Connective Tissue

- connective tissue is everywhere in the body
- CT is versatile
- epithelium can be identified by sheets of identical cells
- connective tissue is identified by 3 features:
  - cells
  - fibers
  - ground substances

General Features

- Connective tissue provides a matrix that supports and physically connects other tissues and cells together to form the organs of the body.
- The interstitial fluid of connective tissue gives metabolic support to cells as the medium for diffusion of nutrients and waste products.
- Composed of cells (fixed and wandering), fibers and ground substance.
- Variable vascularity. → has blood vessels : some CT could be avascular, while others could be highly vascular
- Variable regenerative power.

could be high/low

cartilage

bone

no blood vessels = low metabolic rate = no cell division = no regeneration

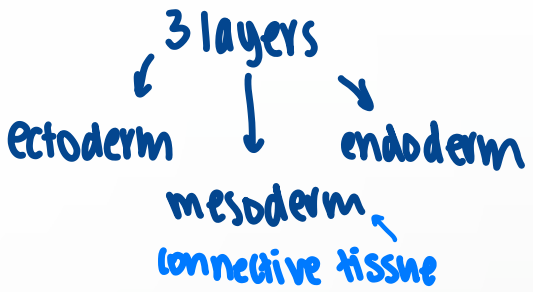
not a rule of thumb for avascular tissues

ex. epithelial cells are avascular but can regenerate

Functions

1. Structural framework for body. skeleton (bone, cartilage, ligament)
2. Transportation of fluids and dissolved substances.
3. Protection of delicate organs. → capsules in glands
4. Supports, surrounds, and connects other tissues.
5. Storage of energy in the form of lipids. → adipose tissue
6. Defend the body against microorganisms. → WBCs

Origin

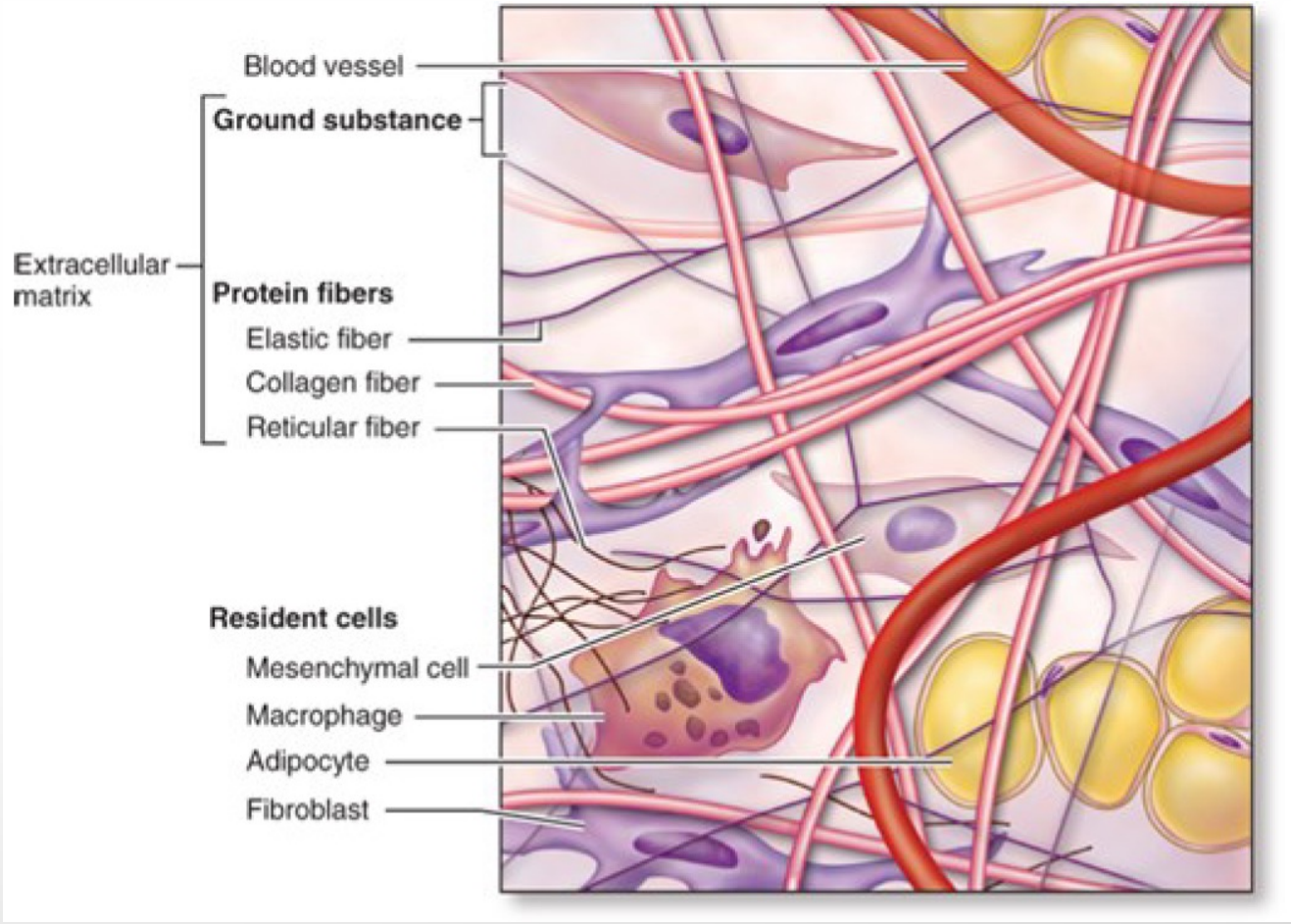


- All connective tissues originate from embryonic mesenchyme, a tissue developing mainly from the middle layer of the embryo, the mesoderm.
- Mesenchyme consists largely of viscous ground substance with few collagen fibers.
- Mesenchymal cells are undifferentiated and have large nuclei, with prominent nucleoli and fine chromatin.
- Mesenchymal cells are spindle-shaped---- with their scant cytoplasm extended as two or more thin cytoplasmic processes

Components

- Cells
- Fibers
- Ground substance

} matrix

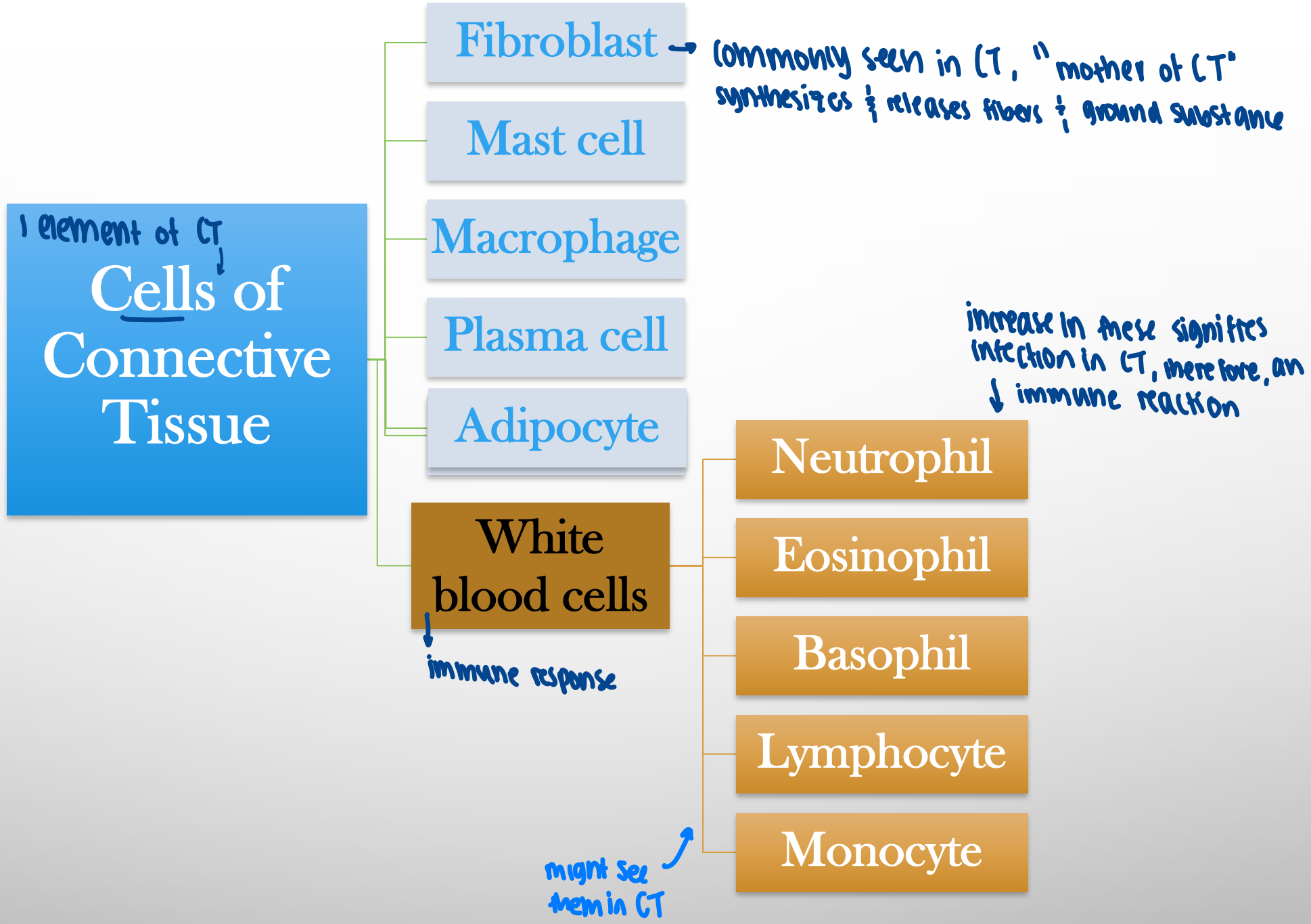


Ground substance

- Ground substance is a complex of anionic, hydrophilic proteoglycans, glycosaminoglycans (GAGs), and multiadhesive glycoproteins (laminin, fibronectin, etc.)

differences in CT depend on:

- number of cells
- number and nature of fibers
- difference in functions of ground substances


1 element of CT
Cells of Connective Tissue
Fibroblast
commonly seen in CT, "mother of CT"
synthesizes & releases fibers & ground substance
Mast cell
Macrophage
Plasma cell
Adipocyte
White blood cells
immune response
increase in these signifies infection in CT, therefore, an ↓ immune reaction
Neutrophil
Eosinophil
Basophil
Lymphocyte
Monocyte
might see them in CT

actively synthesizes & releases the matrix

after having its job done

- dormant: "retired" but isn't dead

1. Fibroblast
2. Plasma cell
3. Adipocyte
4. large lymphocyte
5. Macrophage
6. Fibrocyte
7. Eosinophil
8. Neutrophil
9. Cell with pigment granules
10. Small lymphocyte
11. Mast cell

Connective tissue cells

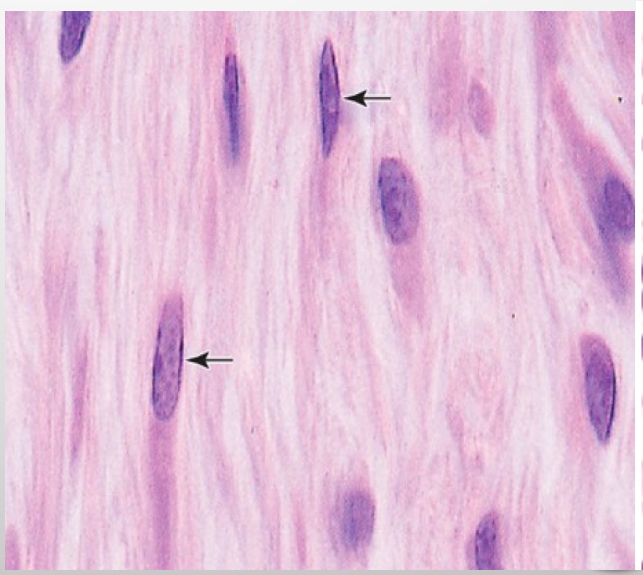
Cell Type	Major Product or Activity
Fibroblasts (fibrocytes)	Extracellular fibers and ground substance
Plasma cells	Antibodies
Lymphocytes (several types)	Various immune/defense functions
Eosinophilic leukocytes	Modulate allergic/vasoactive reactions and defense against parasites
Neutrophilic leukocytes	Phagocytosis of bacteria
Macrophages	Phagocytosis of ECM components and debris; antigen processing and presentation to immune cells; secretion of growth factors, cytokines, and other agents
Mast cells and basophilic leukocytes	Pharmacologically active molecules (eg, histamine)
Adipocytes	Storage of neutral fats

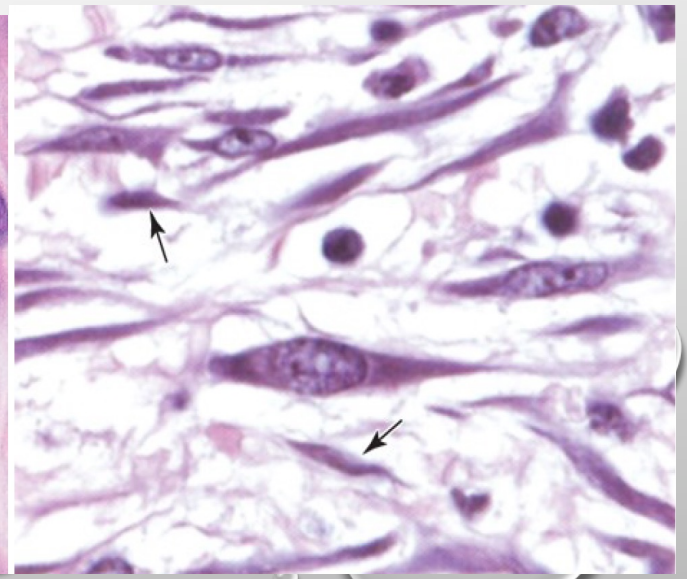
Fibroblast

- is almost everywhere
- is responsible for healing - superficial cuts (same tissue)
- is deep cuts cause scarring (different tissue - scarred tissue its lighter in color & is shinier)

- The most common cells in connective tissue proper
- Produce and maintain most of the tissue's extracellular components.
- Most of the secreted ECM components undergo further modification outside the cell before assembling as a matrix.

Fibroblast **Fibrocyte**



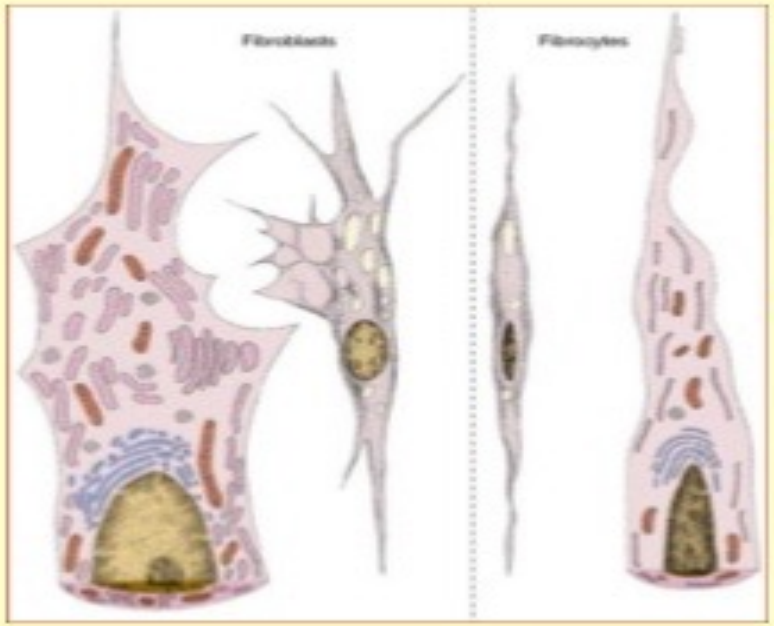


Fibroblasts _ Fibrocytes

larger

✓ Fibroblasts

- the most common cells in connective tissue
- cells responsible for the synthesis of extracelullar matrix components
- an abundant and irregularly branched cytoplasm
- ovoid, large and pale staining nucleus with nucleolus
- rich in RER and well developed Golgi complex
- produce the growth factors → influence growth and cells differentiation
- proliferate when the additional fibroblasts are required



smaller (shrunken)

✓ Fibrocytes

- smaller than fibroblasts
- fewer processes
- smaller, darker, elongated nucleus
- small amount of RER

• small amount of organelles, enough to keep the cell alive

Two stages of activity

The active cells → Fibroblasts

The quiescent cells → Fibrocytes

Macrophage

function: engulfs bacteria & destroys all of it using lysosomes (mostly), except for the ID of the bacteria (antigen)

process: antigen presentation → then it will attach the antigen to a specific molecule on its membrane, it releases cytokines for communication between cells (bioactive materials language of WBCs)

cell: antigen presenting cell

- Macrophages have highly developed phagocytic ability and specialize in turnover of protein fibers and removal of apoptotic cells, tissue debris, or other particulate material
- Being especially abundant at sites of inflammation.
- Size and shape vary considerably, corresponding to their state of functional activity.
- A typical macrophage measures between 10 and 30 µm in diameter and has an eccentrically located, oval or kidney-shaped nucleus.
- They generally have well-developed Golgi complexes and many lysosomes.

Mononuclear Phagocyte System

Cell Type	Major Location	Main Function
Monocyte - WBC	Blood	Precursor of macrophages
Macrophage	Connective tissue, lymphoid organs, lungs, bone marrow, pleural and peritoneal cavities	Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing, and presentation
Kupffer cell	Liver (perisinusoidal)	Same as macrophages
Microglial cell	Central nervous system	Same as macrophages
Langerhans cell	Epidermis of skin	Antigen processing and presentation
Dendritic cell	Lymph nodes, spleen	Antigen processing and presentation
Osteoclast (from fusion of several macrophages)	Bone	Localized digestion of bone matrix
Multinuclear giant cell (several fused macrophages)	In connective tissue under various pathological conditions	Segregation and digestion of foreign bodies

resides in

resides in

resides in

resides in

bone prefix

immune-related functions

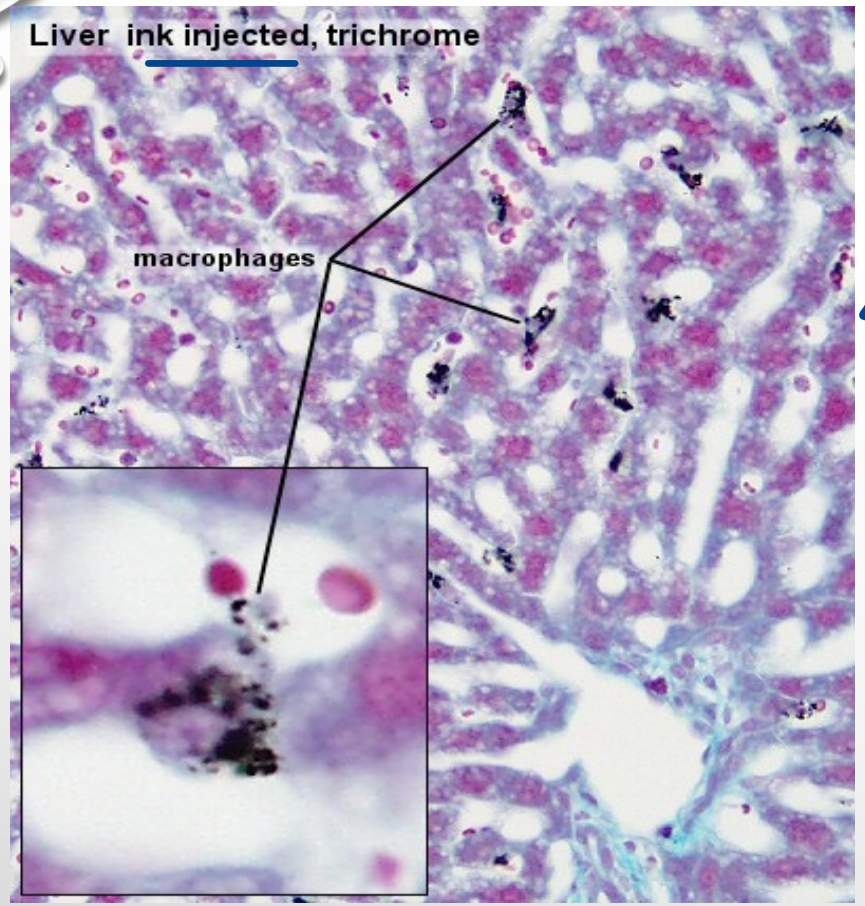
different function

bone is in constant state of reshaping, break down & build

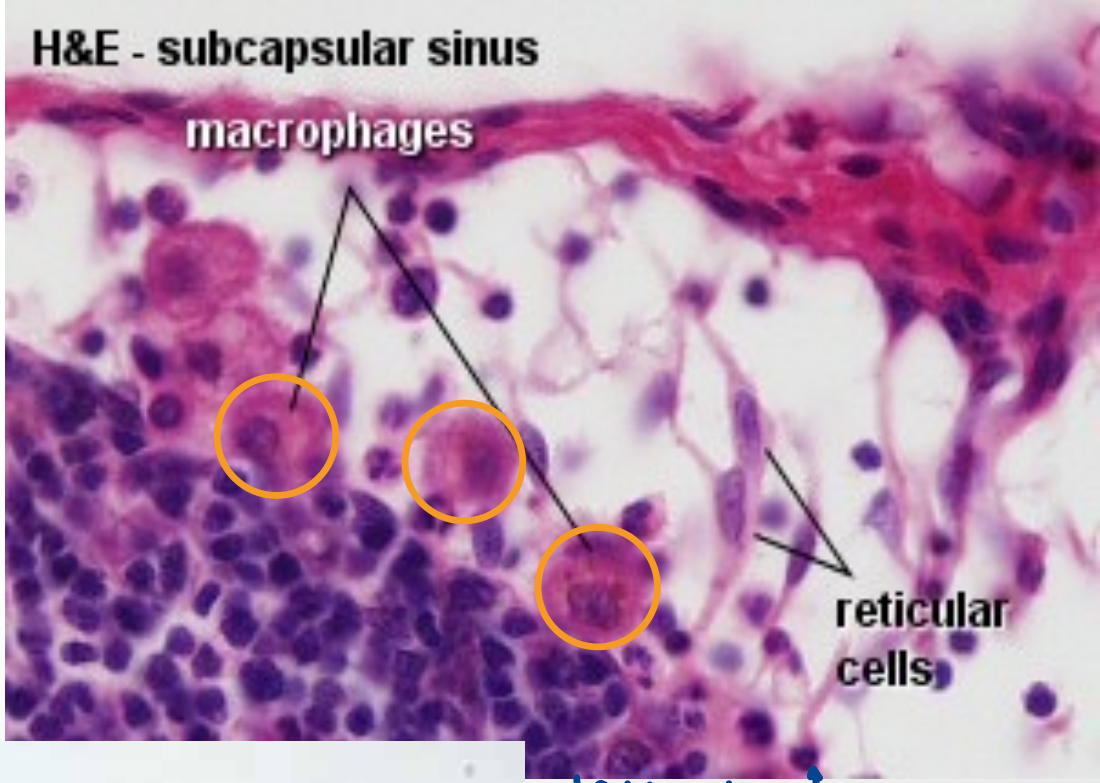
inorganic - can't breakdown

circulates

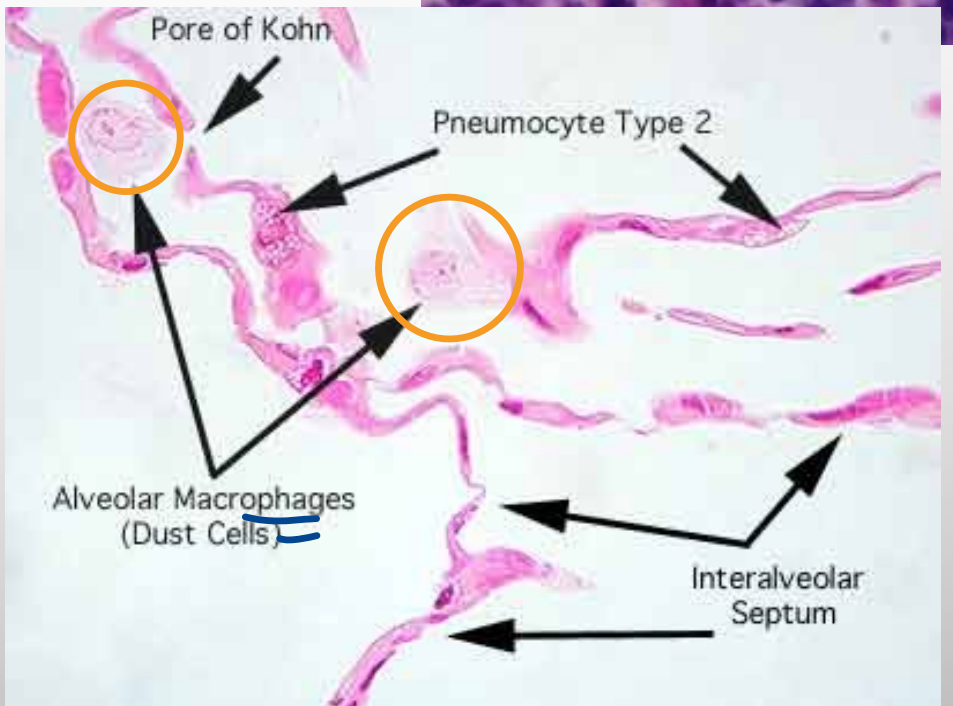
ink → blood → liver → stored in kupffer cells



kupffer cells
↙ storage of ink



large size)



mosquito bite: needle reaches CT
saliva of mosquito contains proteins that alert immune response
high temp, swelling, etc.

Mast Cell → 1st line alerter of the immune system

- Mast cells are oval or irregularly shaped cells of connective tissue,
- Filled with basophilic secretory granules that often obscure the central nucleus
- Mast cells function in the localized release of many bioactive substances, includes the following:

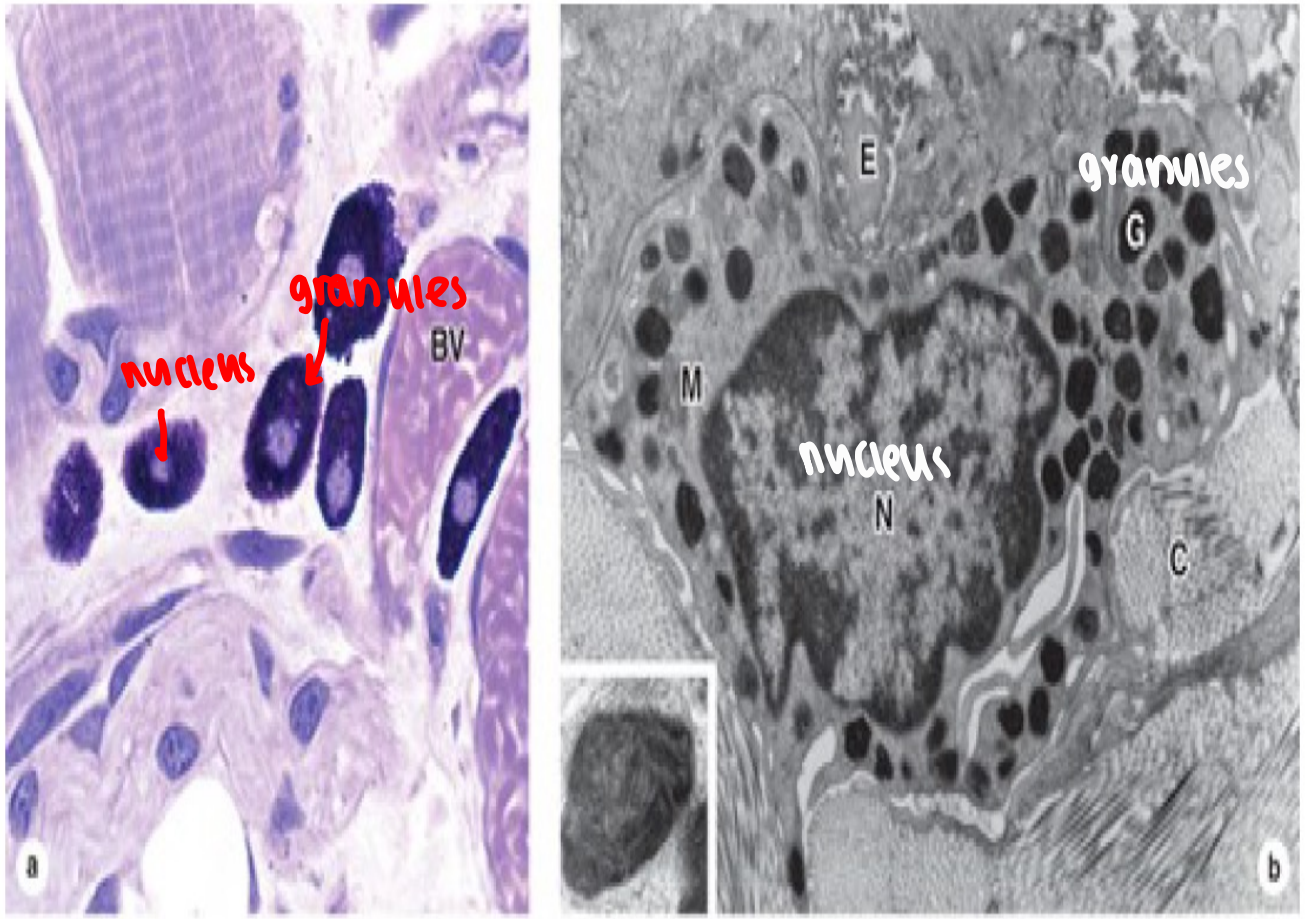
1. Heparin, a sulfated GAG that acts locally as an anticoagulant
2. Histamine: promotes increased vascular permeability and smooth muscle contraction
3. Serine proteases: activate various mediators of inflammation
4. Eosinophil and neutrophil chemotactic factors: attract those leukocytes
5. Phospholipid precursors: converted to other important lipid mediators of the inflammatory reaction.

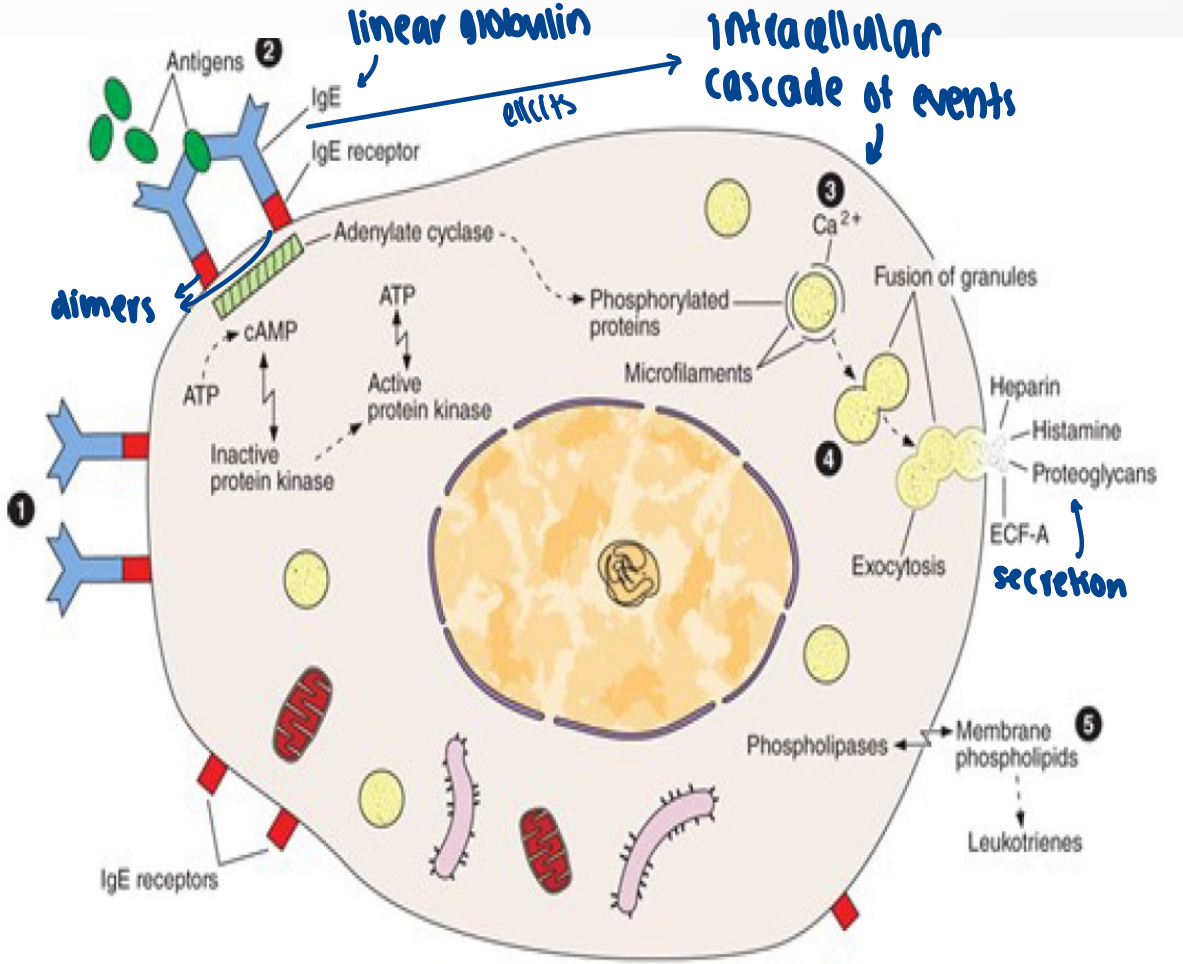
temp inc is a result of circulation of blood
↳ vasodilation = ↑ blood = red color, increase in size

↳ calls other WBCs to fight microorganisms

MAST CELL

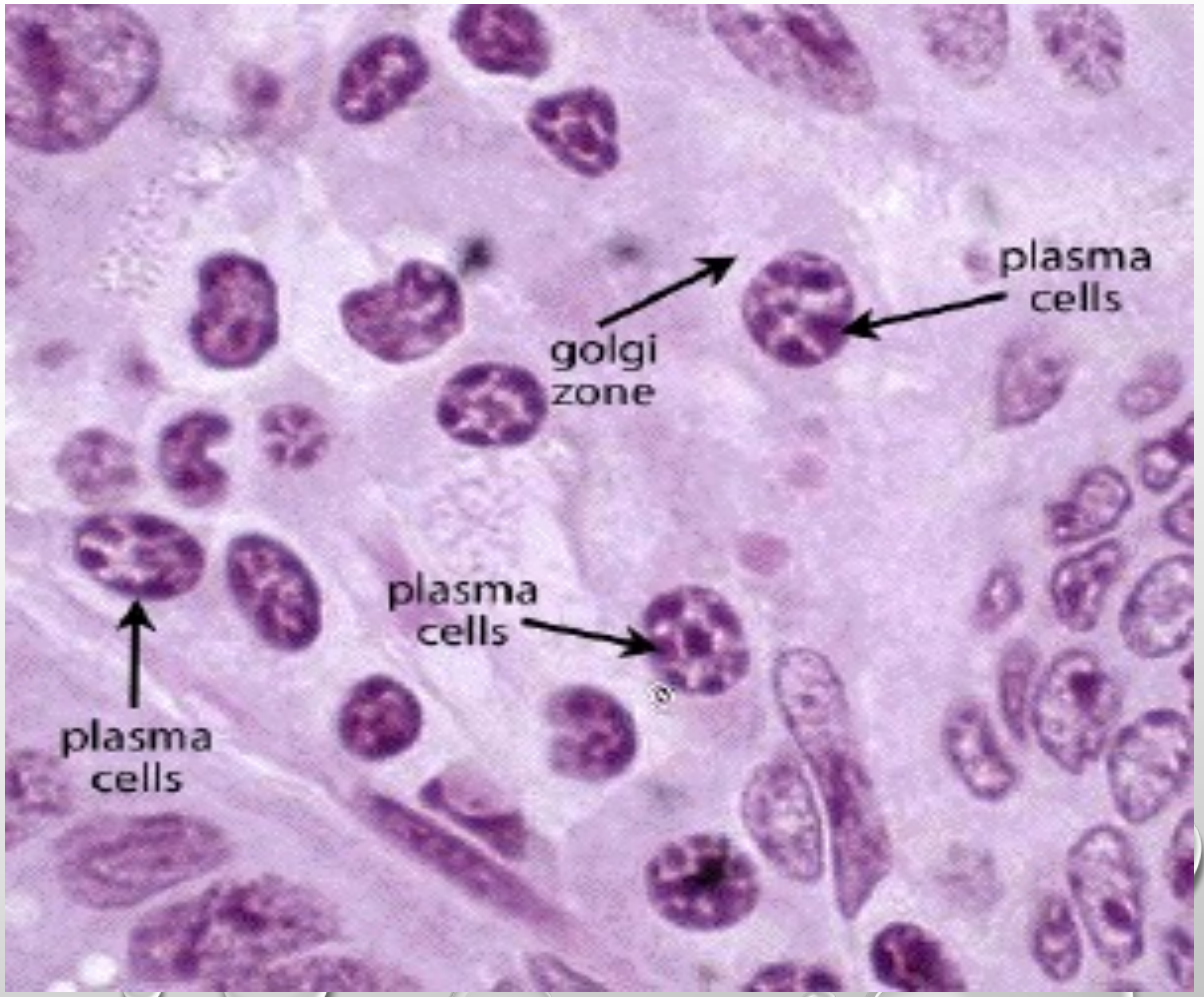
TEM - so we can view granules ← bioactive material





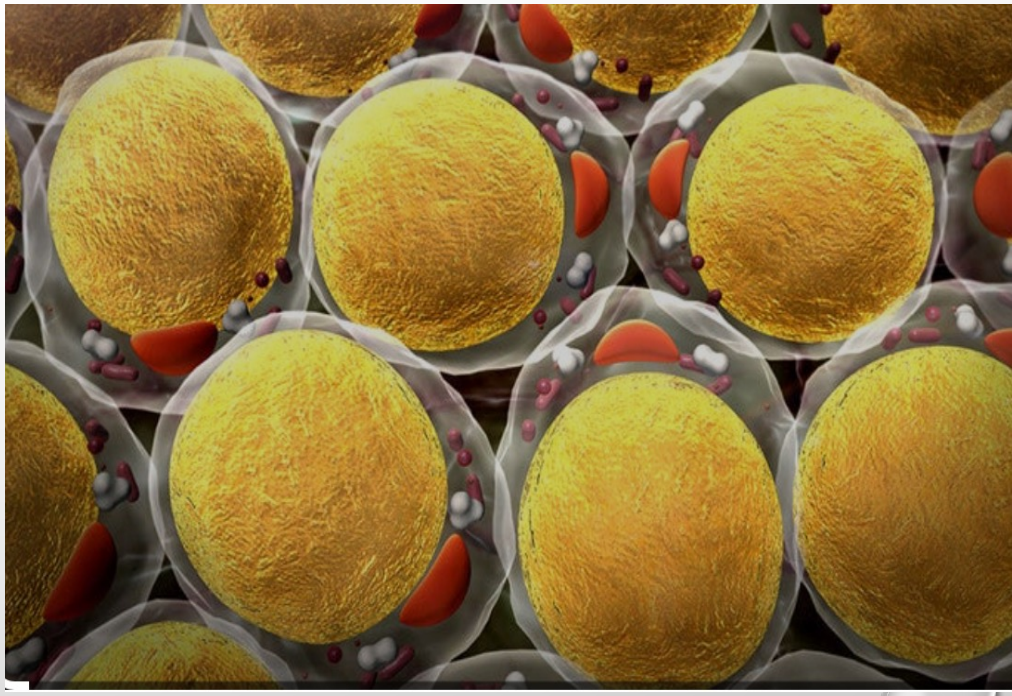
Plasma Cell

- Plasma cells are B lymphocyte-derived, antibody-producing cells.
- Relatively large, ovoid cells have basophilic cytoplasm rich in RER.
- Large Golgi apparatus near the nucleus that may appear pale in routine histologic preparations



Adipose Cells

- Fat cells
- Found in the connective tissue of many organs.
- Large, mesenchymal-derived cells are specialized for cytoplasmic storage of lipid as neutral fats, or less commonly for the production of heat.
- Tissue with a large population of adipocytes, called adipose connective tissue, serves to cushion and insulate the skin and other organs.



Connective Tissue Fibers/Collagen

- Form various extracellular fibers, sheets, and networks.
- Extremely strong and resistant to normal shearing and tearing forces. → ligaments
- Collagen is a key element of all connective tissues, as well as epithelial basement membranes and the external laminae of muscle and nerve cells.
- Most abundant protein in the human body, representing 30% of its dry weight.
- A family of 28 collagens exists in vertebrates.

• collagen I & II can be stained w/ H&E & trichrome staining

Collagen types

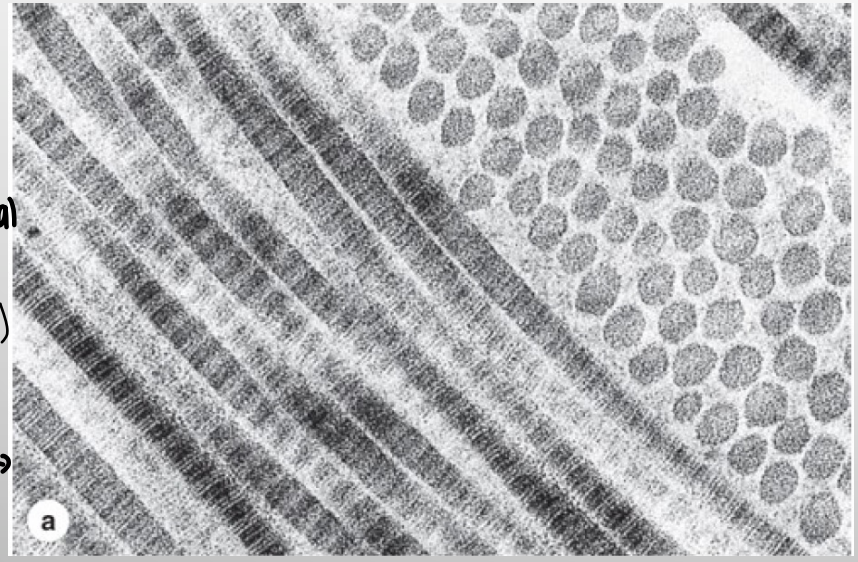
28 collagen types are divided further

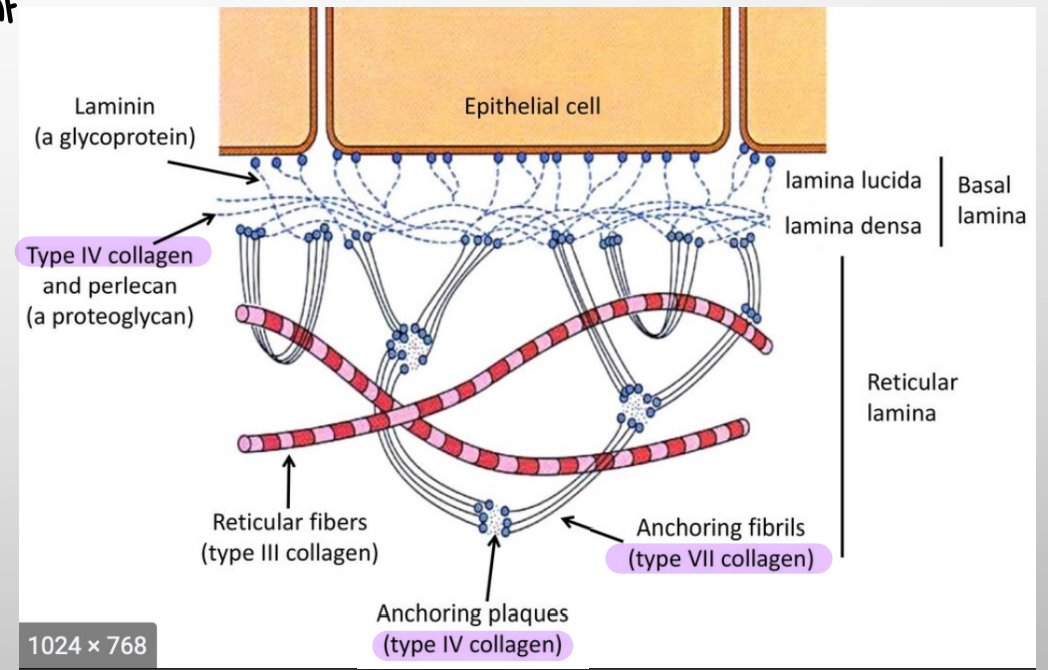
- **Fibrillar collagens**, notably collagen types I, II, and III. Form structures such as tendons, organ capsules, and dermis. → extremely strong, present in structures that offer protection & resistance of tensile forces
- **Network or sheet-forming collagens** such as type IV collagen have subunits produced by epithelial cells and are major structural of external laminae and all epithelial basal laminae.
- **Linking/anchoring** collagens are short. → can link different proteins together

collagen VII & IX

Side-by-side cross sections through fibers + longitudinal sections → has striations (light & dark sections)

Transmission Electron Microscope →





Striations: caused by the assembly of collagens

Collagen Assembly

procollagen subunits ↓

1. Rodlike triple-helix collagen molecules, each 300-nm long, self-assemble in a highly organized, lengthwise arrangement of overlapping regions. → collagen fibrils

2. The regular, overlapping arrangement of subunits continues as large collagen fibrils are assembled.

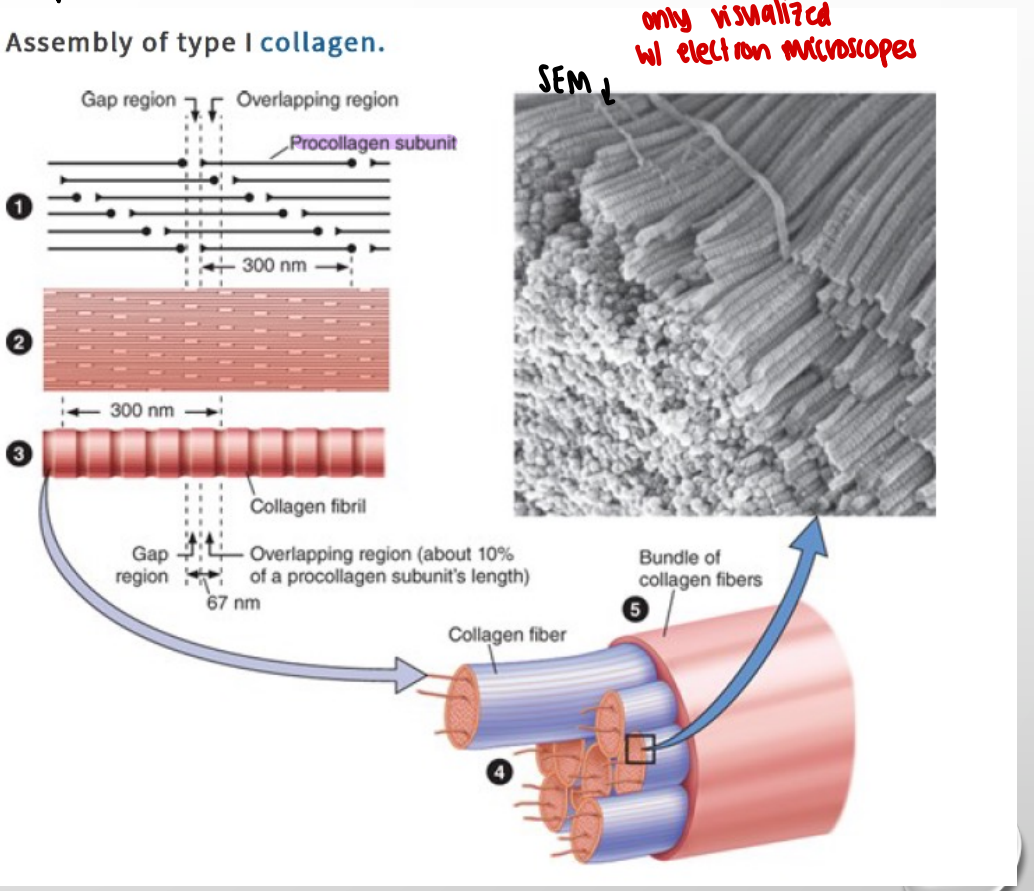
3. This structure causes fibrils to have characteristic cross striations with alternating dark and light bands when observed in the EM.

overlapping of gaps

4. Fibrils assemble further and are linked together in larger collagen fibers visible by light microscopy.

5. Type I fibers often form into still larger aggregates bundled and linked together by other collagens.

how smaller subunits of collagen are assembled → how they look like the SEM image



- assembly of procollagen subunits is in a way that doesn't make tight ends facing each other, there is a smaller gap in each one. This gap takes many rows of procollagen lines for tube gaps to meet → light areas

collagen III

Connective Tissue Fibers/Reticular

- Found in delicate connective tissue of many organs, notably in the immune system.
- Consist mainly of collagen type III, which forms an extensive network.
- Seldom visible in hematoxylin and eosin (H&E) but are stained black after impregnation with **silver** salts.

(1)

(2)

carbonydrates

- Periodic Acid–Schiff (PAS) positive-----due to the high content of sugar chains.
- Reticular fibers contain up to 10% carbohydrate as opposed to 1% in most other collagen fibers.
- Produced by fibroblasts.

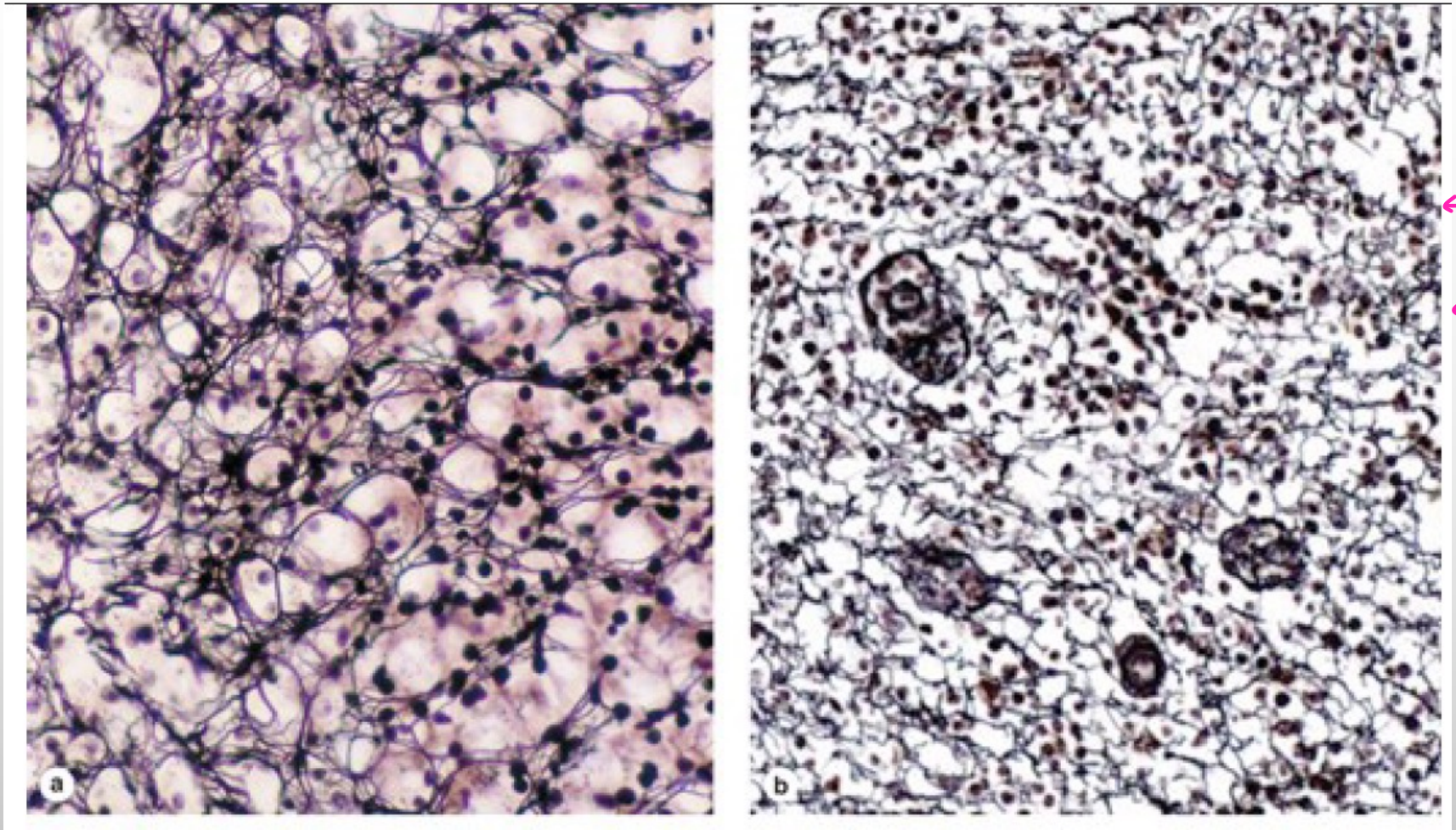
fat cells

- Surround adipocytes, smooth muscle and nerve fibers, and small blood vessels.
- Serve as the supportive stroma for the parenchymal secretory cells, liver and endocrine glands.

creates 3D structure where it protects & houses hepatocytes

- Stroma of hemopoietic tissue (bone marrow), the spleen, and lymph nodes

RETICULAR FIBERS



Lymph nodes- silver stain

← dark black spots: nuclei

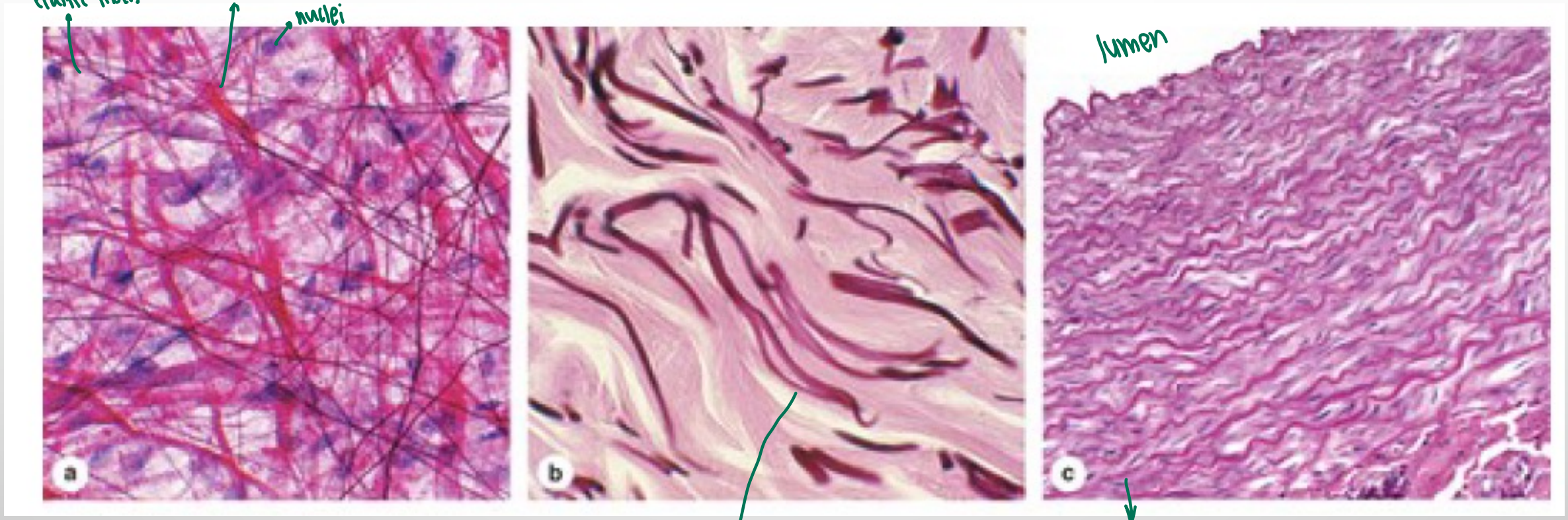
← irregular structures: reticular fibers

offer elasticity (stretches then recoils)

Connective Tissue Fibers/Elastic

- Thinner than the type I collagen fibers and form sparse networks interspersed with collagen bundles in many organs (subject to regular stretching or bending).
  - lungs
  - large blood vessels
  - dermis → skin is pulled & stretched
- Have rubberlike properties that allow tissue containing to be stretched or distended (lungs).
- In the wall of large blood vessels, especially arteries, elastin also occurs as fenestrated sheets called **elastic lamellae**.
- Elastic fibers and lamellae are not strongly acidophilic and stain poorly with H&E.
- Stained more darkly than collagen with other stains such as orcein and aldehyde fuchsin.
  - orcein → brown/blackish
  - aldehyde → maroon/red

Connective Tissue Fibers/Elastic



A- Hematoxylin and orcein)
B-Aldehyde fuchsin)
C- H&E

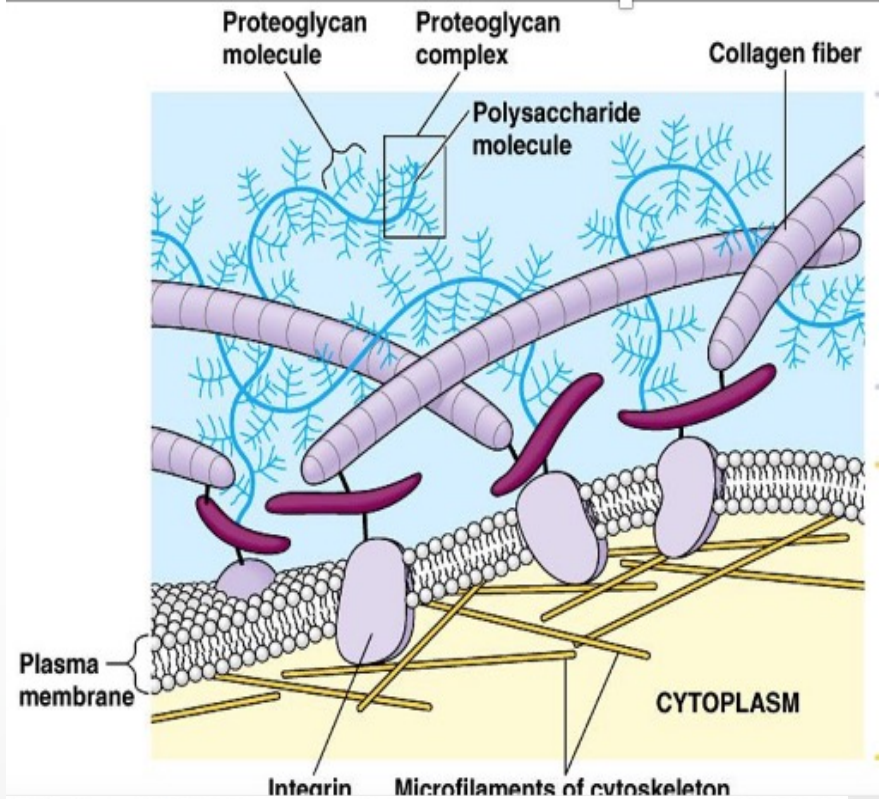
Ground Substance

rich w/ sulfate ↓

- A semi- fluid gel (highly hydrated) and transparent material
- The ground substance of the ECM is a highly hydrated (with much bound water), transparent, complex mixture of three major kinds of macromolecules: glycosaminoglycans (GAGs), proteoglycans, and multiadhesive glycoproteins. specific GS based on types of CT
- Filling the space between cells and fibers in connective tissue.
- Allows diffusion of small molecules.
- Because it is viscous---lubricant and a barrier to the penetration of invaders.

ex. umbilical cord

• halts abilities of microorganisms to cause more destruction



GS Component pt. 1:

GAGs

Glycos Amino Glycans

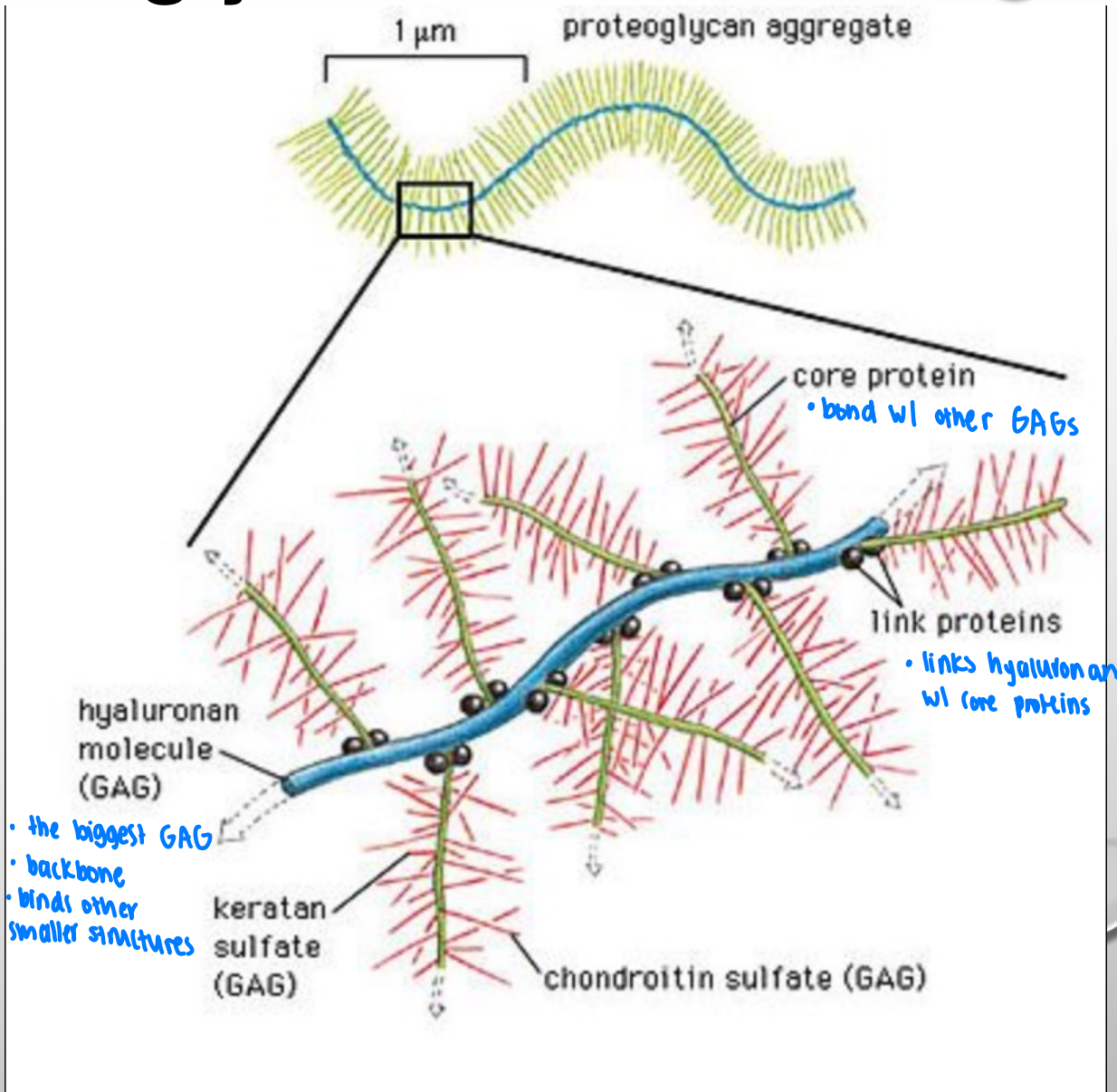
- GAGs (mucopolysaccharides) are long polymers of repeating disaccharide units, usually a hexosamine and uronic acid. different sugar : different GAGs
- The largest and most ubiquitous is hyaluronan (hyaluronate or hyaluronic acid).
- Hyaluronan forms a viscous, pericellular network that binds a considerable amount of water (diffusion through connective tissue and in lubricating various organs and joints). like in the umbilical cord

GAGs

- All other GAGs are much smaller, sulfated, bound to proteins (as parts of proteoglycans). have sugars & proteins
- Major GAGs found in proteoglycans are dermatan sulfate, chondroitin sulfates, keratan sulfate, and heparan sulfate (different disaccharide units)
- Their high negative charge forces GAGs to an extended conformation and causes them to sequester cations as well as water. → stain basic, appear blue
- These features provide GAGs with space-filling, cushioning, and lubricant functions.

GAGs that form proteoglycans

- Hyaluronic acid
- Chondroitin 4-sulfate
- Chondroitin 6-sulfate
- Dermantan sulfate
- Heparan sulfate
- Heparin
- Keratan sulfate



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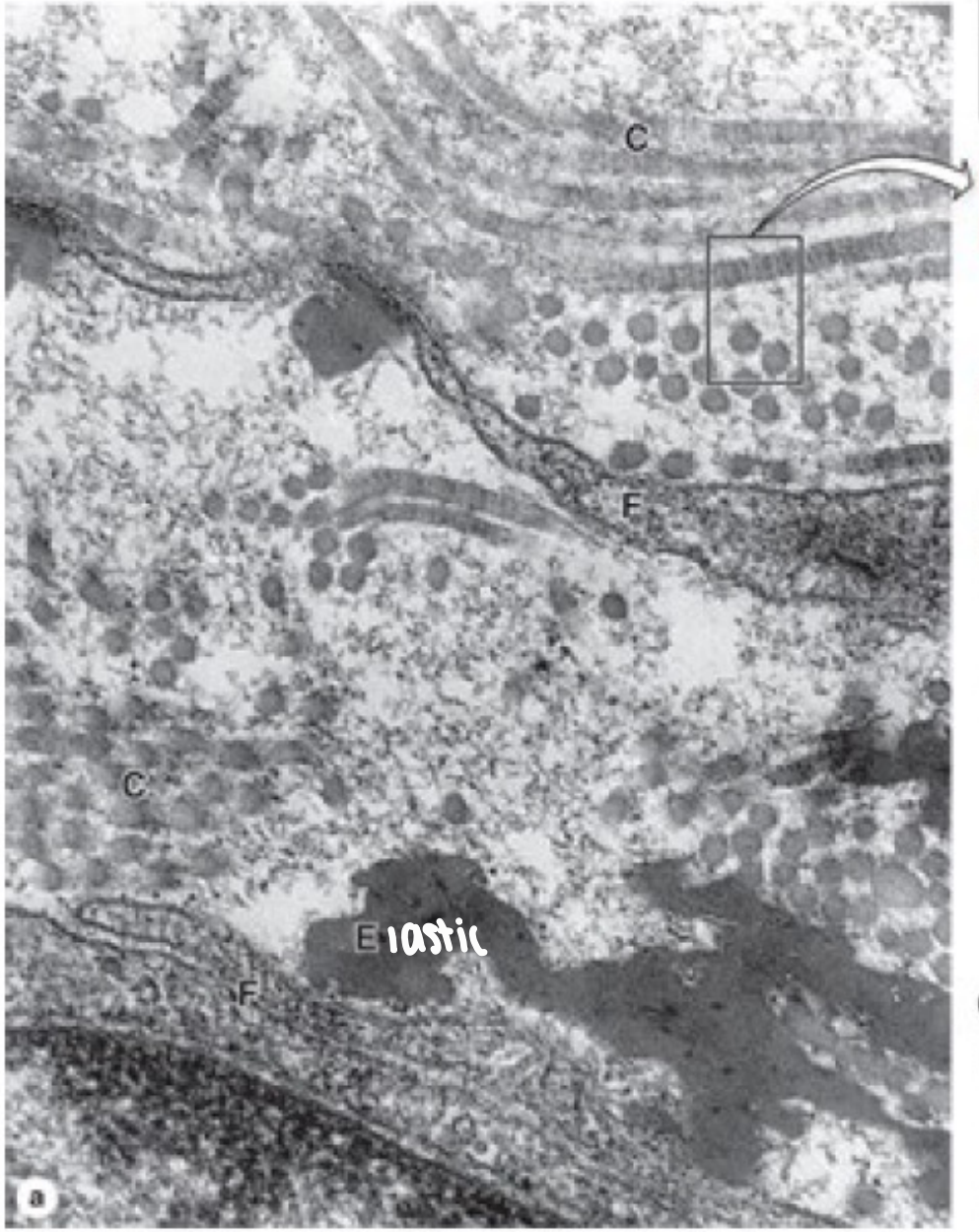
C
F
C
Elastic
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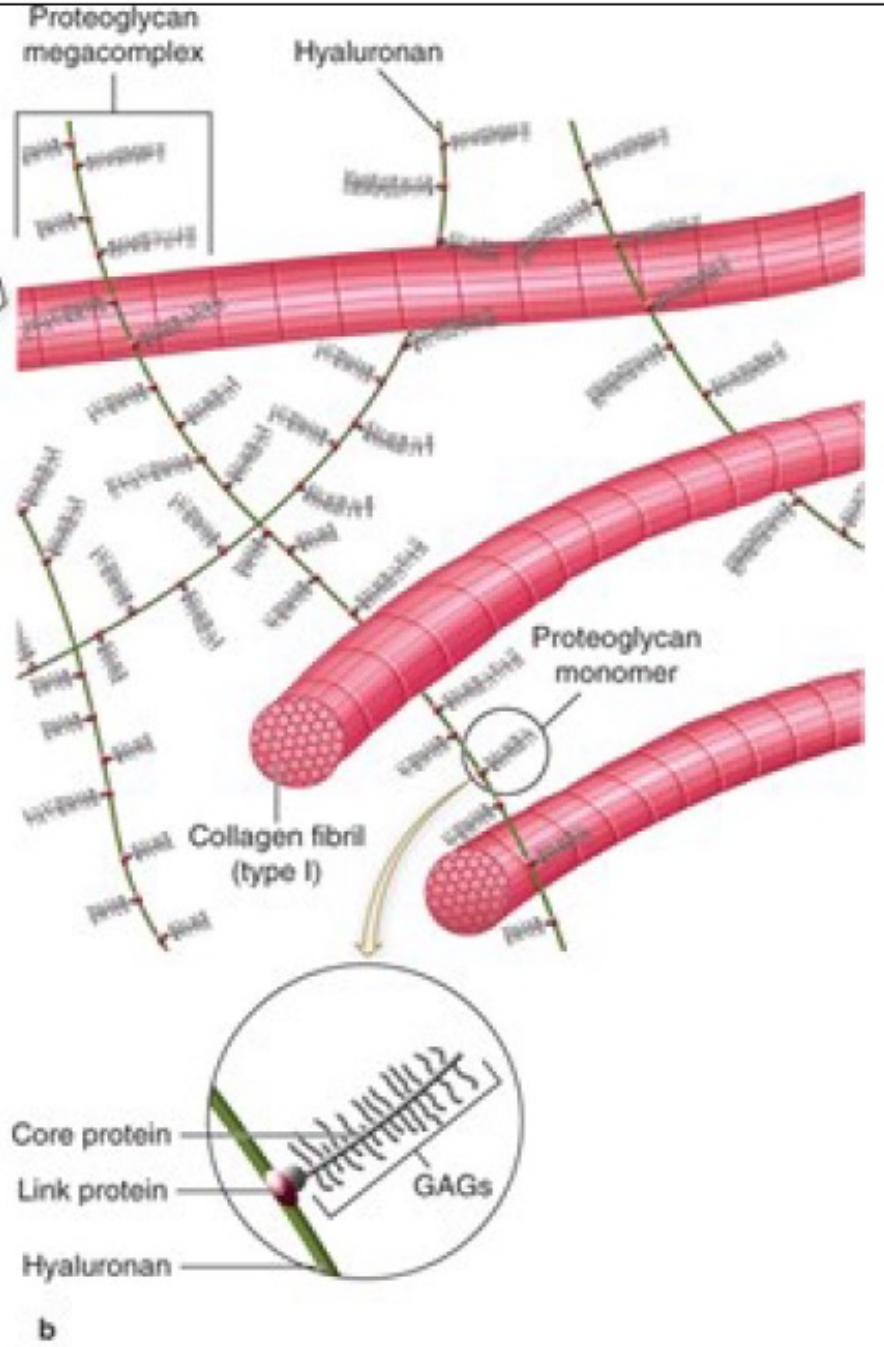

Proteoglycan megacomplex
Hyaluronan
Proteoglycan monomer
Collagen fibril (type I)
Core protein
Link protein
Hyaluronan
GAGs
b

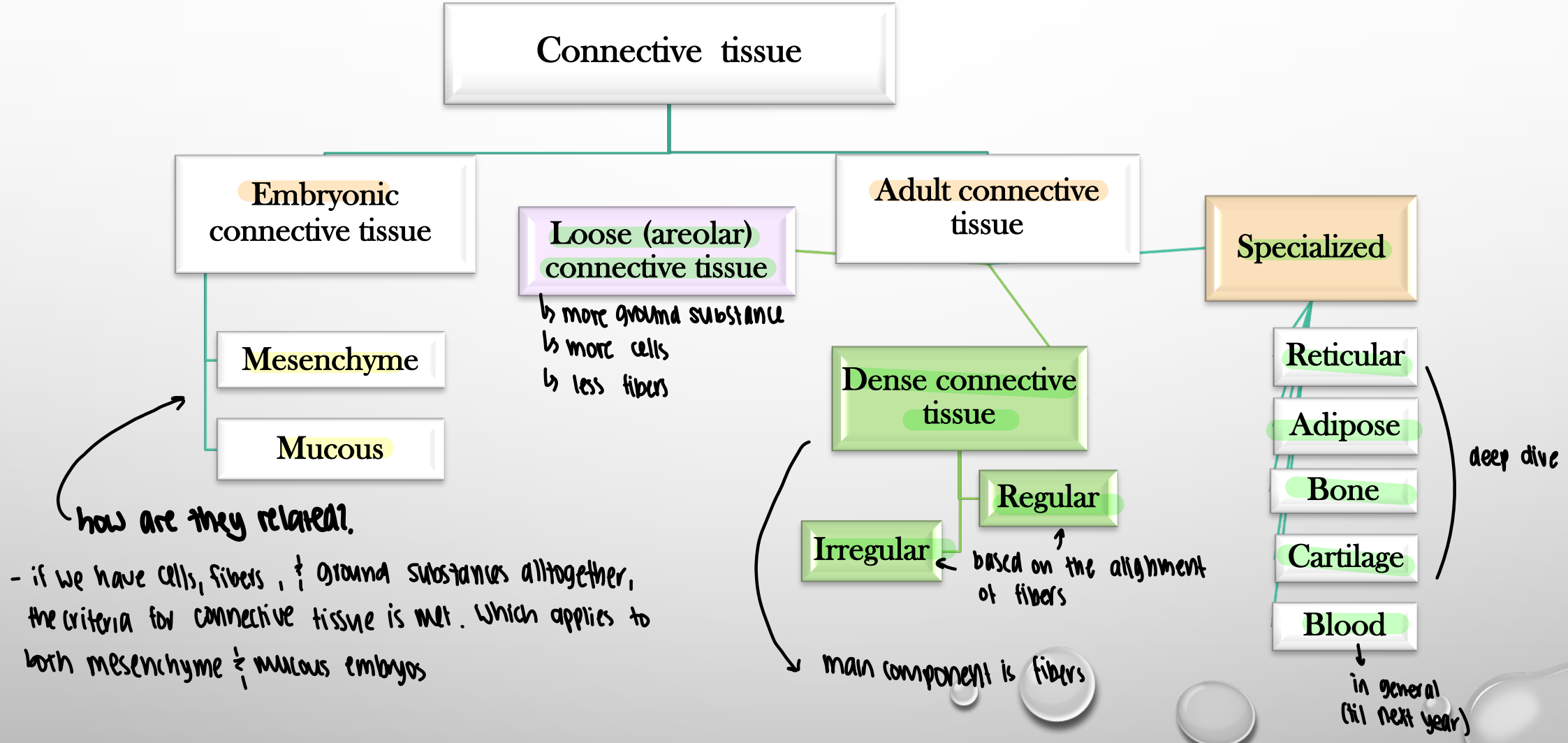
GAGs

MEMORIZE

Read only

Glycosaminoglycan	Repeating Disaccharides		Distribution	Will acquire down the road Electrostatic Interaction with Collagen
	Hexuronic Acid	Hexosamine		
Hyaluronic acid	D-glucuronic acid	D-glucosamine	Umbilical cord, synovial fluid, vitreous humor, cartilage	
Chondroitin 4-sulfate	D-glucuronic acid	D-galactosamine	Cartilage, bone, cornea, skin, notochord, aorta	High levels of interaction, mainly with collagen type II
Chondroitin 6-sulfate	D-glucuronic acid	D-galactosamine	Cartilage, umbilical cord, skin, aorta (media)	High levels of interaction, mainly with collagen type II
Dermatan sulfate	L-iduronic acid or D-glucuronic acid	D-galactosamine	Skin, tendon, aorta (adventitia)	Low levels of interaction, mainly with collagen type I
Heparan sulfate	D-glucuronic acid or L-iduronic acid	D-galactosamine	Aorta, lung, liver, basal laminae	Intermediate levels of interaction, mainly with collagen types III and IV
Keratan sulfate	D-galactose	D-glucosamine	Cartilage, nucleus pulposus, annulus fibrosus	None

Classification Of Connective Tissue

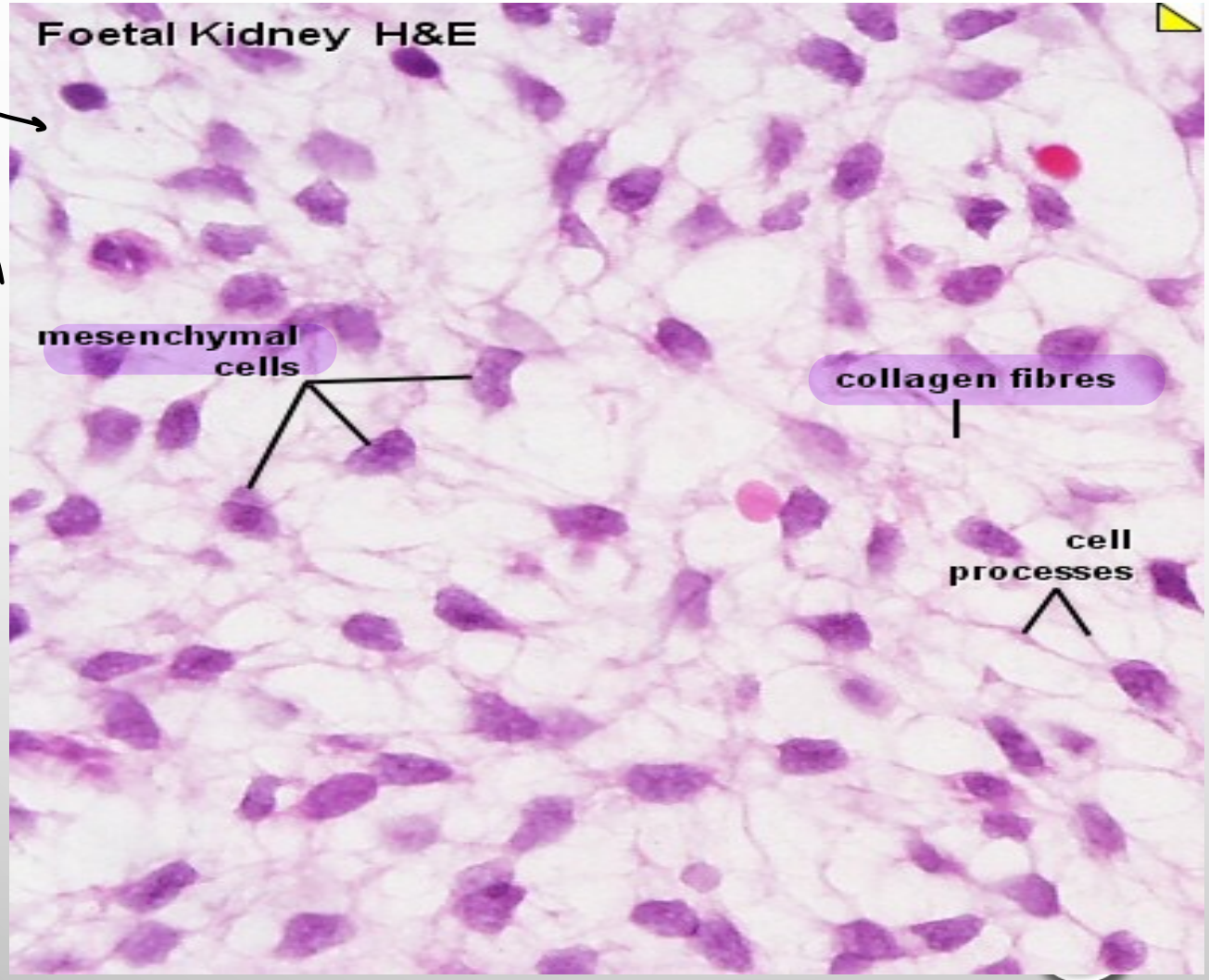


Classification-Embryonic CT

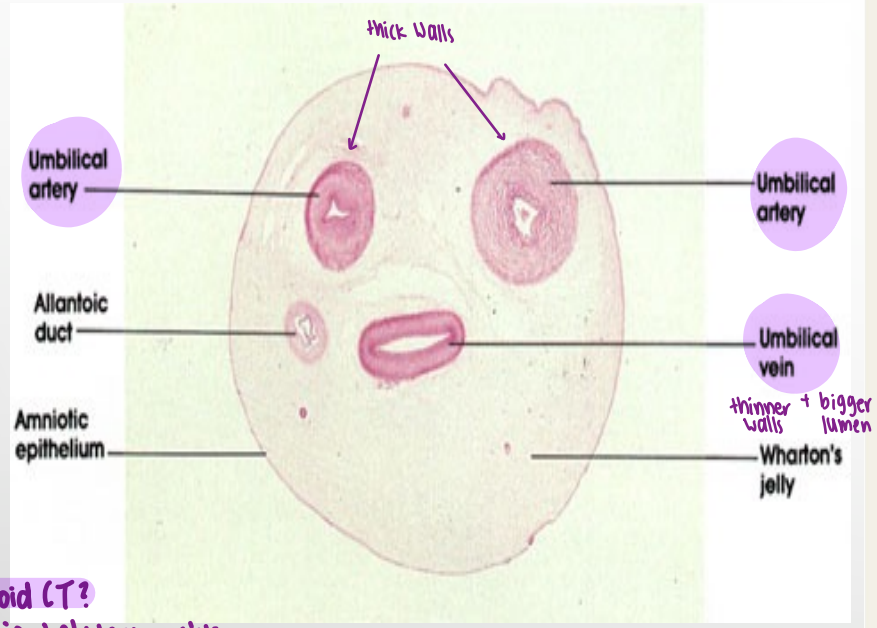
Embryonic Connective Tissues	General Organization	Major Functions	Examples
Mesenchyme ↳ source for various types of CT	Sparse, undifferentiated cells, uniformly distributed in matrix with sparse collagen fibers scattered	Contains stem/progenitor cells for all adult connective tissue cells → fibroblasts, osteoblasts, etc depending on type of CT • usually they are surrounded by the matrix which will contain collagen fibers (not a lot) & a decent amount of ground substance & hyaluronic acid (largest glycosaminoglycans in that family)	Mesodermal layer of early embryo
Mucoid (mucous) connective tissue	Random fibroblasts and collagen fibers in viscous matrix	Supports and cushions large blood vessels	Matrix of the fetal umbilical cord ↳ born w/ the baby

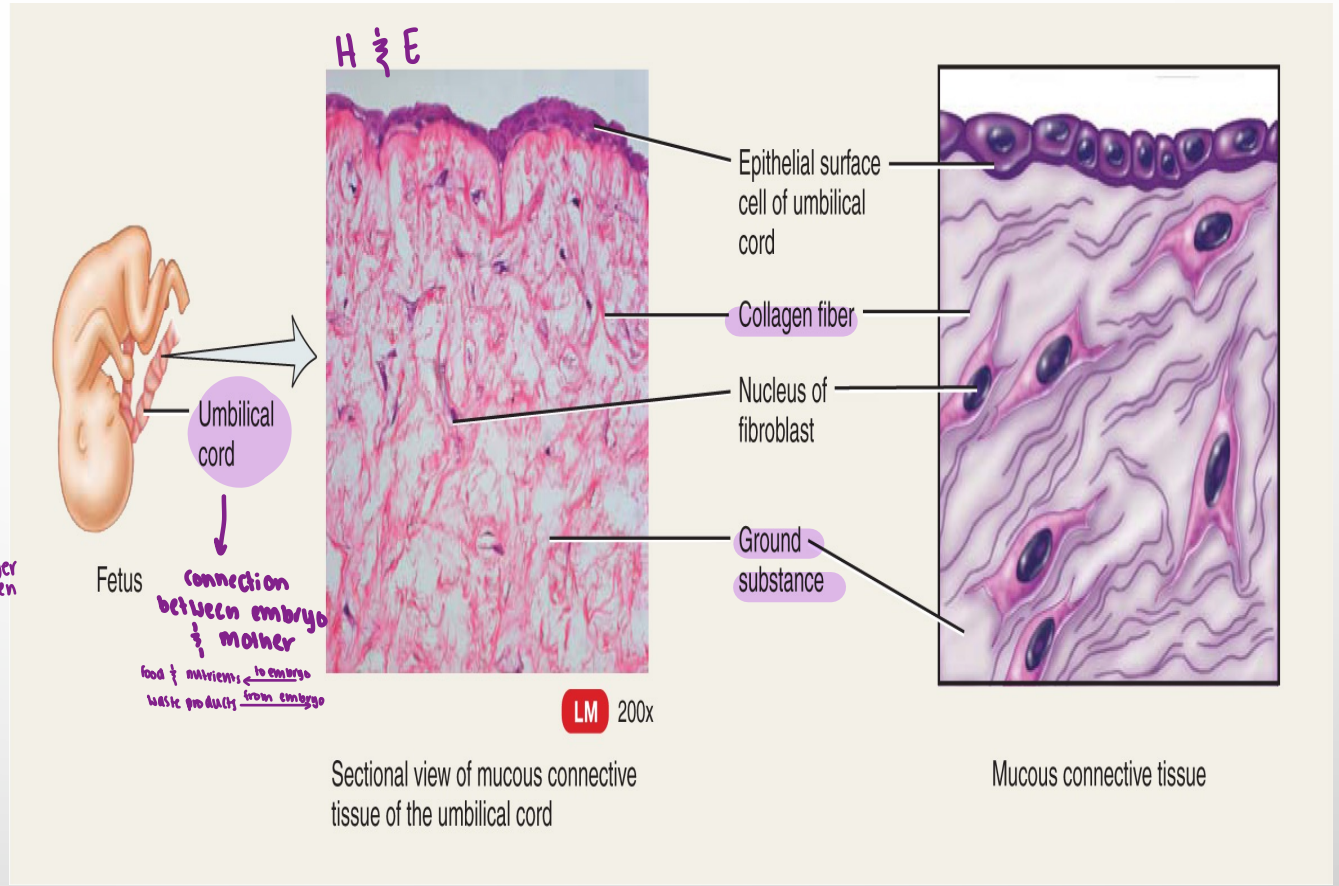
Mesenchyme

- White spaces are not empty, they contain ground substances
- evenly distributed



Mucous Connective Tissue





where is the mucoid CT?
- it is running in between, filling all spaces, surrounding, separating, & cushioning these vessels + protecting them from any damage that could lead to their blockage

what is in the mucoid CT?
- number of fibroblasts
- have a really low # of mesenchymal cells :

easier to extract as a baby than as an adult
↓
can be extracted from Mucoid CT in the umbilical cord after delivery

why?

because mesenchymal stem cells can help cure diseases for the baby

Classification-Adult CT

regular vs. irregular:
- differ in direction of collagen fibers
- regular (ligaments): run parallel to each other = resistance of tensile strength in a unidirectional scheme
- irregular (dermis): collagen fibers are in different directions, therefore offering resistance of tensile forces in different directions

	General Organization	Major Functions	Examples
Connective Tissue Proper		• found wherever cushioning & support of delicate structures e.g. blood vessels	
loose: cushion & support Loose (areolar) connective tissue	Much ground substance; many cells and little collagen, randomly distributed	Supports microvasculature, nerves, and immune defense cells	Lamina propria beneath epithelial lining of digestive tract
dense: protection & strength Dense irregular connective tissue	Little ground substance; few cells (mostly fibroblasts); much collagen in randomly arranged fibers	Protects and supports organs; resists tearing	Dermis of skin, organ capsules, submucosa layer of digestive tract
↳ more fibers Dense regular connective tissue	Almost completely filled with parallel bundles of collagen; few fibroblasts, aligned with collagen	Provide strong connections within musculoskeletal system; strong resistance to force	Ligaments, tendons, aponeuroses, corneal stroma

(can withstand shearing & tensile forces)
hold 2 bones together, needs strength, contains many collagen fibers

strength
ligaments > steel

Classification-Specialized CT

- create smaller spaces to support delicate cells, nerve cells & smaller vessels

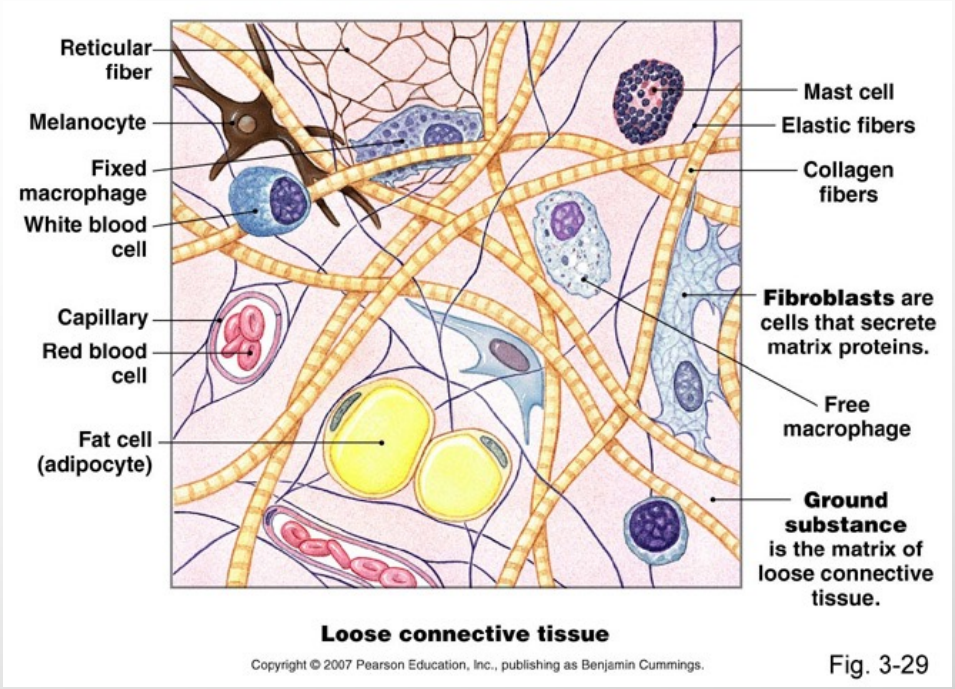
- reticular CT: fibroblasts w/ more specificity to what fiber types they synthesize & release

	General Organization	Major Functions	Examples
Reticular connective tissue (see Chapter 14)	Delicate network of reticulin/collagen III with attached fibroblasts (reticular cells)	Supports blood-forming cells, many secretory cells, and lymphocytes in most lymphoid organs	Bone marrow, liver, pancreas, adrenal glands, all lymphoid organs except the thymus

↳ present in tissues in specific organs where the main fibers are reticular fibers (collagen III)

Loose (Areolar) Connective Tissue

- Consists of all 3 types of fibers, several types of cells, and semi-fluid ground substance.
  - ↳ gives it its features, function, & "looseness"
  - ↳ allows for passage/diffusion of the nutrients from blood vessels in CT to overlying epithelium
- Found in subcutaneous layer and mucous membranes, and around blood vessels, nerves and organs
- Function = strength, support and elasticity



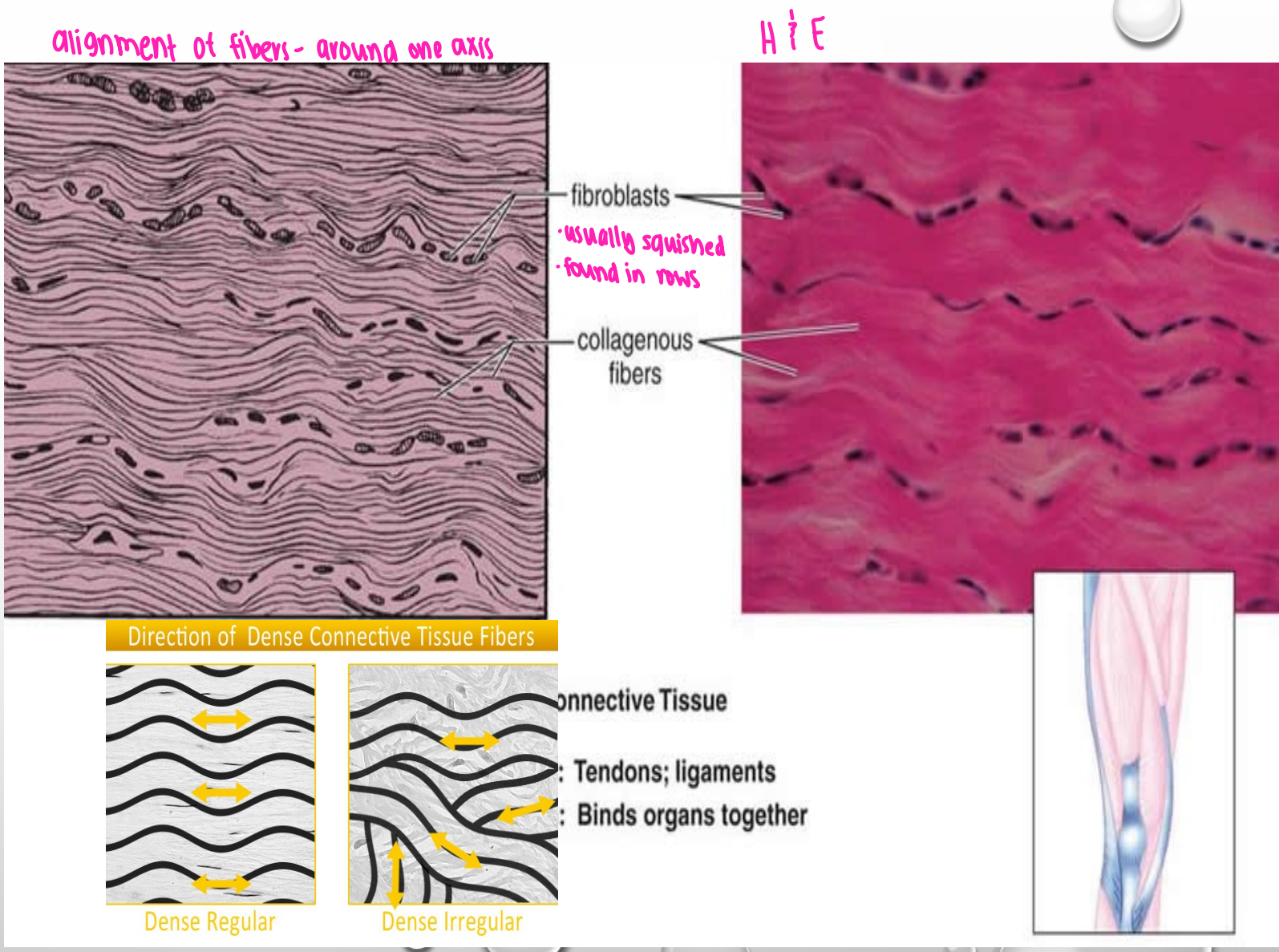
Dense Connective Tissue

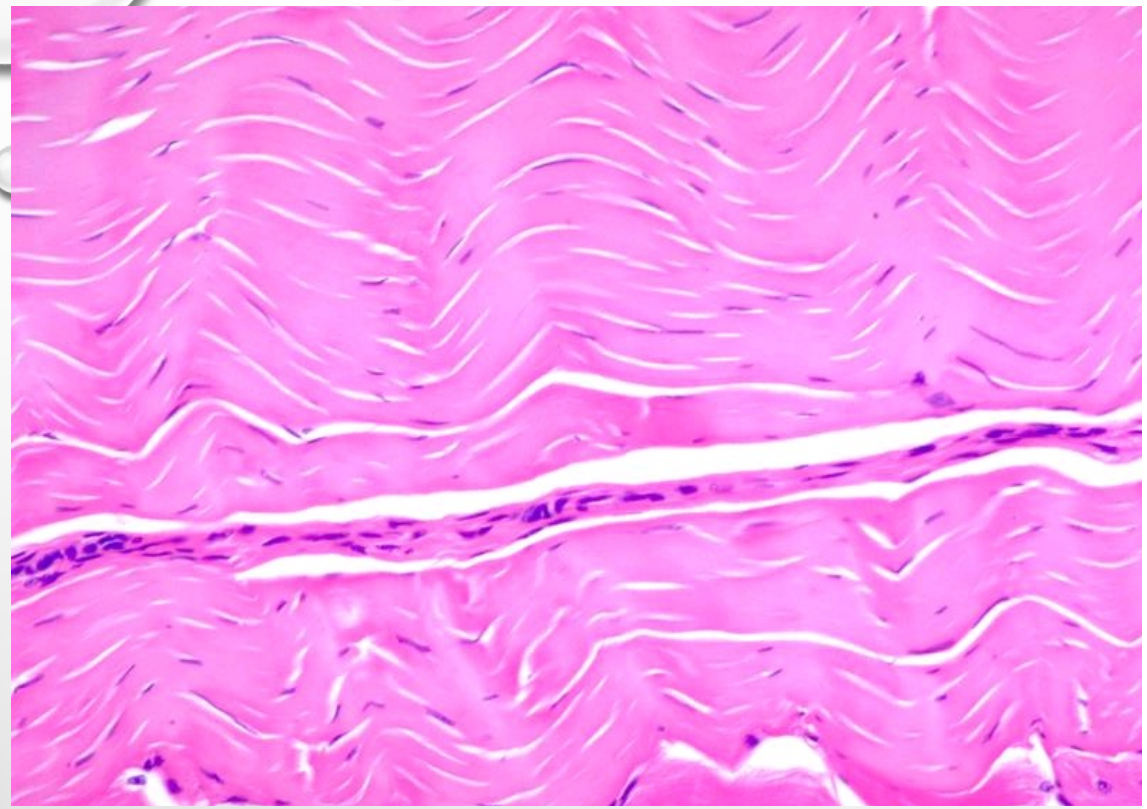
Contains more numerous and thicker fibers and far fewer cells than loose CT.

a. Dense regular connective tissue
   Tendons and ligaments
   CT at the end of muscles
   muscle-bone
   bone-bone
b. Dense irregular connective tissue
   Dermis of skin

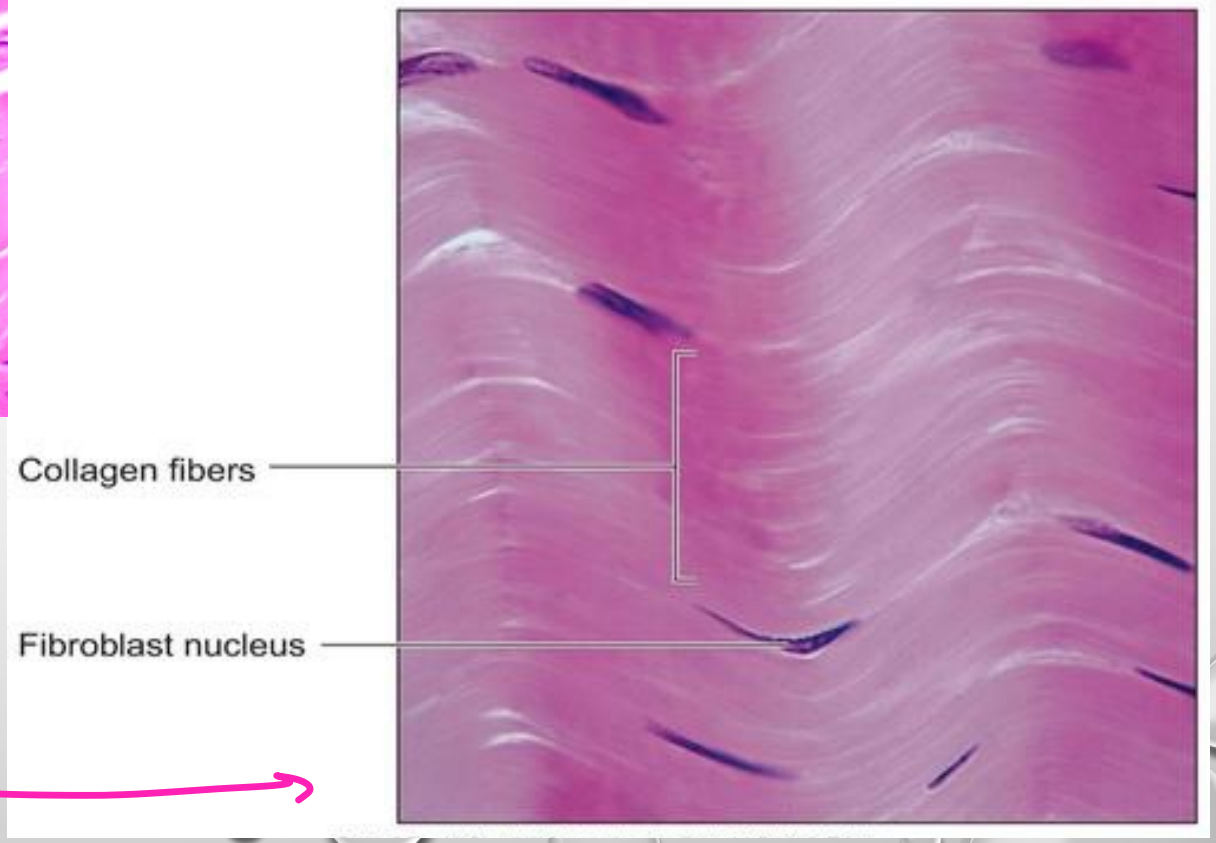
Dense Regular Connective Tissue

- Consists of bundles of collagen fibers and fibroblasts.
- Forms tendons, ligaments.
- Function = provide strong attachment between various structures.





H & E, light microscope



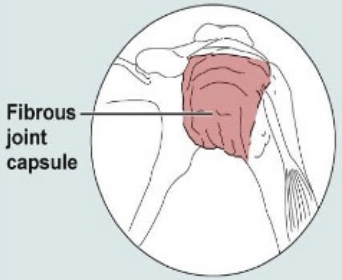
Dense Irregular CT

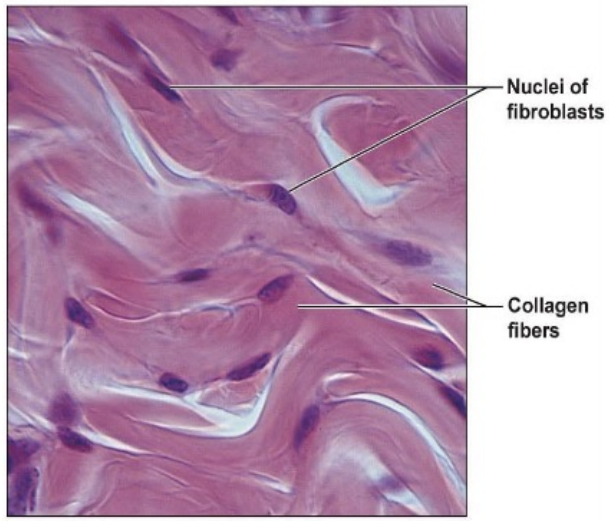
- Consists Of Randomly-arranged Collagen Fibers And A Few Fibroblasts.
- Found In Dermis Of Skin, capsules of joints and organs
- Function = Provide Strength and protection

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

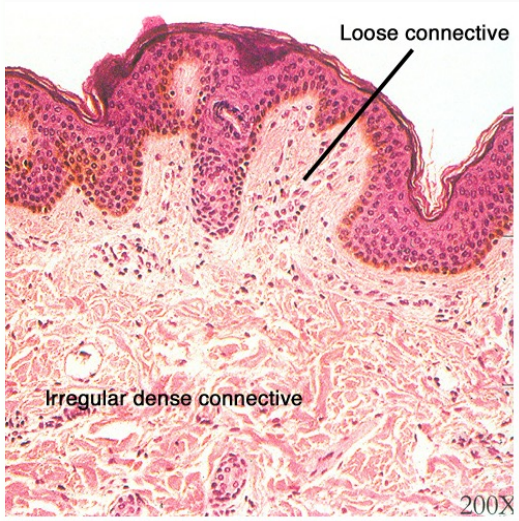
Function: Able to withstand tension exerted in many directions; provides structural strength.

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 (600×).

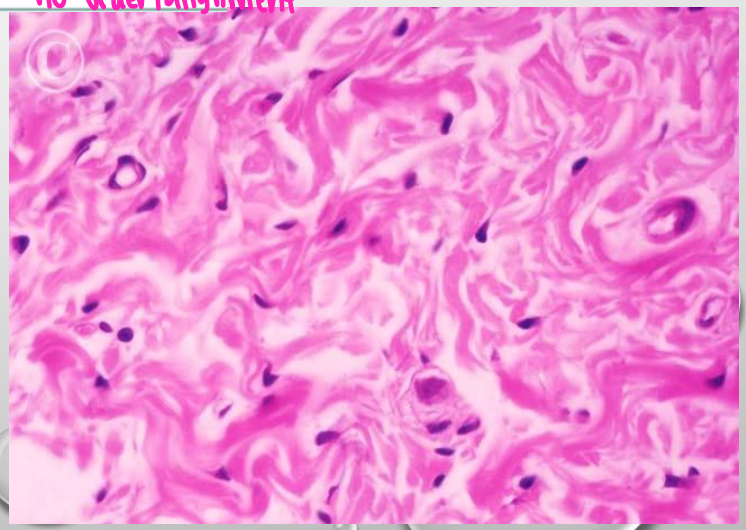


dermis - has 2 layer

loose layer: adjacent to epithelium

dense layer lies deeper

•no order/alignment



Elastic Connective Tissue

↳ Contains lots of elastic laminae in its walls, allows stretching & recoiling.

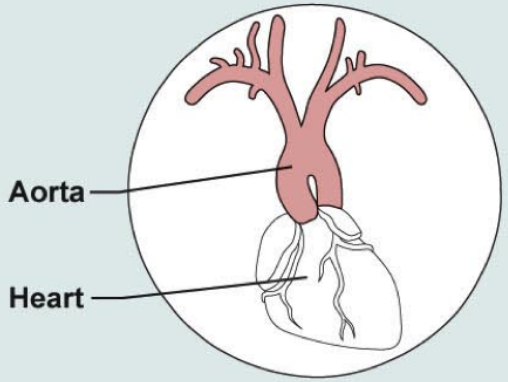
↳ can't be stained properly using H & E, need orcin to visualize & distinguish them from neighboring collagen fibers

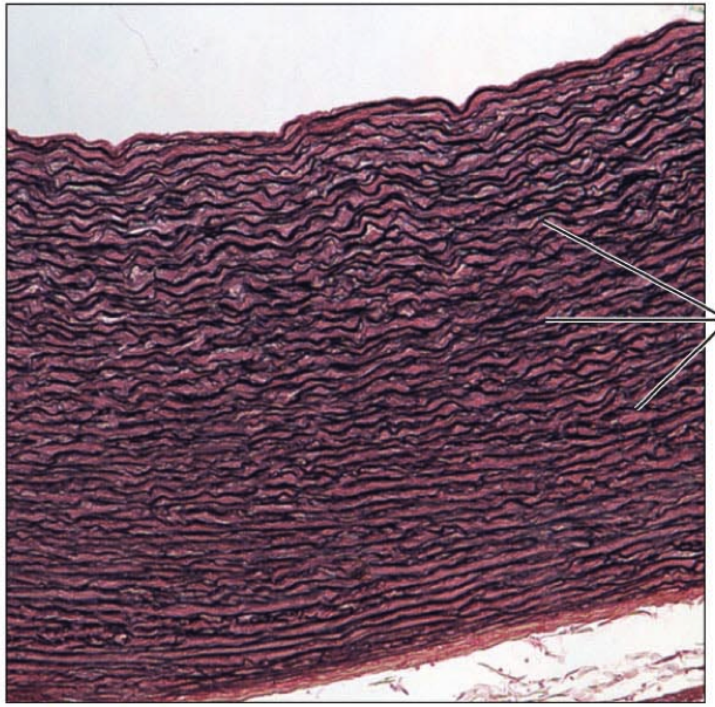
(g) Connective tissue proper: dense connective tissue, elastic

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

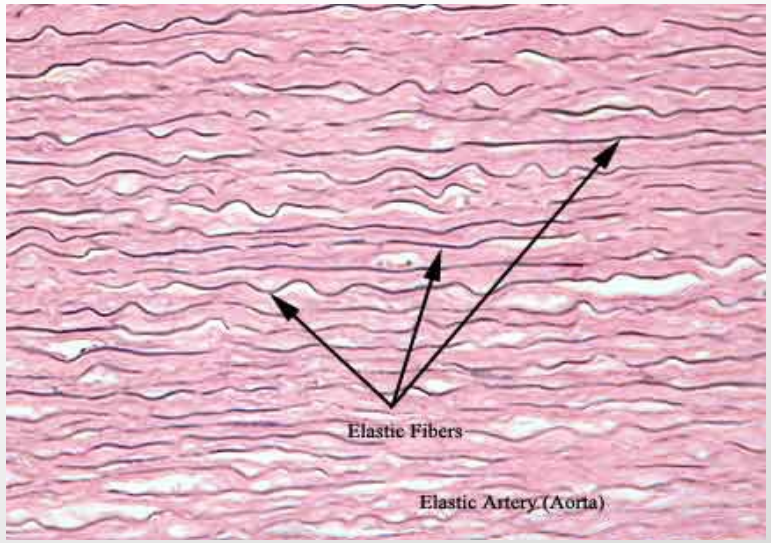
Function: Allows recoil of tissue following stretching; maintains pulsatile flow of blood through arteries; aids passive recoil of lungs following inspiration.

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 (85×).



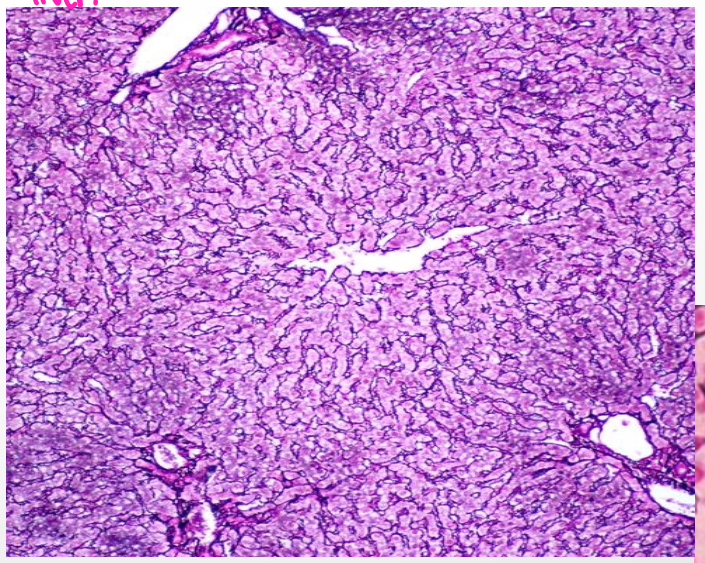
Aorta: Biggest blood vessel that emerges from the LV of the ♡ carries oxygenated blood to the rest of the body.

RETICULAR CT

• reticular cells : cells that synthesize & release reticular fibers

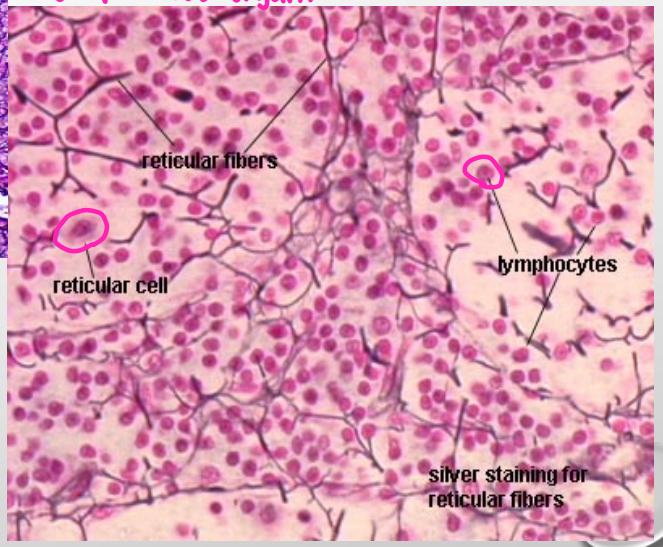
- Consists of fine interlacing reticular fibers and reticular cells.
- Found in liver, spleen and lymph nodes.
  (delicate tissues) (+ bone marrow)
- Function = forms the framework (stroma) of organs and binds together smooth muscle tissue cells.

liver:



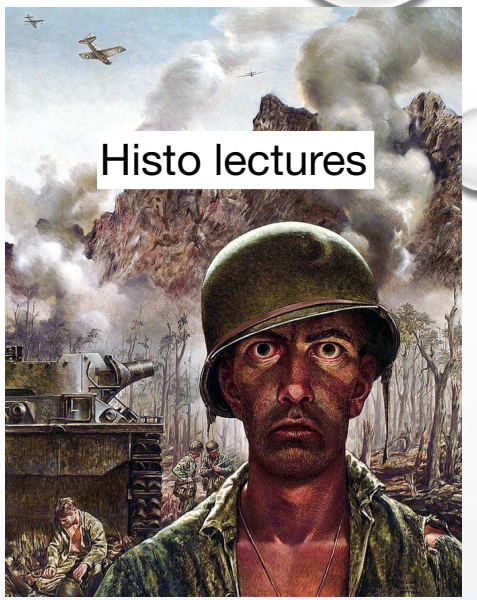
darker areas that are reticular fibers, which support, surround, & protect the hepatocytes (liver cells)

lymph node organ:



lymphocytes < reticular cells in nucleus size

Medical Application Collagen



Scurvy	Lack of vitamin C, a required cofactor for prolyl hydroxylase	Ulceration of gums, hemorrhages
Osteogenesis imperfecta	Change of 1 nucleotide in genes for collagen type I	Spontaneous fractures, cardiac insufficiency