

Connective Tissue

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One of the most versatile tissues in the human body



General Features

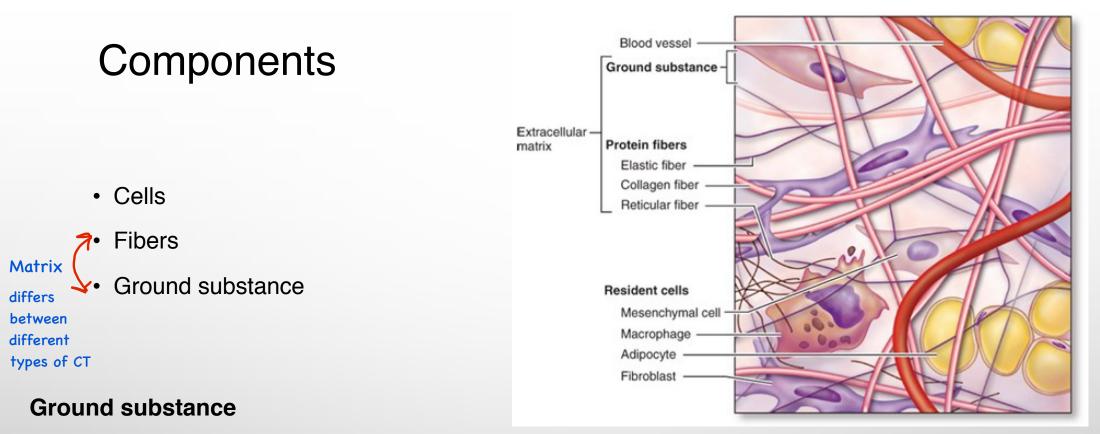
- <u>Connective tissue provides a matrix that supports and physically connects other tissues</u> and cells together to form the organs of the body.
- The interstitial fluid of connective tissue gives metabolic support to cells as the medium for diffusion of nutrients and waste products.
- Composed of cells (fixed and wandering), fibers and ground substance.
- Variable vascularity.
- Variable regenerative power. Depend on vascularity

Functions

- 1. Structural framework for body. bones, and associated cartilage
- 2. Transportation of fluids and dissolved substances. ^{blood}
- 3. Protection of delicate organs. Gland and kidney surrounded by capsule
- 4. Supports, surrounds, and connects other tissues. ligaments and fascia
- 5. Storage of energy in the form of lipids. adipose tissues
- 6. Defend the body against microorganisms. White blood cell

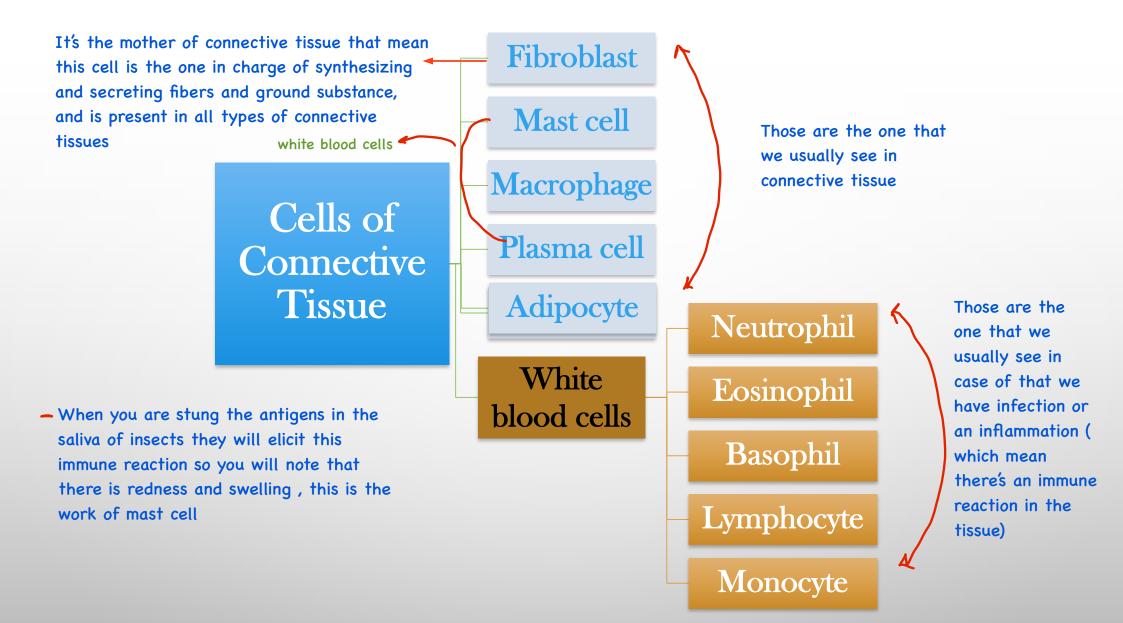
Origin

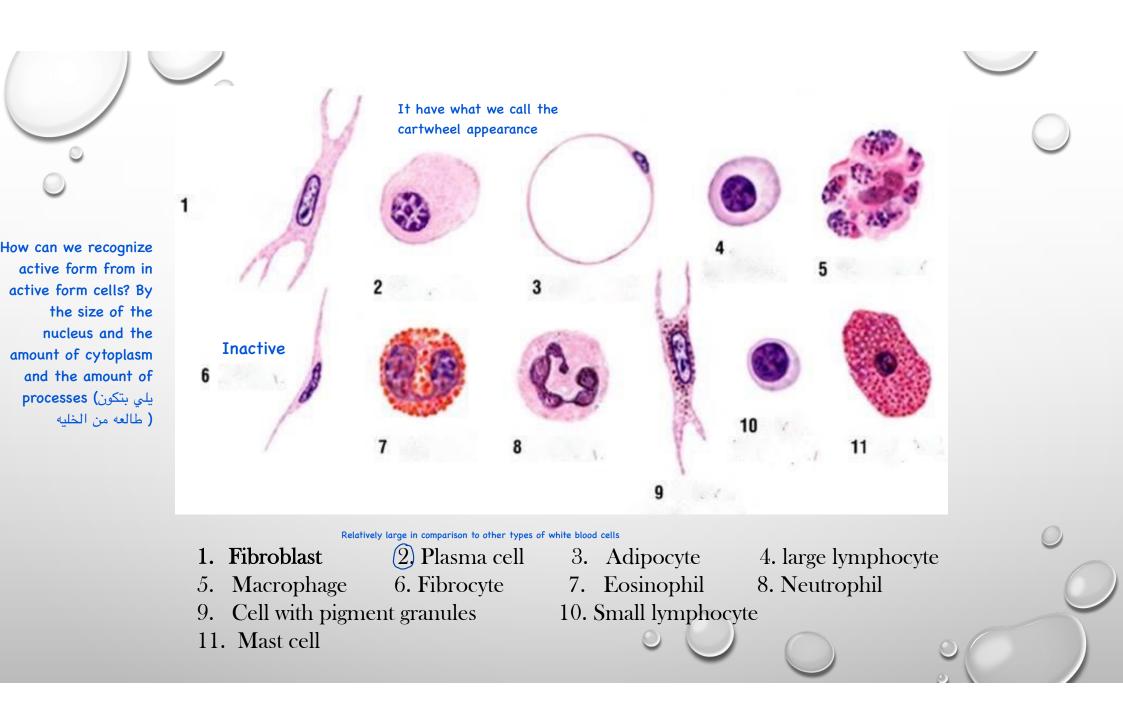
- All connective tissues originate from embryonic mesenchyme, a tissue developing mainly from the middle layer of the embryo, the mesoderm.
- Mesenchyme consists largely of viscous ground substance with few collagen fibers.
- Mesenchymal cells are undifferentiated and have large nuclei, with prominent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



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

It differ bas on the type of connective tissues





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 It's first line responders, it's emergency cell	
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	



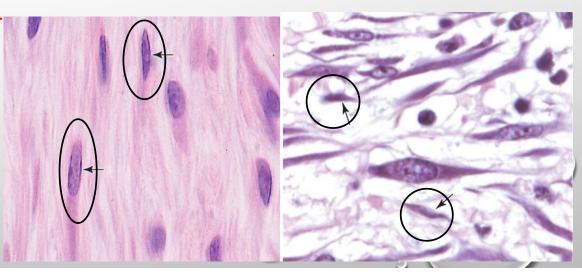
Fibroblast

- 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.

the برضو لاحظوا amount of cytoplasm around the nucleus Euchromatic when the genetic material is free, accessible so we can easily get copies and messengers RNA which will go to the cytoplasm so we can translate this into proteins **Fibroblast**

Heterochromatic , the chromatine will clump on itself and it will highly folded versus the chromatine in the fiber blast.

Fibrocyte



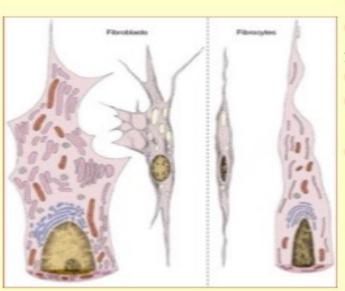
Fibroblasts _ Fibrocytes

Fibroblasts

- the most common cells in connective tissue
- cells responsible for the synthesis of extracelullar matrix components
- an abundant and irregularly

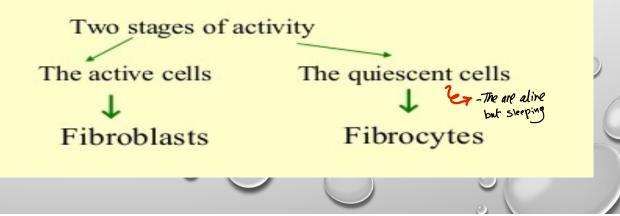
branched cytoplasm

- 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



Fibrocytes smaller than fibroblasts

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



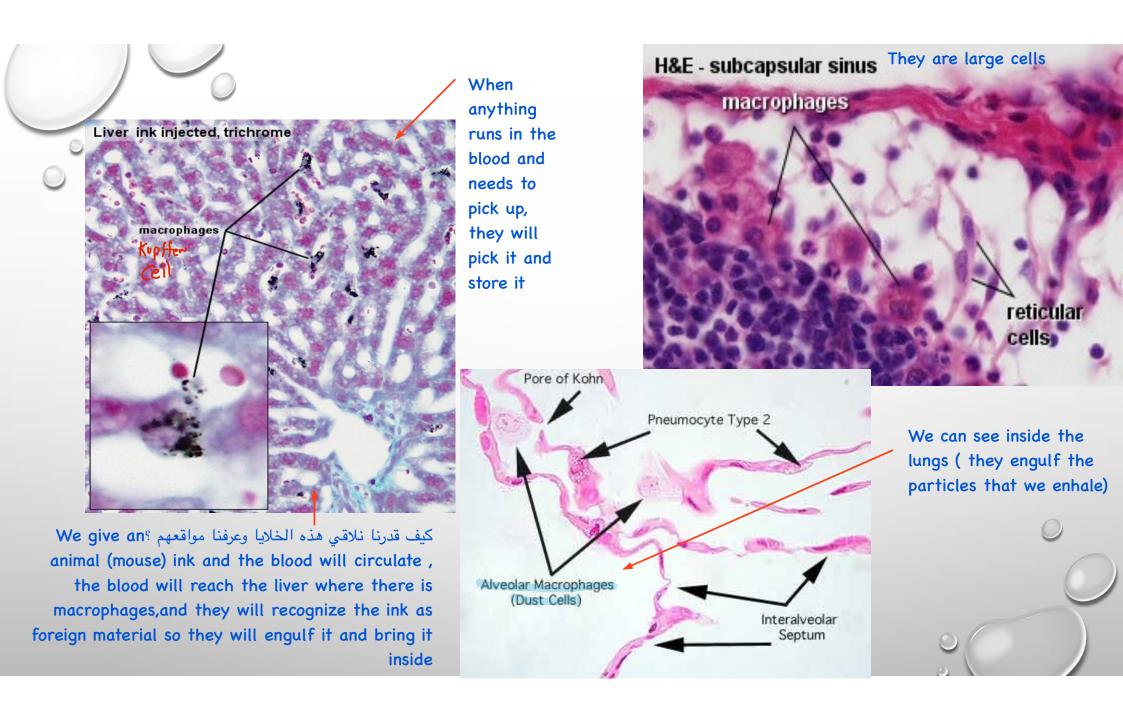
-When they are in the blood they called monocytes , when they are in connective tissue they called macrophages

Those are white blood cells but they have left the blood and resided somewhere else (موجودين تقريبا في كل مكان بجسمنا) لا تنتقل الخليه monocytes من الدم وتروح لهاي الأماكن رح يصير لها بعض التغيرات رح تظل immune related function ولكن بطريقه مختلفه

- 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

Ce	ell Type	Major Location	Main Function
Mo	onocyte	Blood	Precursor of macrophages
Ma	acrophage	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
Ku	upffer cell	Liver (perisinusoidal)	Same as macrophages
Mi	icroglial cell	Central nervous system	Same as macrophages
La	angerhans cell	Epidermis of skin	Antigen processing and presentation
De	endritic cell	Lymph nodes, spleen	Antigen processing and presentation
	steoclast (from fusion several macrophages)	Bone	Control to the process we help liberate calcium and pump it back into the blood so we can restore the calcium level
(se	ultinuclear giant cell everal fused acrophages)	In connective tissue under various pathological conditions	Segregation and digestion of foreign bodies



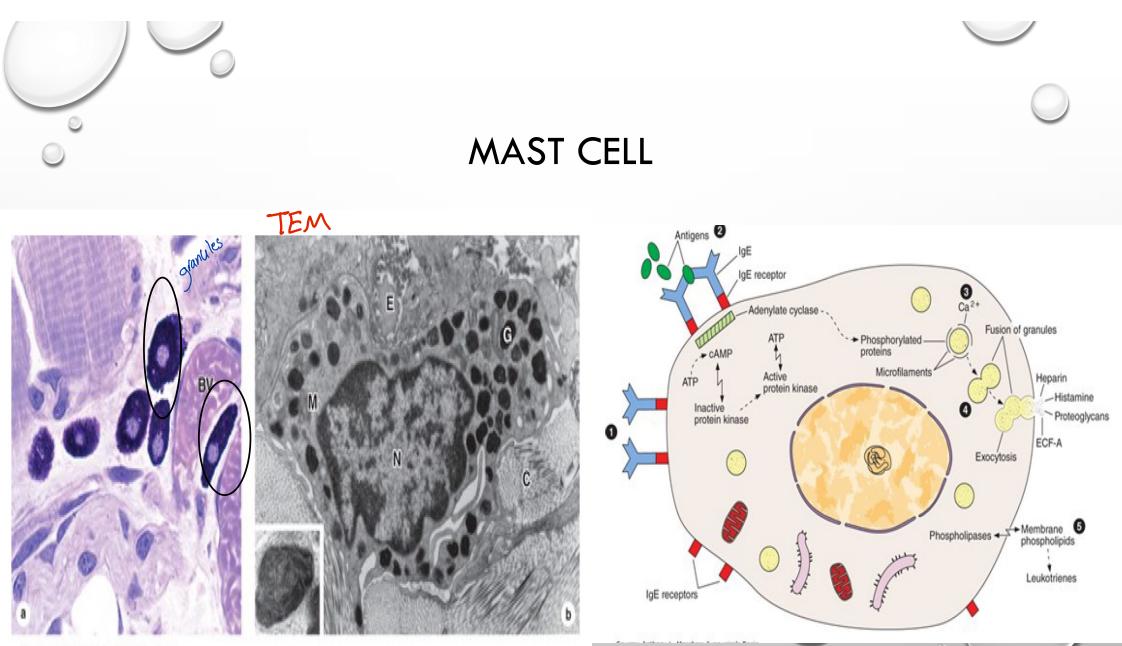
Mast Cell

- 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:
 Blood vessels they are usually not permeable, when we have lots of histamine that make the capillaries more
- 1. <u>Heparin</u>, a sulfated GAG that acts locally as an anticoagulant leaky, so when it's bigger the blood that's coming will be more -- more red in the region -- the temperature will
- 2. <u>Histamine</u>: promotes increased vascular permeability and smooth muscle contraction

لما يصير عندنا تضيق بالقناه

الهوائيه بسبب الحساسيه من القطط أو تغير الفصول مثلاً

- 3. <u>Serine proteases</u>: activate various mediators of inflammation
- 4. <u>Eosinophil and neutrophil chemotactic factors</u>: attract those leukocytes
- 5. Ph<u>ospholipid precursors</u>: converted to other important lipid mediators of the inflammatory reaction.



Record Andrew C. Manhou R. and Shi Roda

Plasma Cell

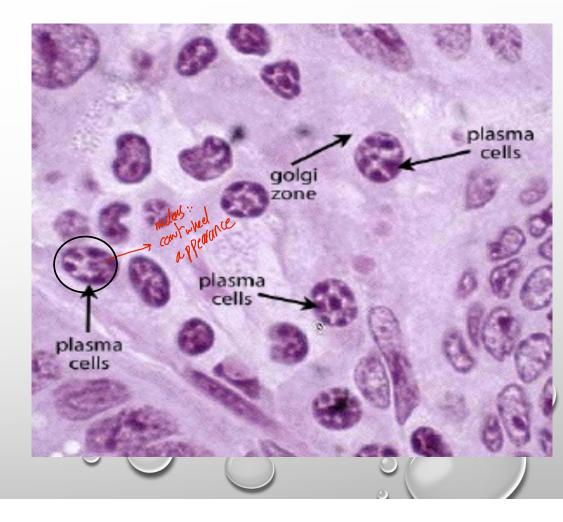
In the blood we have cell that's called lymphocytes and they are two major family: B lymphocytes and T lymphocytes

→ plasma cell → memory cell :-

- Plasma cells are B lymphocyte-derived, antibodyproducing cells.
 B lymphocyte it's small کبیره because those are antibody secreting so the need golgi, ? ribosomes so I need a good amount of cytoplasm
- Relatively large, ovoid cells have basophilic cytoplasm rich in RER.
- Large Golgi apparatus near the nucleus that may appear pale in routine histologic preparations

When they encounter a pathogen part of them eventually will store code for this pathogen will give us plasma cell and another one memory cell

The base of immunization, if we encounter this pathogen in the future They will alert the human Body and then they can fight that antigen quite easily

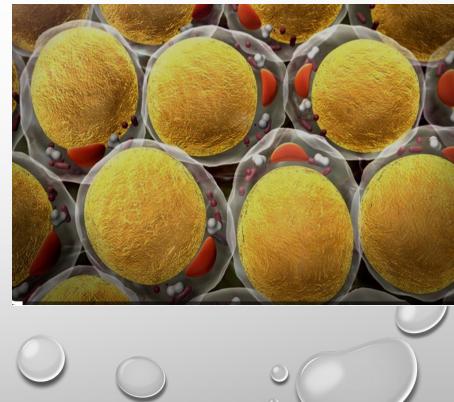


Adipose Cells

Usually they are found in the glands

- 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.

Appear as rings with empty white space because after undergoing tissue processing fat will be dissolved leaving an empty white space with flattened nuclei



Connective Tissue Fibers/Collagen

- Form various extracellular fibers, sheets, and networks.
- Extremely strong and resistant to normal shearing and tearing forces.
- 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.

These fibers have different arrangement in different types of CT for example loose connective tissues have less fibers and more ground substance While ligaments have an extensive amounts of fibers aligned well around each other with a lower amount of ground substance

Collagen types

Those are the one that are extremely strong

- Fibrillar collagens, notably collagen types I, II, and III. Form structures such as tendons, organ capsules, and dermis.
 We can see it in those places where protection and resistance of tensile forces is offered
- 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. Supports the epithelium
- different proteins together Linking/anchoring collagens are short. such as type 7 and 9 Epithelial cell Laminin (a glycoprotein) lamina lucida Basal lamina lamina densa Type IV collagen and perlecan (a proteoglycan) Reticular lamina **Reticular fibers** Anchoring fibrils (type III collagen) (type VII collagen) Anchoring plaques 1024 × 768 (type IV collagen)

Collagen Assembly

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

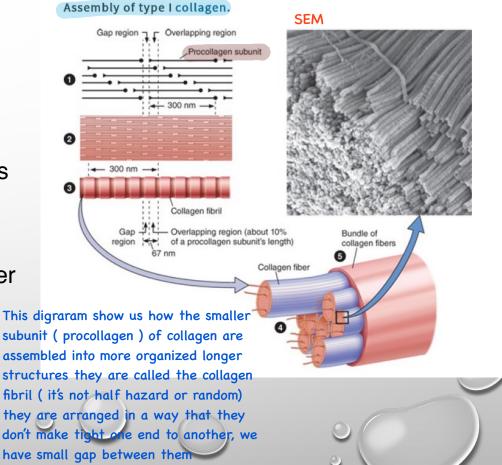
2. The regular, overlapping arrangement of subunits continues as large collagen fibrils are assembled.

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

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.

 Collagen bundles are the biggest, they are formed of several collagen fibers, each colagen fibers is made of number of collagen fibrils and collagen fibrils come from many of procollagen subunits



Connective Tissue Fibers/Reticular

Delicate oranges:Endocrine glands , lymph nodes, bone marrow, liver

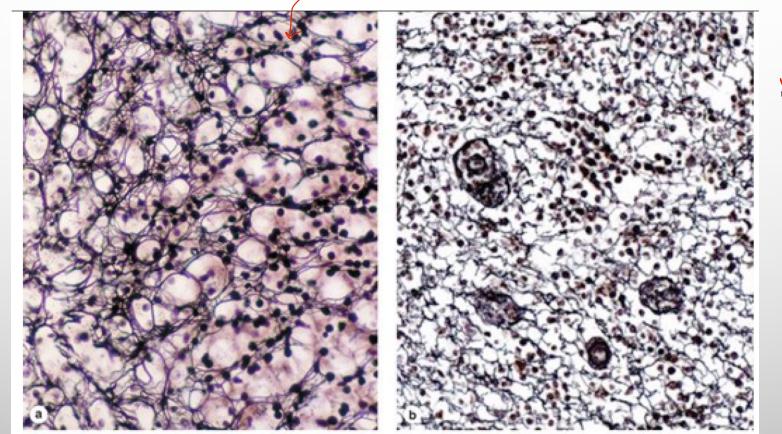
- Found in delicate connective tissue of many organs, notably in the immune system.
- Consist mainly of collagen type III, which forms an extensive network.
- Seldom visible in hematoxylin and eosin (H&E) but are stained black after impregnation with silver salts. They will appear like darkish fine light under microscope
- 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.
 best location to study it is liver becau
- · Produced by fibroblasts.

best location to study it is liver because it creates 3D structure that can protect and house the liver cells which are called Hepatocytes

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

RETICULAR FIBERS

∼Dark dots nuclei



Lymph nodessilver stain rich with reticular fibers

Fine blackish irregular structures its reticular fibers

They create tiny compartmen tso they support the interior delicate cells

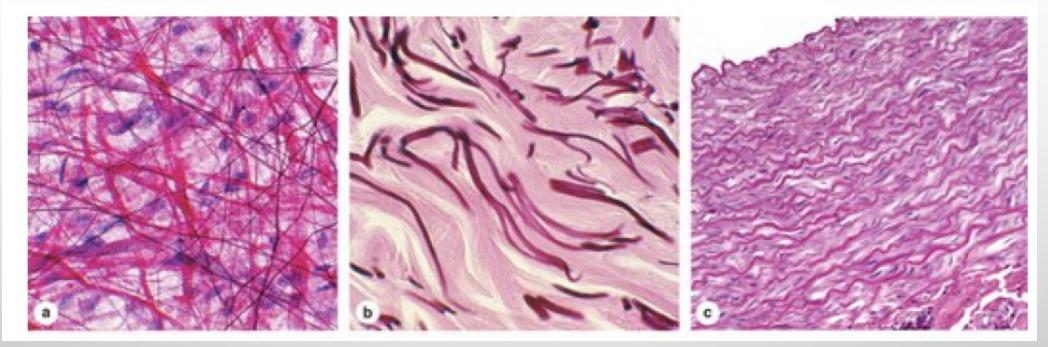
Connective Tissue Fibers/Elastic

- Thinner than the type I collagen fibers and form sparse networks interspersed with collagen bundles in many organs (subject to regular stretching or bending).
- Have rubberlike properties that allow tissue containing to be stretched or distended (lungs).
 rely on those fibers, because they enable them to stretch slightly

rely on those fibers , because they enable them to stretch slightly to accommodate incoming blood from heart,

- 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. Another location for elastic fibers is Dermis (connective tissue , supports the epidermis that second layer in the skin second , skin doing a lot of stretching and pulling forces so present of elastic fibers is important and it's rich with collagen and elastic fibers

Connective Tissue Fibers/Elastic



A- Hematoxylin and orcein) B-Aldehyde fuchsin) C- H&E When we have good amount of elastic fibers elstacked together they tend to show more color in contrast of collagen and smooth muscles

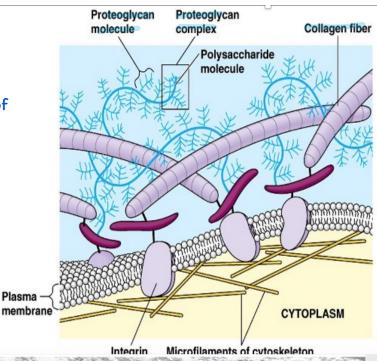
It's Part of the wall , the Wavy dark pinkish lines or structures elastic lamina

Ground Substance

facilitate diffusion of nutrients

Because they rich with sulfate and lots of negative chargers carried in their moleculers

- 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.
- Filling the space between cells and fibers in connective tissue.
- Allows diffusion of small molecules. movement of microorganisms
 Because it is viscous---lubricant and a barrier to the penetration of invaders. lubrication in specific location such as umbilical cord provide protection to blood vessels and allow diffusion







GAGs

Depending on the type of sugar there will be different types of GAGs

- GAGs (mucopolysaccharides) are long polymers of repeating disaccharide units, usually a hexosamine and uronic acid.
- 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).



GAGs

- All other GAGs are much smaller, sulfated, bound to proteins (as parts of proteoglycans).
- 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.
- These features provide GAGs with space-filling, cushioning, and lubricant functions.

Cartilage matrix is basophilic (due to negatively charged gaps such as Chondroitin sulfate) stained with hematoxylin

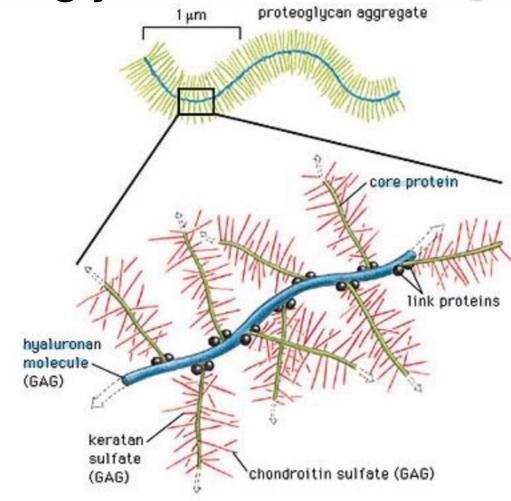
GAGs that form proteoglycans

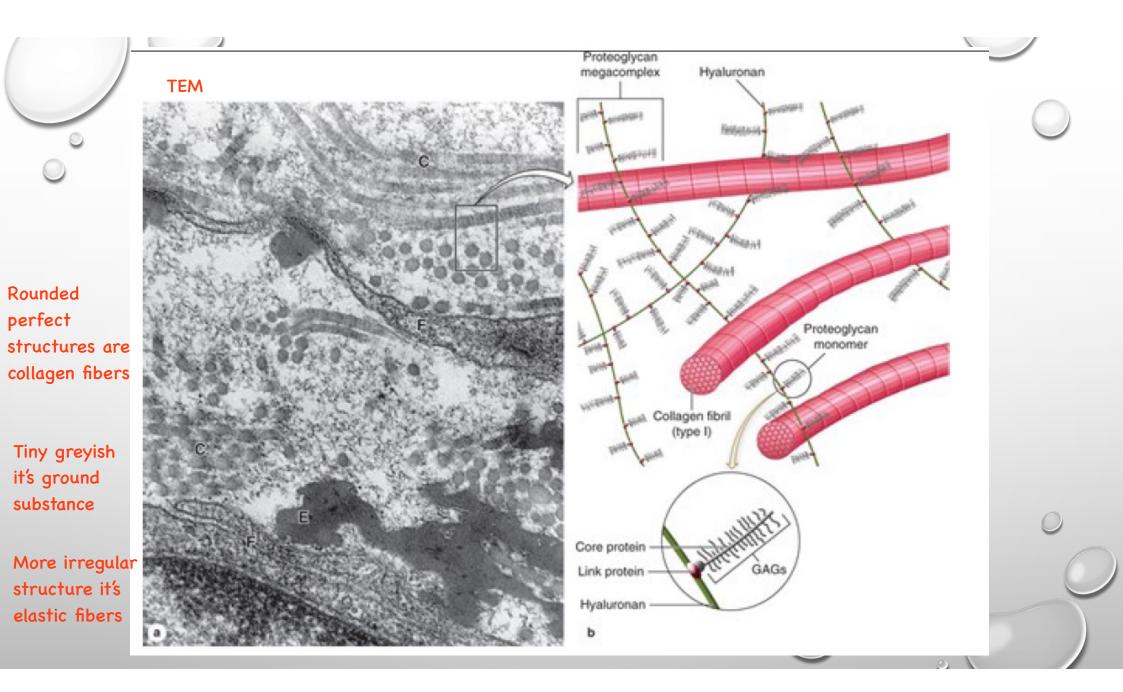
The Diagram is a proteoglycan aggregate After expanding it .

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

Type of GAGs depend on the type of tissue

Hyaluronic backbone that binds smaller structures And these smaller structures have a core protein Which binds to many GAGs



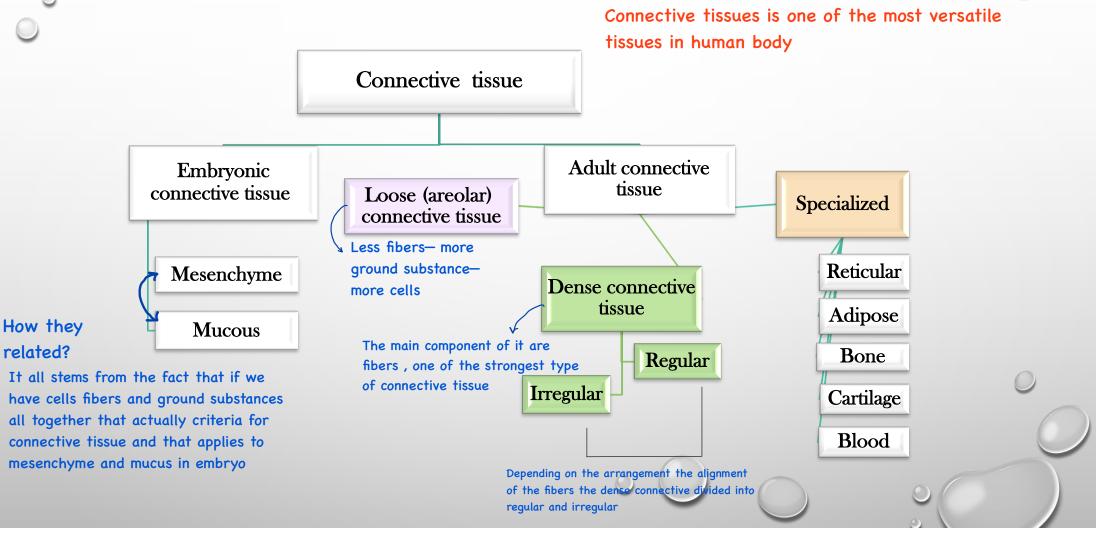


GAGs

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Glycosaminoglycan	Repeating Disaccharides		Distribution	Electrostatic Interaction with Collagen	
Giycosaninogiycan	Hexuronic Acid	Hexosamine	Distribution		
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	

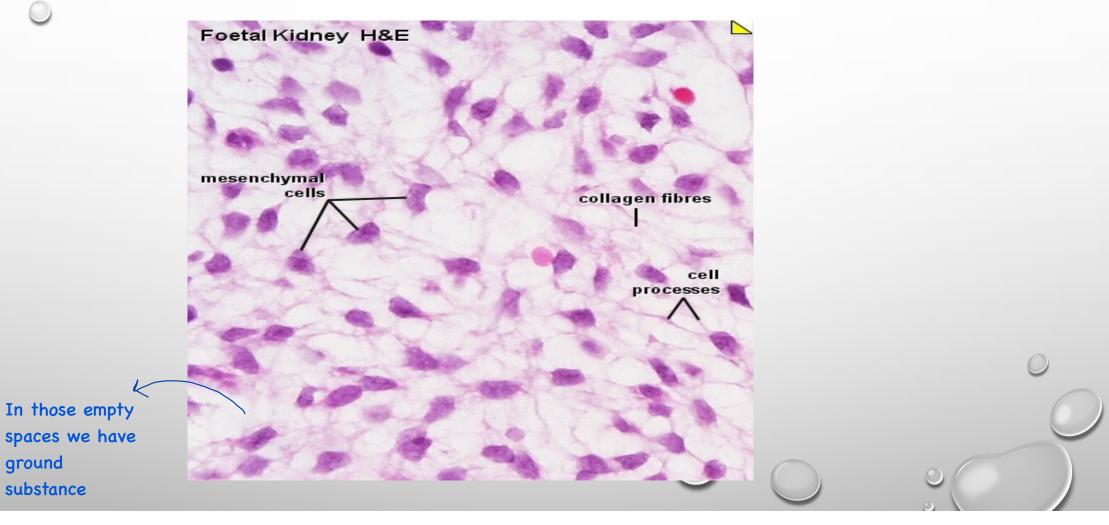
Classification Of Connective Tissue





Embryonic Conne	ctive Tissues	General Organization		Major Functions	Examples
Mesenchyme The source for the various types of CT	Sparse, undifferentiated cells, uniformly distributed in matrix with sparse collagen fibers			ns stem/progenitor cells for all onnective tissue cells	Mesodermal layer of early embryo
Mucoid (mucous) connective tissue	Random fibro viscous matri	oblasts and collagen fibers in x	Suppor	ts and cushions large blood vessels	Matrix of the fetal umbilical cord

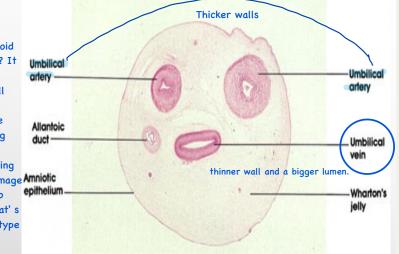
Mesenchyme



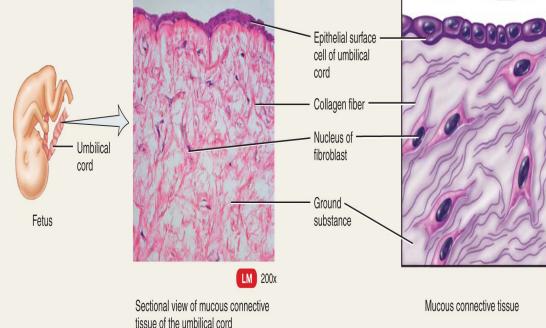
It is present in the umbilical cord ,the umbilical cord is actually where the embrye is attached to the placenta of the mother, where the embryo gets its nutrients, gases and from the mother and can send the waste product to the mother , you're going to find blood vessels in it and ducts

Mucous Connective Tissue

where is the mucoid connective tissue? It is simply runr in between, filling all the spaces surrounding those vessels, separating them, cushioning them and protecting them from an damage that could lead to their blockage.that's why we have th type of tissues



what do we usually have in it? We have a number of fibroblasts. We do have some in chemists themselves, an their number is quite low, we also have some collagen fibers and a ground substance



one important aspect of the umbilical cord is that's a trend that has started

title a while back and still running (we have some mesenchyme themselves in the in this tissue), So after delivery, you could make arrangement with specific companies where they can come and they take this umbilical cord and they extract those mesenchyme themselves and they store them for the baby. This is important because the use of mesenchymal stem cells to treat diseases is actually on the rise. So you want to make sure that this baby has his own mesenchymal stem cells whenever they needs them, instead of subjecting the patients to a much harder way of extraction of these cells when they are adults.

Classification-Adult CT

loose means cushioning and supporting, whereas dense means protection, means strength.

	General Organization	Major Functions	Examples	Loose CT ,We will find it
Connective Tissu	e Proper			wherever we need cushioni and support o
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	delicate structures suc as blood vessels, such immune cells,
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 it can protect any pressure that is being applied to those organs from any direction and allow for their protection.	epithelium.
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 are dense regular connective tiss that they bind or hold two bones together.		



Classification-Specialized CT

Regular , irregular what is actually the difference? or why does the direction of the of the fibers precisely collagen, could make a difference in these two different types?

Because when we say ligaments, and that's a regular, that means collagen fibers running parallel to each other's that means they are resisting the pulling or the tensile strength in more or less in a unidirectional scheme. Whereas the dense irregular, one example foris the dermis and the dermis(the second layer under the epidermis in skin)so that also resists the tensile forces in different directions and that is offered by the different directions of collagen fibers they are present there.

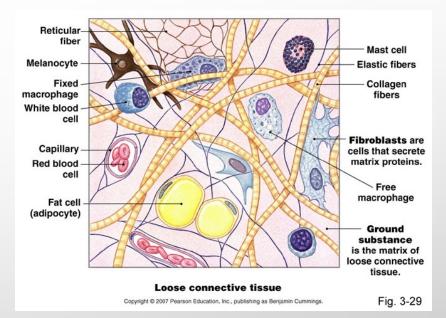
	General Organization	Major Functions	Examples
Reticular connective tissue	Delicate network of reticulin/collagen III with attached fibroblasts (reticular cells)	Supports blood-forming cells, many secretory cells, and lymphocytes in most	Bone marrow, liver, pancreas, adrenal glands, all lymphoid organs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

Reticular connective tissue, this is where we have tissue in specific organs where the dominant type of fibers are actually reticular fibers(Reticular fibers are simply collagen type three)So they create those smaller spaces to support those delicate cells, smaller vessels, or nerves and because we have so much of those, they have decided to separate it from the connective tissue proper and put it in the in the special types , they also went above that and they've called those cells that they specialize in reticular fiber synthesis and secretion, and they call them reticular cells.

But in fact, they are actually, a fibroblast that they have more specialty to what type of fibers they synthesize and release. Reticular fibers, it's where we have delicate structures and organs. So that means liver, that means pancreas, that means glands, thymus, and bone marrow.

Loose (Areolar) Connective Tissue

- Consists of all 3 types of fibers, several types of cells, and semi-fluid ground substance.
- Found in subcutaneous layer and mucous membranes, and around blood vessels, nerves and organs
- Function = strength, support and elasticity



when we talked about epithelium, we said the connective tissue underneath is loose, and the ground substance is the one that actually allows the passage and the diffusion of the nutrients from the blood vessels from the connective tissue where they have those blood vessels toward the overlying epithelium.



Dense Connective Tissue

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

a. Dense regular connective tissue

tendons are the connective tissue at the end of the muscles where muscles attach to bones.

Tendons and ligaments

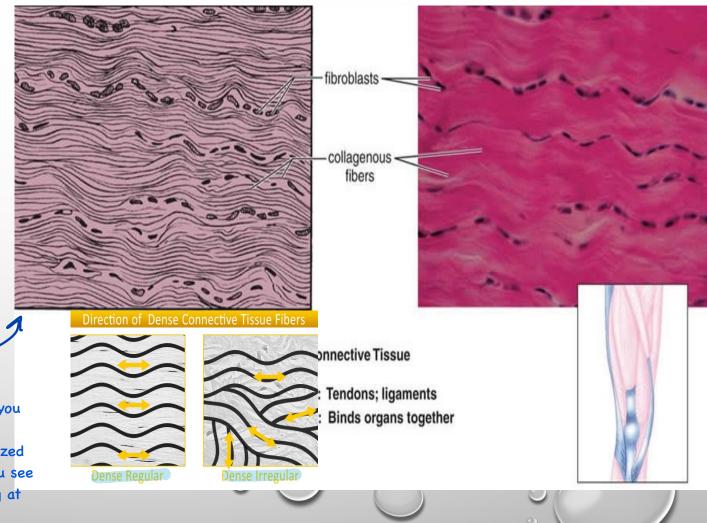
ligaments those are connective tissue structures that they connect two bones together.

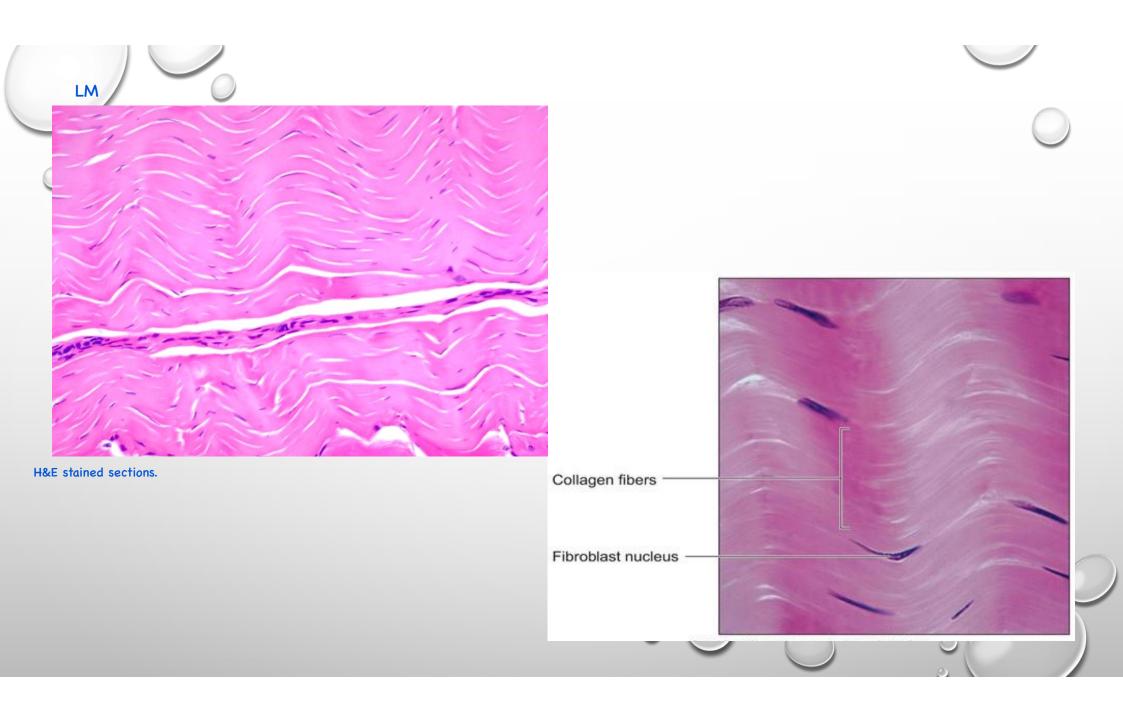
b. Dense irregular connective tissue Dermis of skin

Dense Regular Connective Tissue

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

This is a H&E section through maybe a tendon, and you can see the collagen fibers and the richness of the collagen fibers, and usually the fibroblasts are squeezed in between and they happen to be in rows, When you see this alignment, this regularity, you're actually looking at a dense irregular connective tissue.





this is sectioned through the epidermis. Basal layer, intermediate, and the superficial. And the most superficial part, stratum corneum, is not in the image.

Dense Irregular CT

no order, no alignment, =dense irregular.

- Consists Of Randomlyarranged Collagen Fibers And A Few Fibroblasts.
- Found In Dermis Of Skin, capsules of joints and

organs

Capsules are sheets of connective tissue of the irregular type where they Surround the two bones that they participate in the formation of these joints to isolate them and isolate the joint room.

Function = Provide

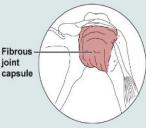
Strength and protection

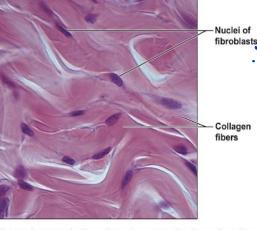
this magnification ,we don't see any alignment because those fibers are not aligned because this isa dense irregular, not regular.

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

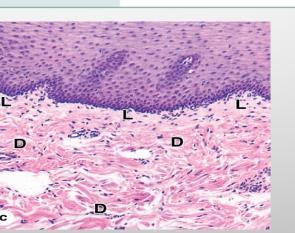
Function: Able to withstand tension exerted in many directions; provides structural strength.

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

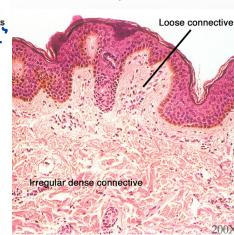




Photomicrograph: Dense irregular connective tissue from the dermis of the skin (600×).



this is the dermis , have two layers, the loos one beneath or adjacent to the epithelium and a deeper dense one.



we have a number of fibroblasts. And those pinkish structures are collagen fibers running in all directions.



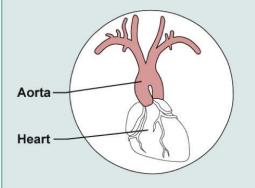
Elastic Connective Tissue

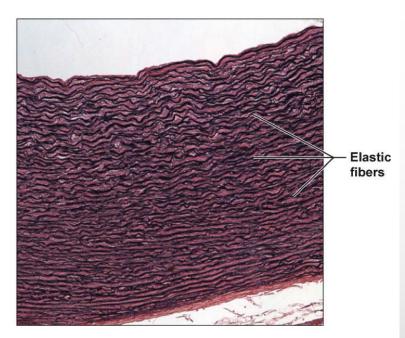
(g) Connective tissue proper: dense connective tissue, elastic

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.

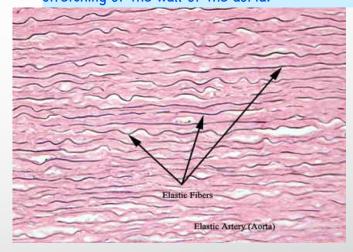
Location: Walls of large arteries; within certain ligaments associated with the vertebral column; within the walls of the bronchial tubes.





Photomicrograph: Elastic connective tissue in the wall of the aorta (85×).

we have specific structures where we have a huge amount of elastic fibers and usually those elastic fibers tend to run parallel to each other, e good location for them is the outer that the largest blood vessel that actually emerges from the left ventricle of the of the heart that's the one will carry the oxygenated the blood to toward the rest of the body and this type, or this blood vessel has lots of elastic lumen in its wall. And due to their elasticity, their stretching, and then recall back, they allow slight stretching of the wall of the aorta.





RETICULAR CT

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

This section through the liver, and you can see all these darker areas that actually where reticular fibers are to surround and support and protect the hepatocytes. this is a lymphoid organ where those are the delicate particular fibers creating those tiny rooms to support those inner cells those lymphoid cells. we can also identify those particular cells because they are bigger than those lymphocytes inside, Lymphocytes are usually smaller nucleus whereas reticular cells, they are larger.

Ivmphocyte

eticular fibe



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

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