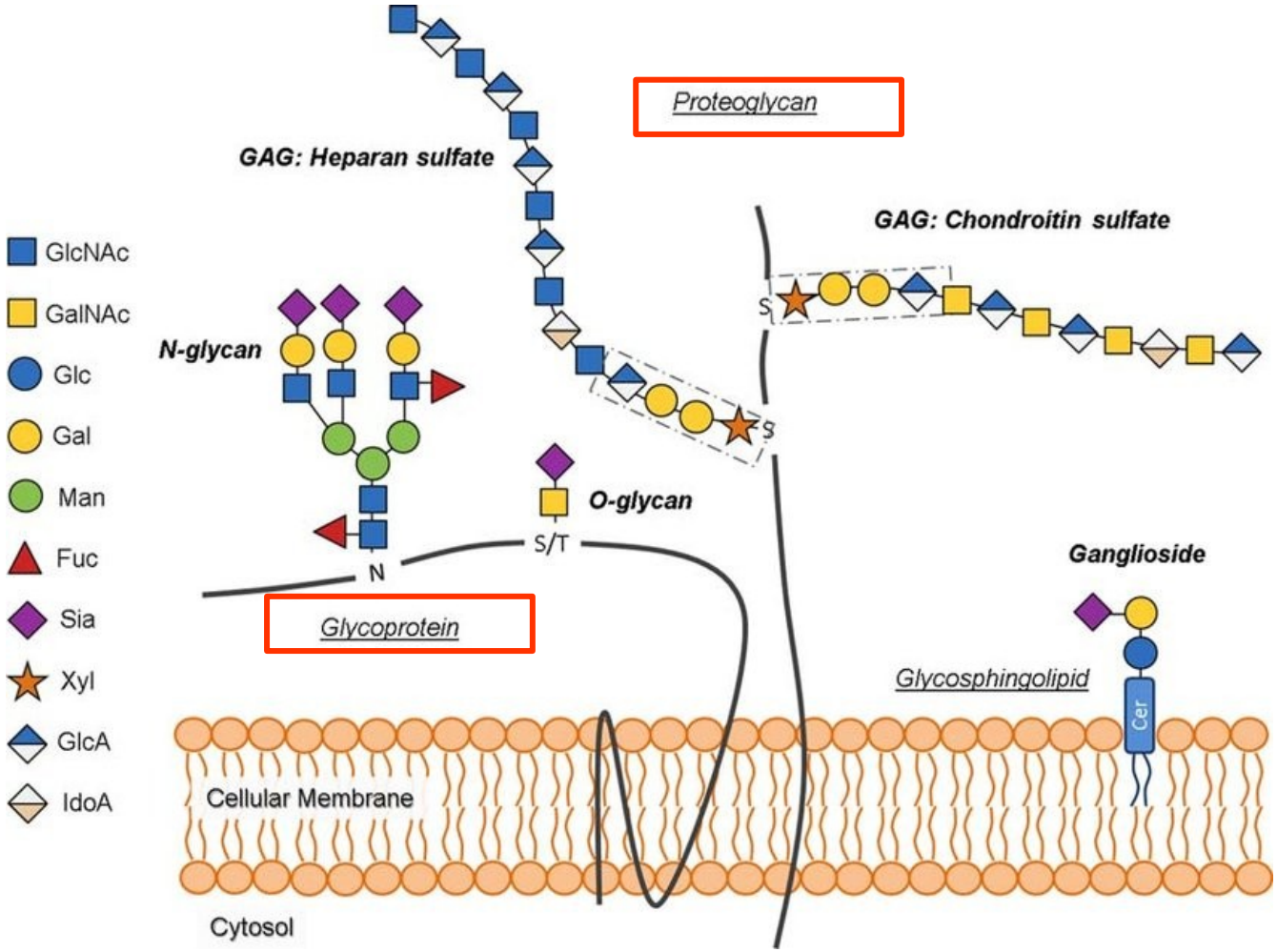
— **laminin** – basal lamina – epithelial integrity

— **chondronectin** – cartilage – adhesion of chondrocytes to collagen

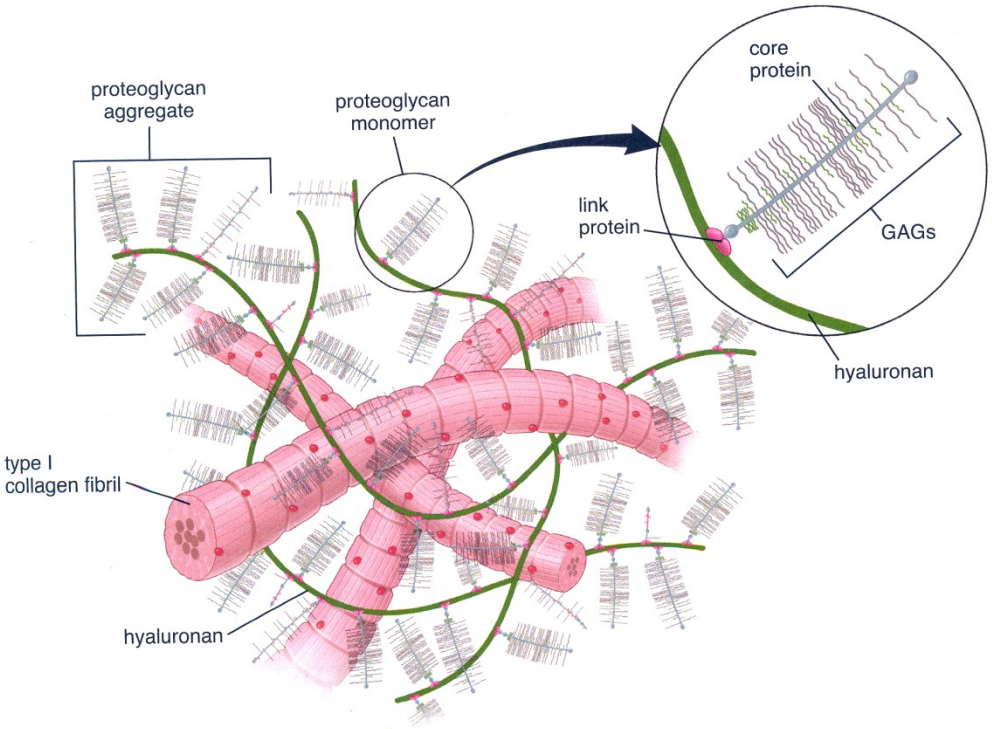


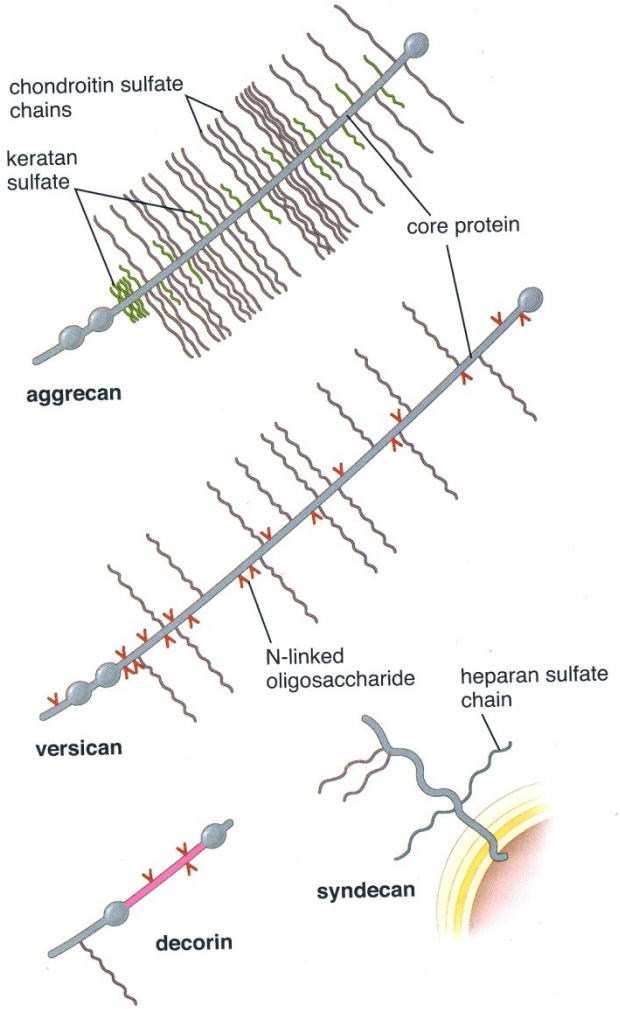
human mesenchymal stem cells (MSC), BD, Alexa Fluor® 488 Mouse Anti-Fibronectin

Glycoproteins vs. proteoglycans

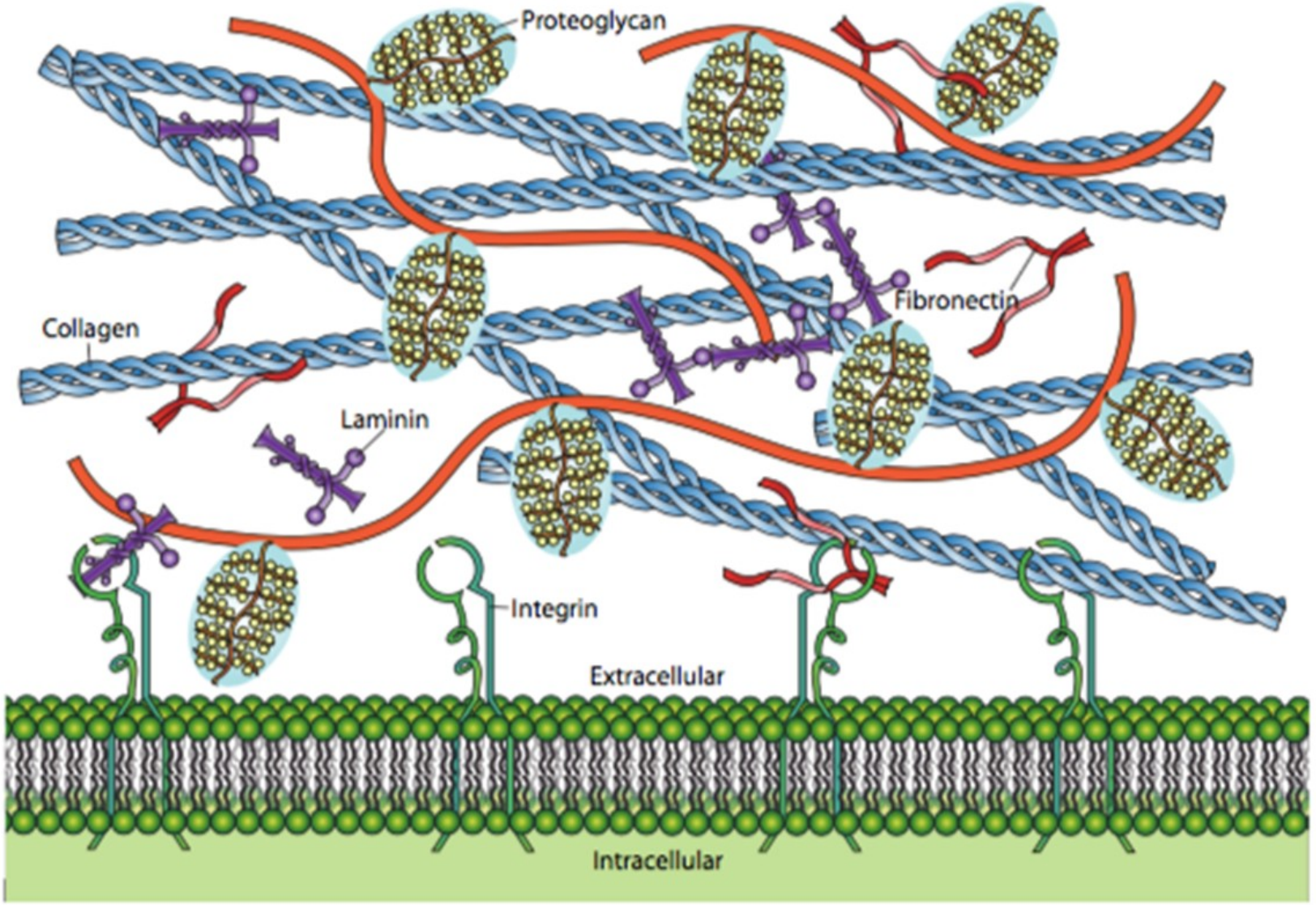


COMPOSITION OF ECM





Cell – ECM interactions



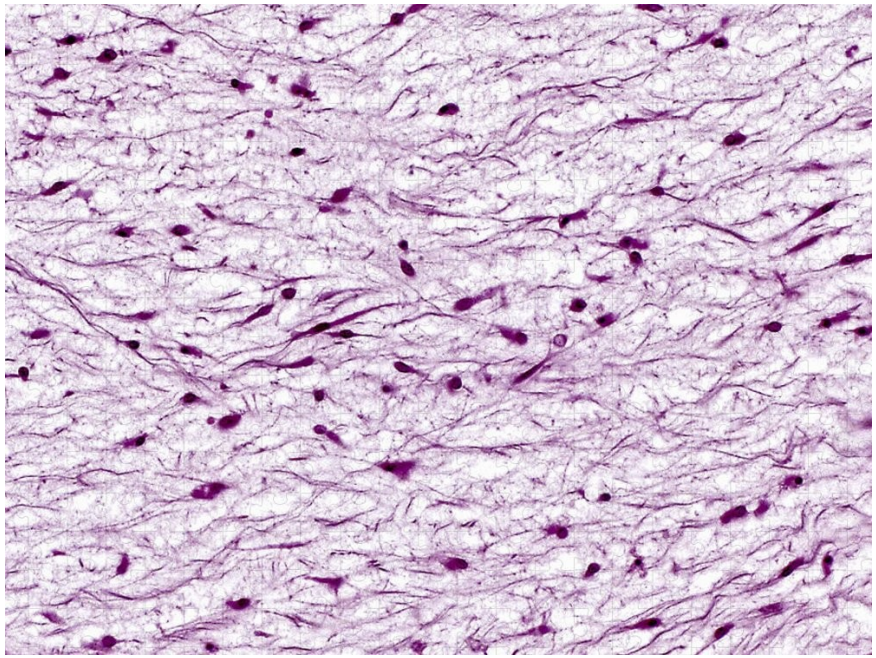
HISTOLOGICAL CLASSIFICATION OF CT PROPER

Embryonic:

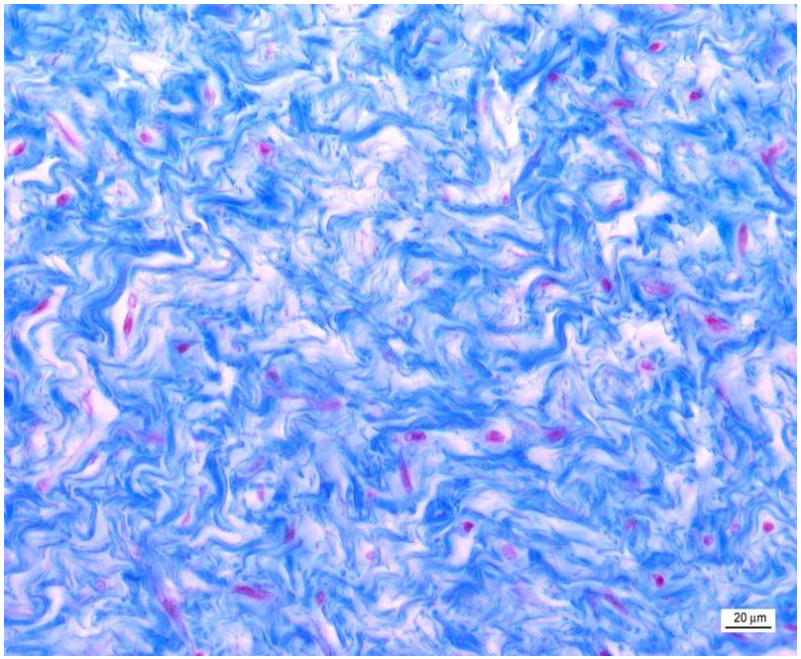
- **Embryonic mesenchyme** and **mucous c.t**. (Wharton's jelly) of umbilical cord

Postnatal (adult):

- **Loose collagen c.t.** (areolar, interstitial)
- **Dense collagen regular** and **irregular c.t.**
- **Elastic c.t.**
- **Reticular c.t.**
- **Adipose c.t.**



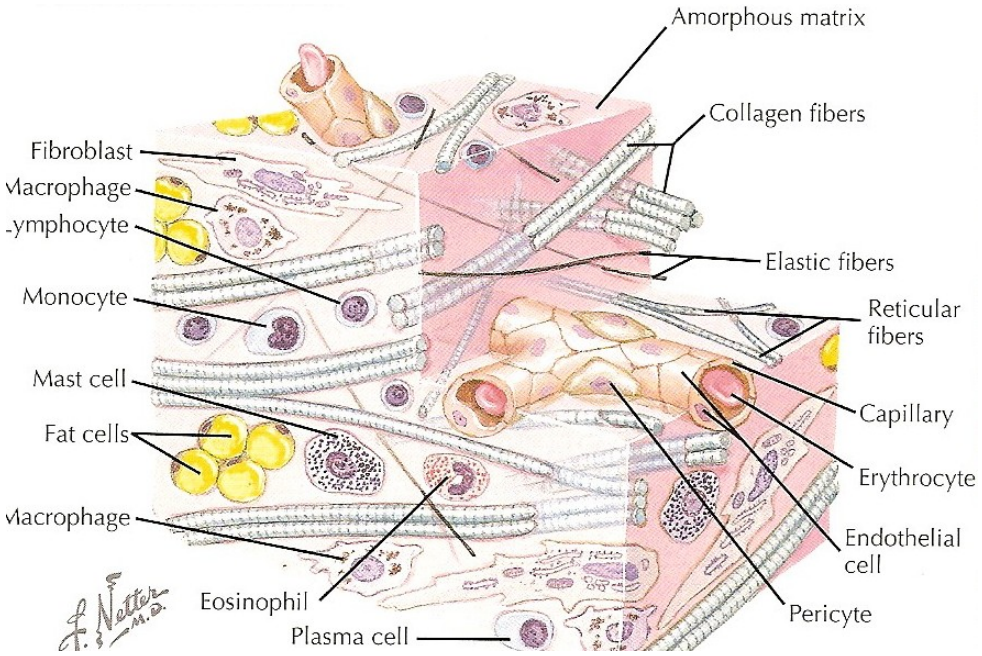
Embryonic mesenchyme



Wharton's jelly

HISTOLOGICAL CLASSIFICATION OF CT PROPER

Loose collagen c.t.

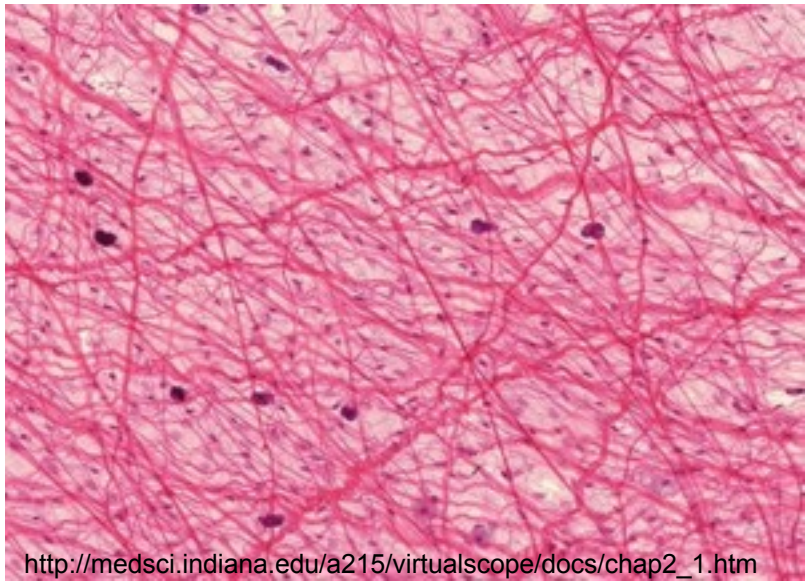


- Most abundant type of CT
- Rich vascularization and innervation

- Walls of hollow organs, interstitium, mucosal and submucosal CT

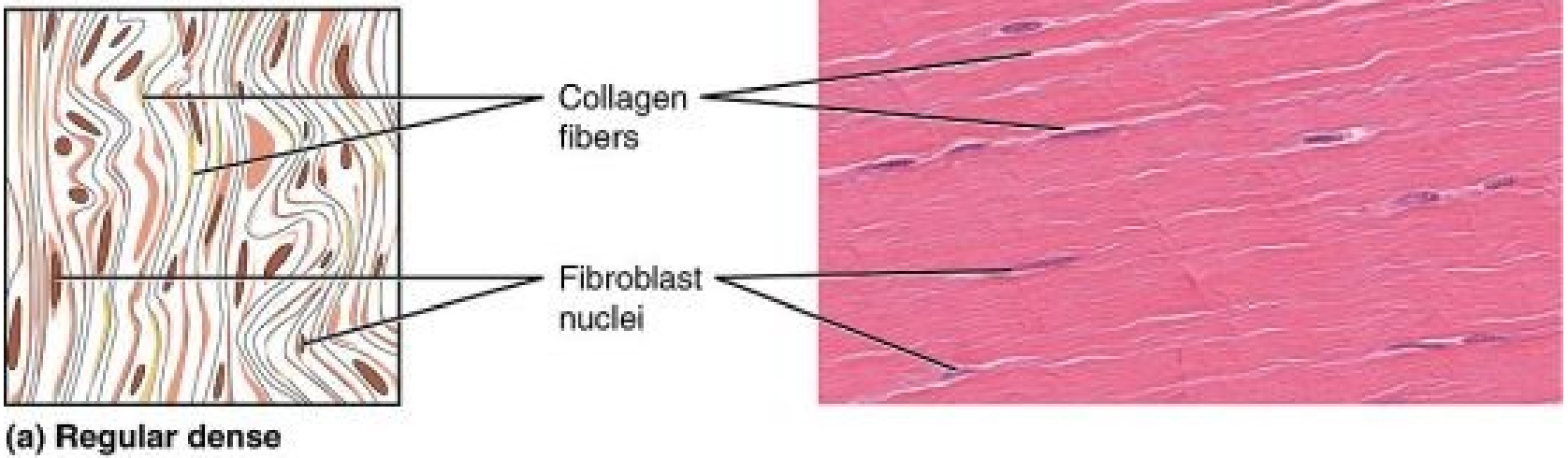
- Permanent fibroblasts, macrophages (histiocytes), occasionally adipocytes
- Other transient cell types (leukocytes)

- Collagen and elastic fibers
- Amorphous ground substance is dominant

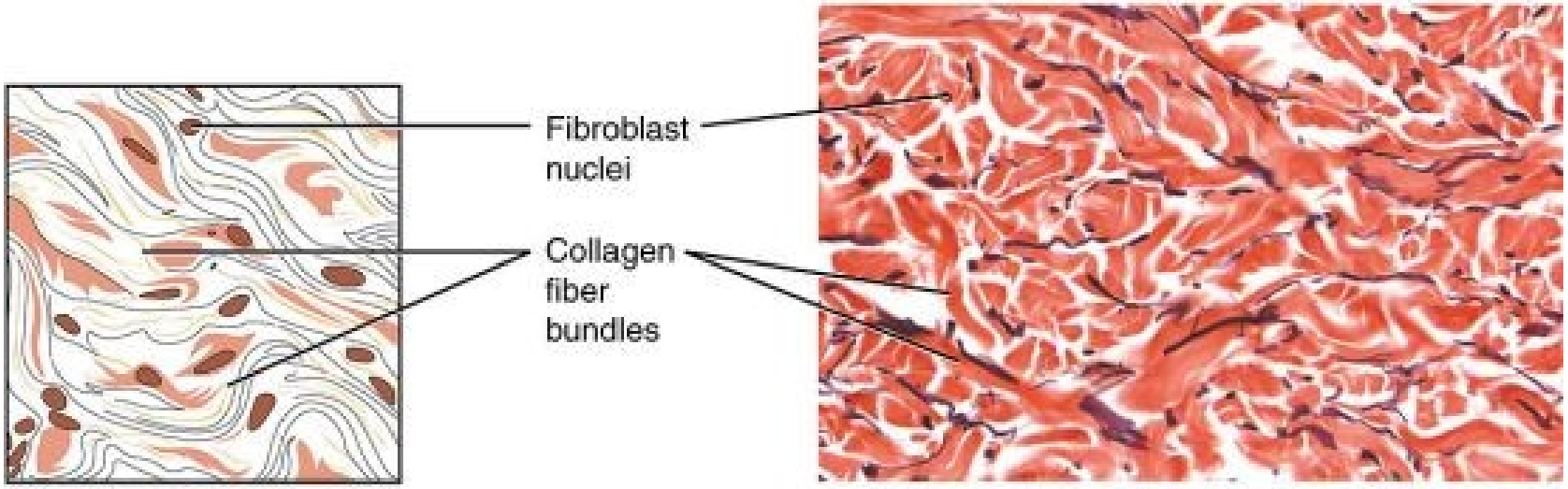


http://medsci.indiana.edu/a215/virtualscope/docs/chap2_1.htm

Dense collagen c.t.



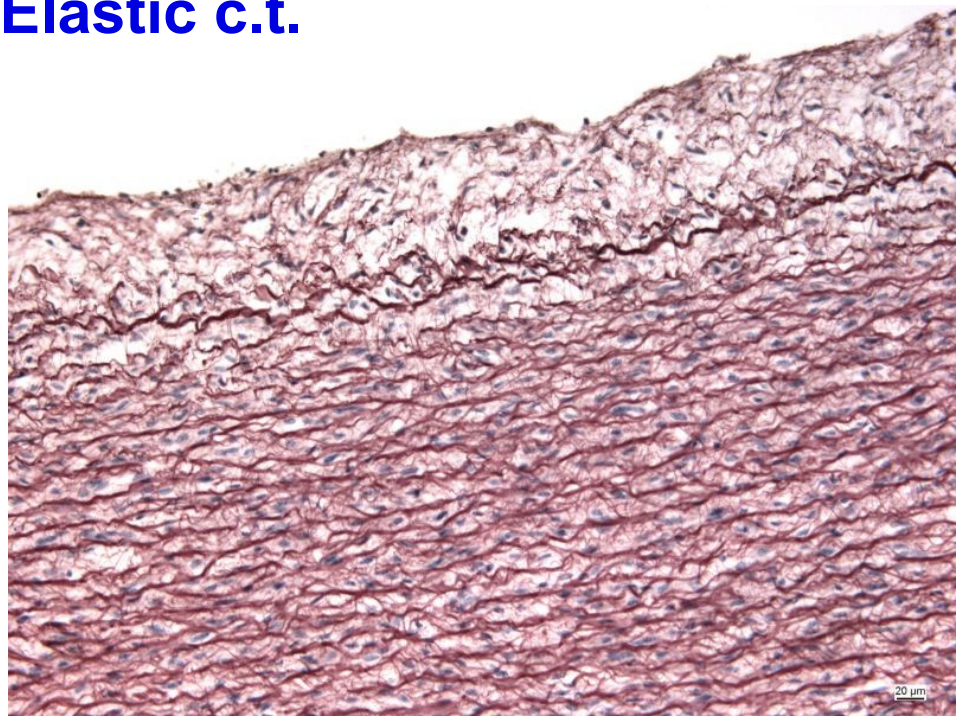
(a) Regular dense



(b) Irregular dense

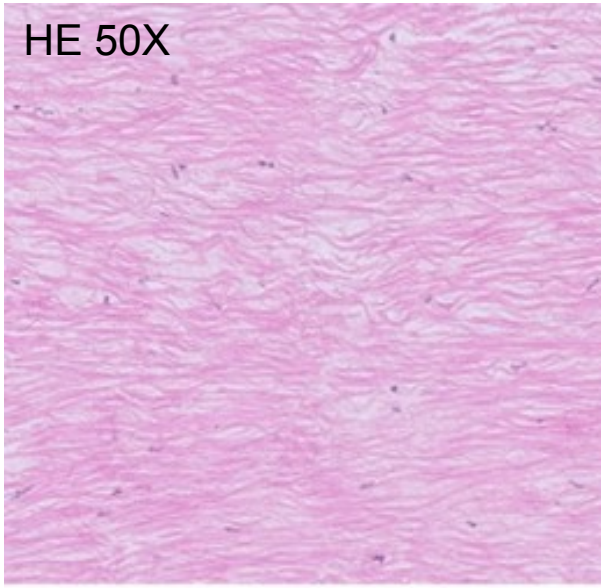
HISTOLOGICAL CLASSIFICATION OF CT PROPER

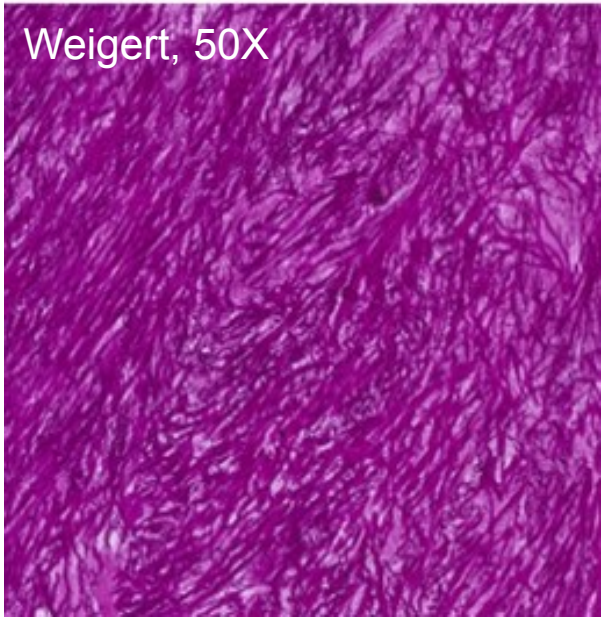
Elastic c.t.



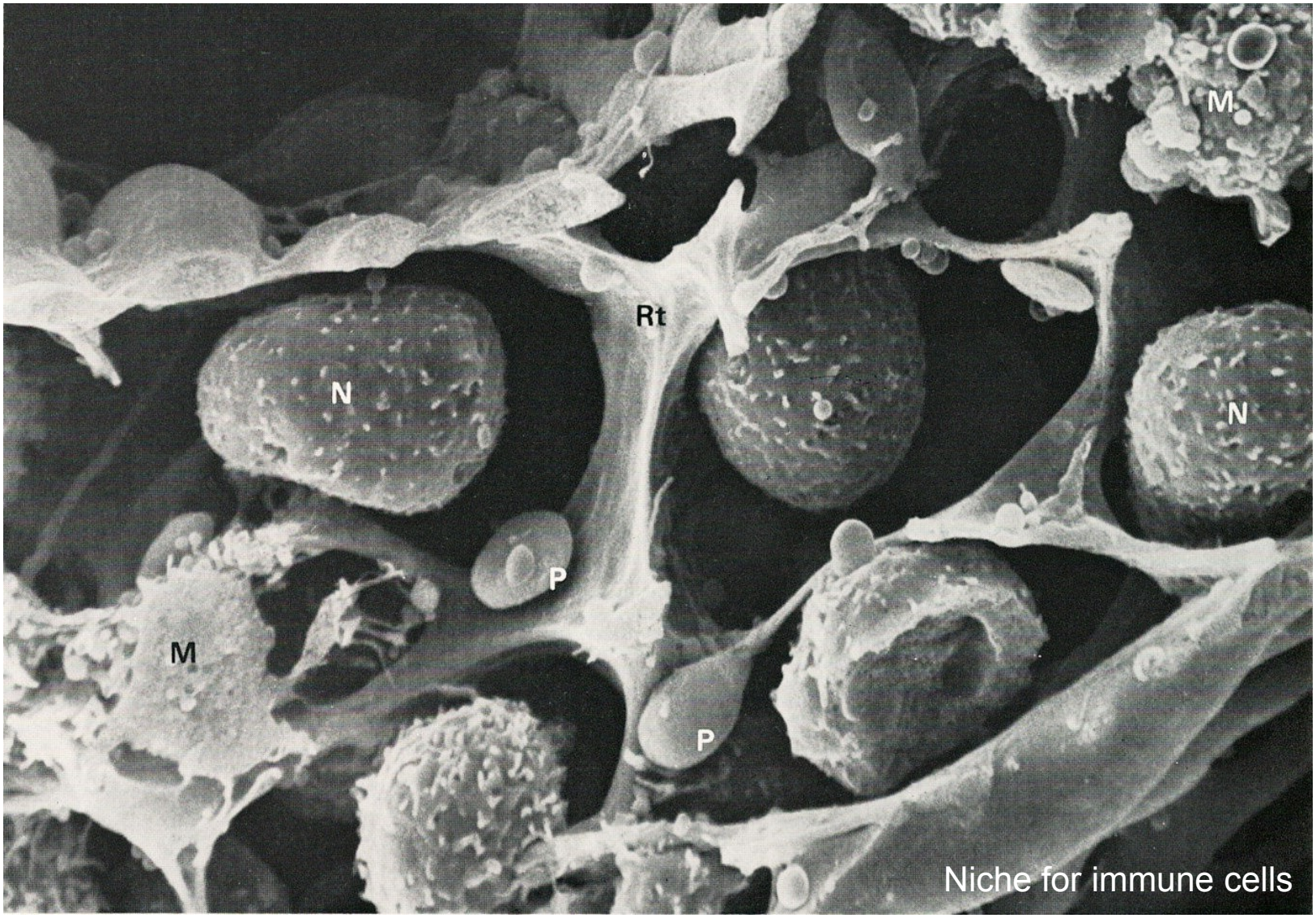
Elastic membranes of aorta

Lig. flava



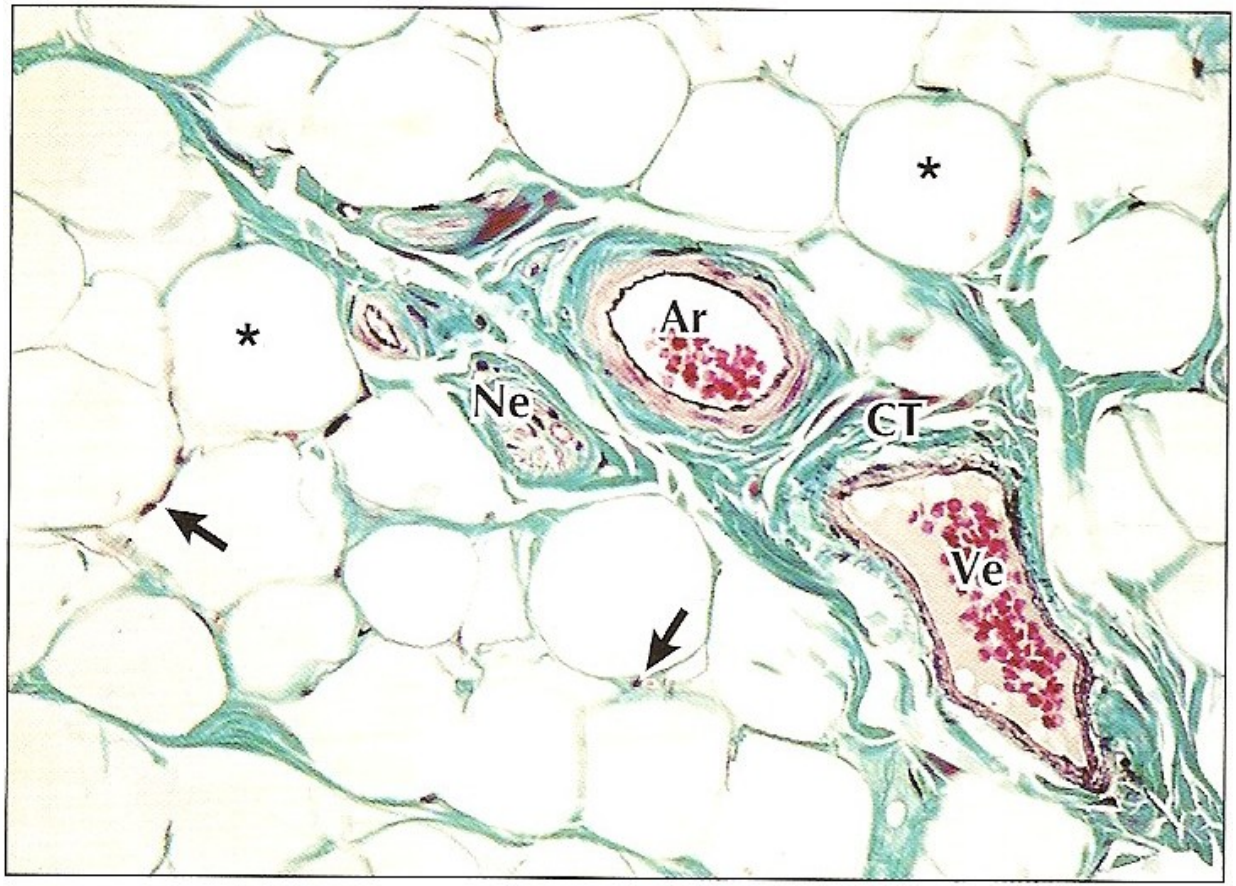


Reticular c.t.



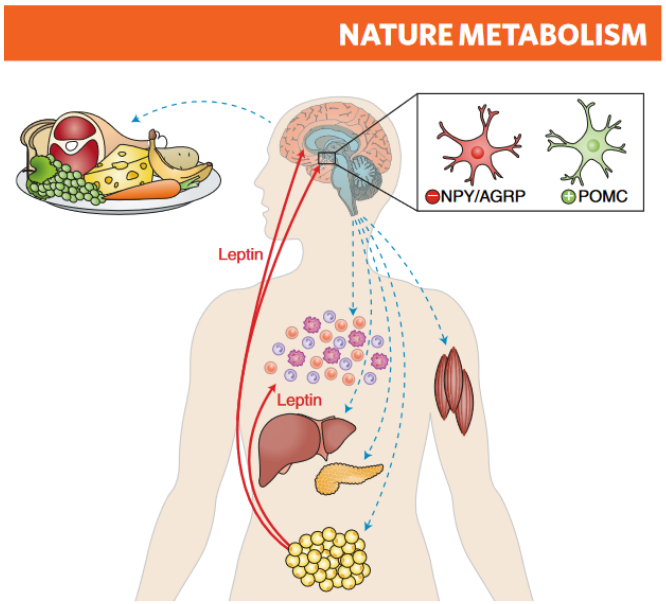
Adipose c.t.

- Adipocytes, fibroblasts, reticular, collagen and elastic fibers, capillaries
- White and brown adipose tissue

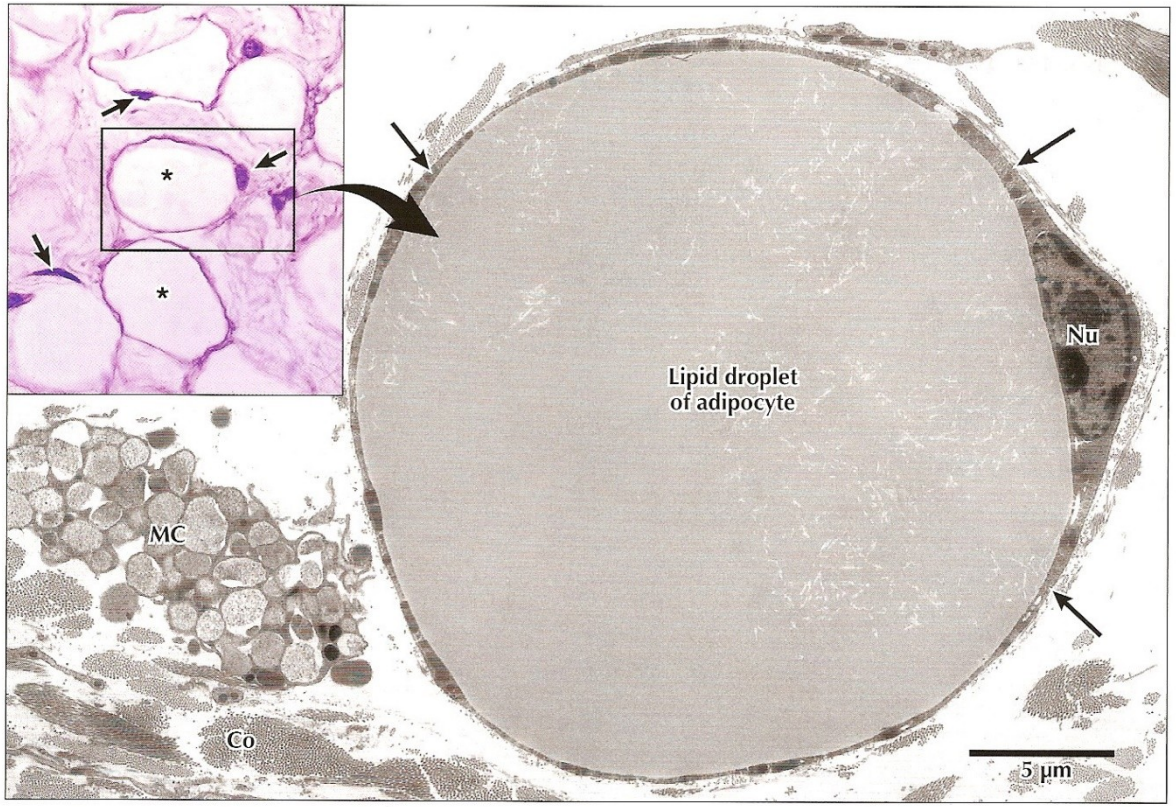


White adipose c.t.

- rich vascularization
- unilocular adipocytes with only one lipid droplet
- endocrine activity - leptins (adipokinins)

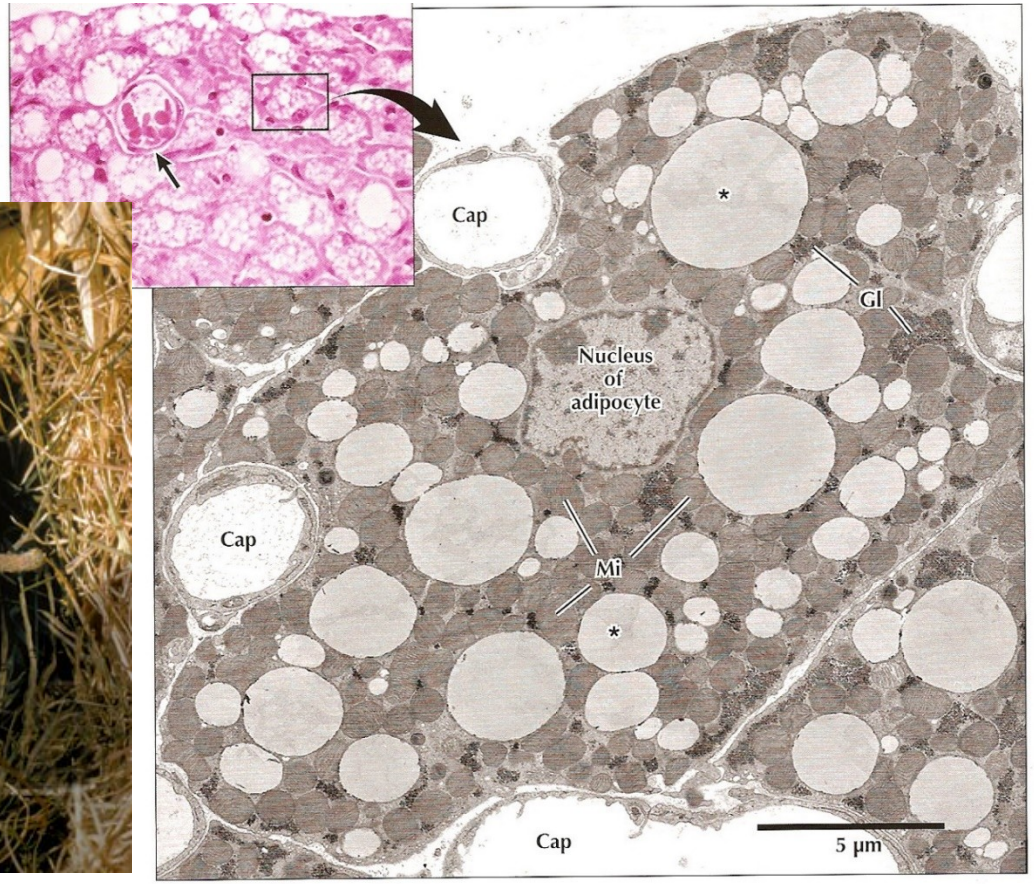


10.1038/s42255-019-0095-y



Brown adipose c.t.

- small cells with numerous fat droplets
- typical localization – between shoulder blades, axilla, mediastinum, around kidneys, pancreas, small intestine
- fetus and children up to 1st year of life
- fast source of energy

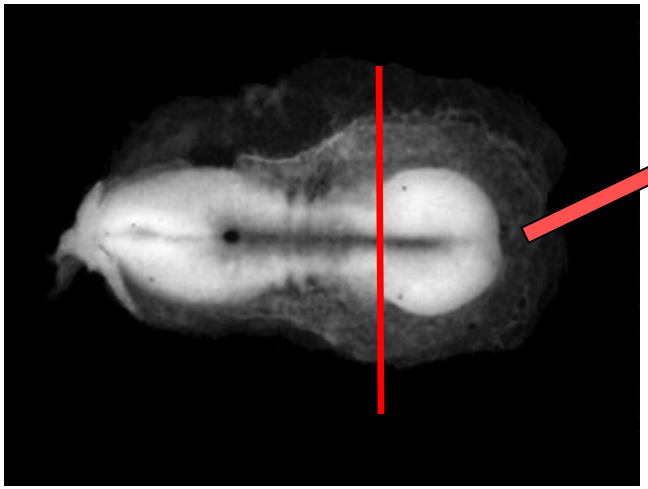


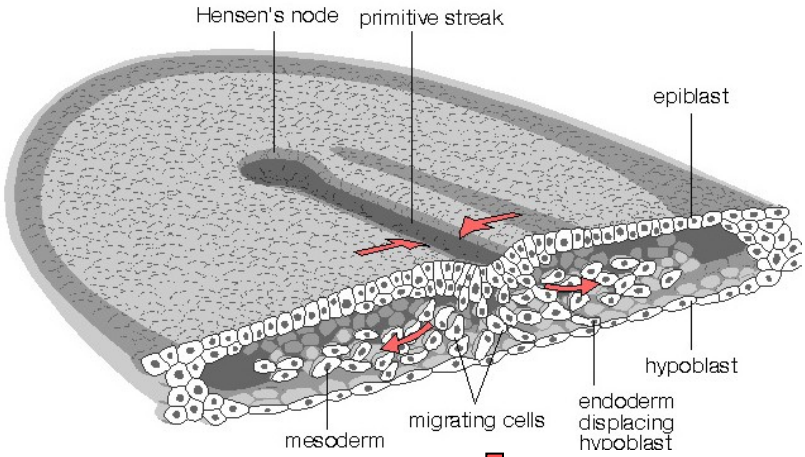
EMBRYONIC ORIGIN OF CONNECTIVE TISSUE

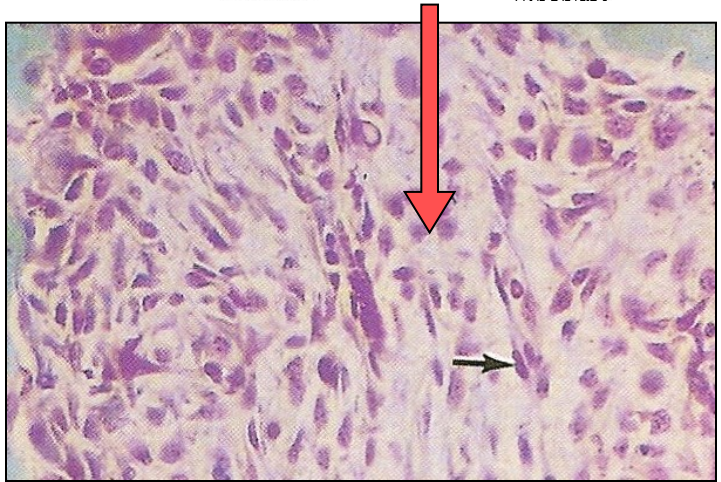
Mesenchyme

- Mesenchyme = loose tissue between germ layers
- Complex network of small, undifferentiated star- or spindle-shaped cells
- Jelly-like amorphous ground substance rich in hyaluronic acid
- Origin in mesoderm (=germ layer) or neural crest

Trilaminar germ disc



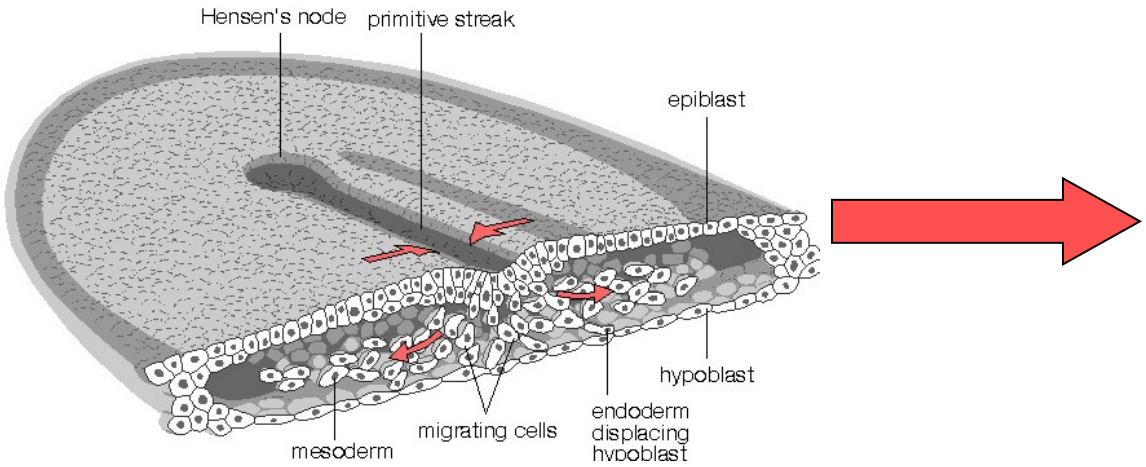


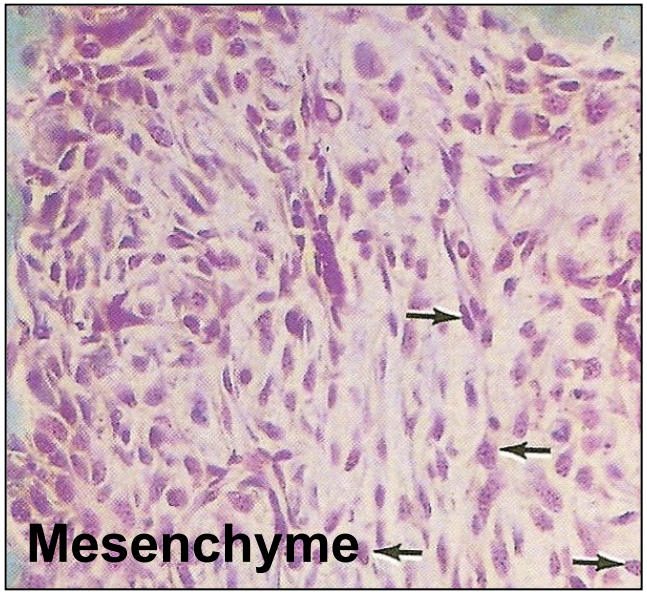


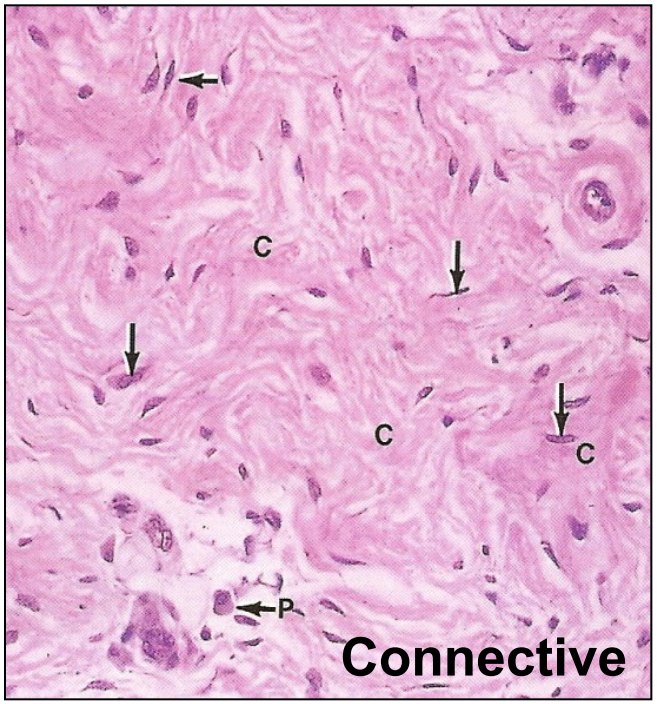
http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_Ch02/DBNModel.html

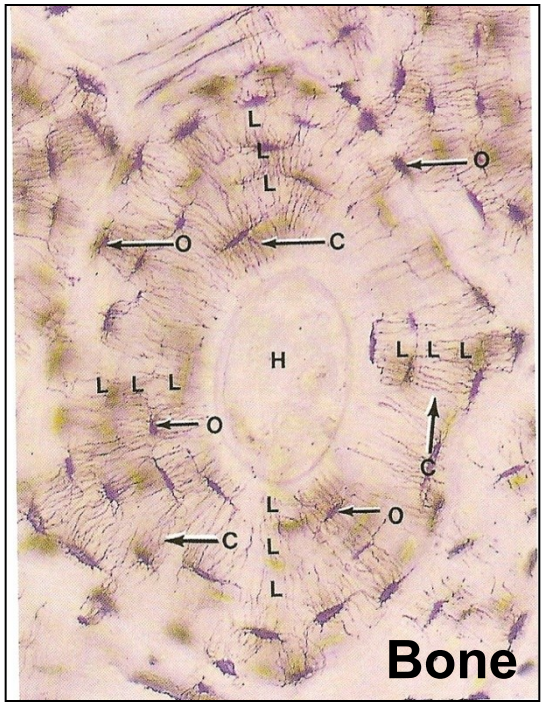
EMBRYONIC ORIGIN OF CONNECTIVE TISSUE

C.t. derivatives of mesenchyme









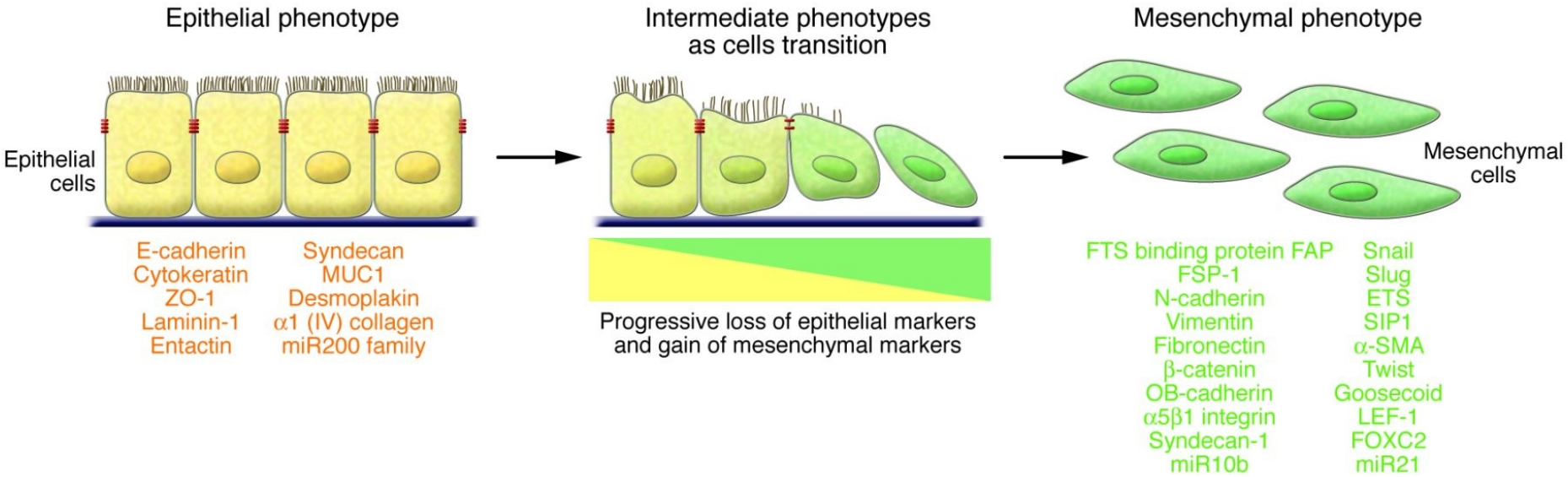
Mesenchyme as embryonic c.t. and a cellular phenotype

- **Embryonic mesenchyme** – undifferentiated embryonic cell population

Term from embryology

- **Mesenchymal phenotype** – set of cell properties: ECM production and remodeling, migration, absence of epithelial polarity and intercellular junctions

Term from cell biology

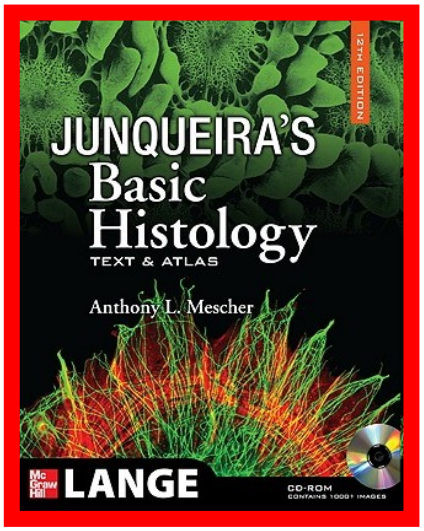


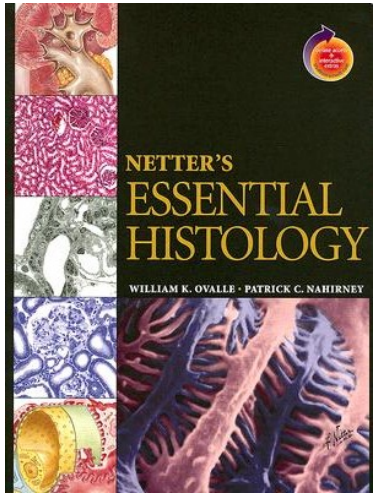
https://doi.org/10.1172/JCI39104.

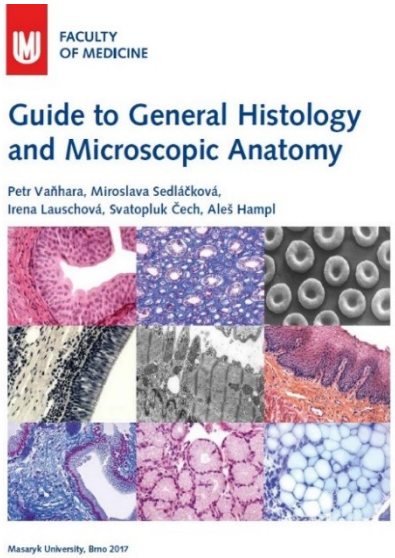
SUMMARY OF CONNECTIVE TISSUE

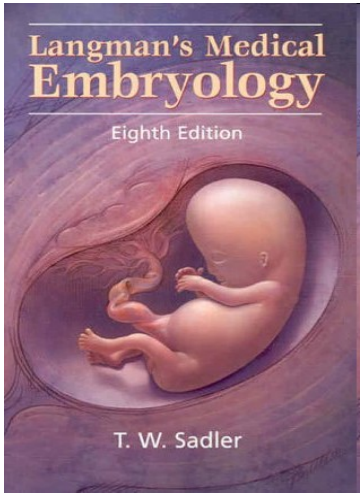
Collagen	**Structure**	**Function and distribution**
Loose collagen CT	Abundant ground substance, collagen fibers with random arrangement	Microvascularisation Innervation
Irregular dense collagen CT	Few ground substance, few cells, many collagen fibers, random arrangement	Mechanically resistant organ capsules
Regular dense collagen CT	Tightly arranged collagen fibers with fibroblasts intercalated between them	Part of musculoskeletal system. Tendons, ligaments
Embryonic		
Mesenchyme	Undifferentiated cells uniformly dispersed in ground substance, few collagen fibers	Undifferentiated progenitors
Wharton's jelly	Viscous amorphous matrix with collagen fibers. ECM-producing stromal cells with MSC properties.	Matrix of umbilical cord
Special		
Reticular CT	Network of collagen III fibers and reticular cells	Support of hematopoietic and lymphatic cells
Elastic	Rich in elastic fibers	Lig. flava, lig. vocale. Lung interstitium, flexible support to elastic arteries and aorta
Adipose	Adipocytes	Energy storage (white fat), heat production (brown fat)
Cartilage	Chondroblasts, chondrocytes	Mechanical support
Bone	Osteoblasts, ostecoytes, osteoclasts	Mechanical support, calcium and phospate metabolism
Blood	See lecture on blood & hematopoiesis this semester	

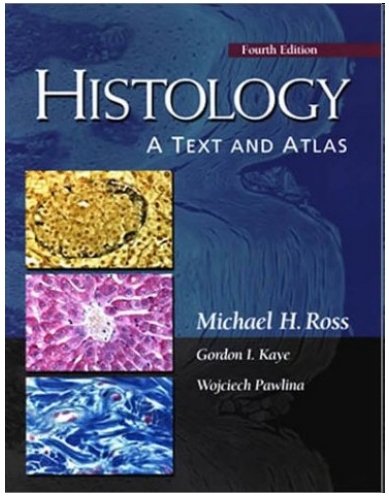
FURTHER STUDY











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Thank you for attention