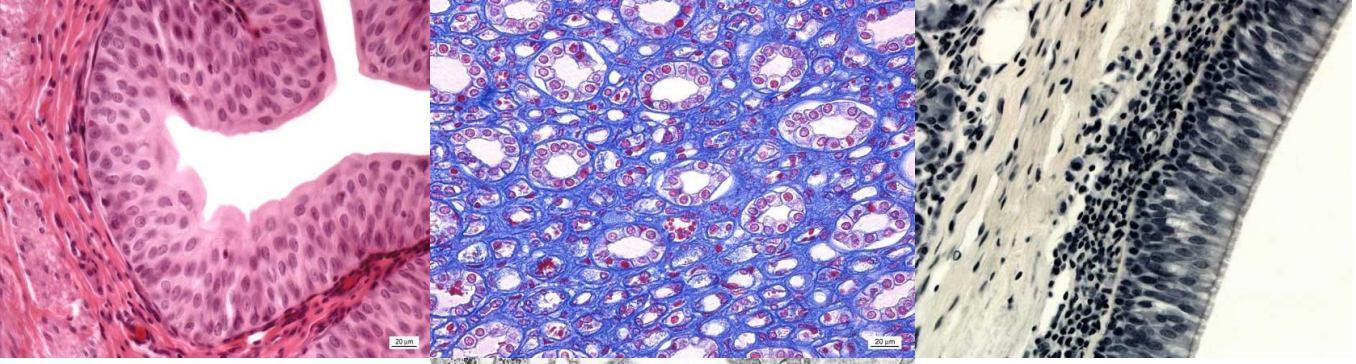
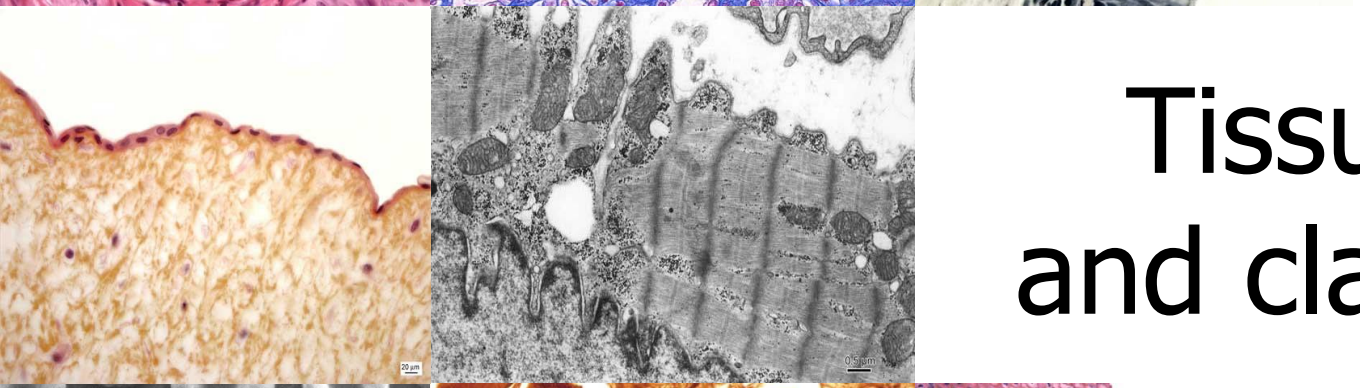
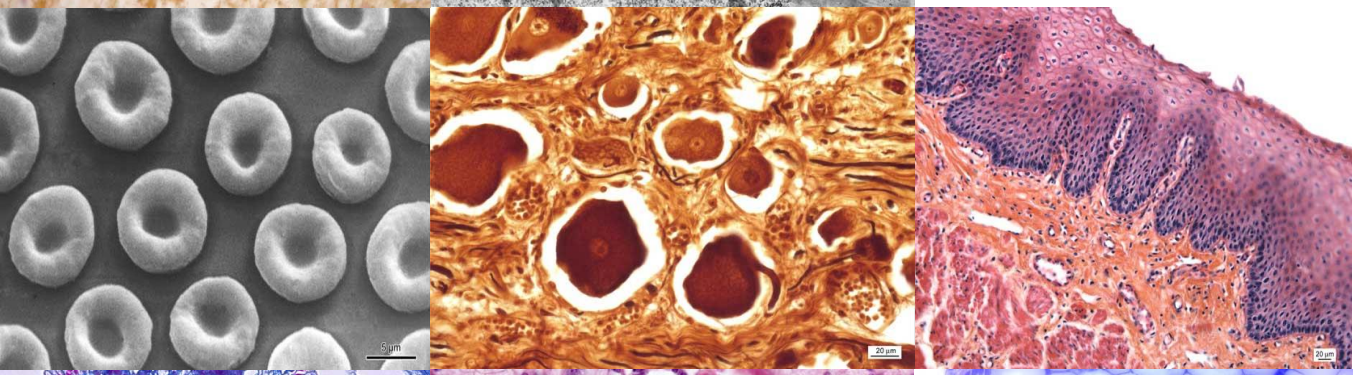


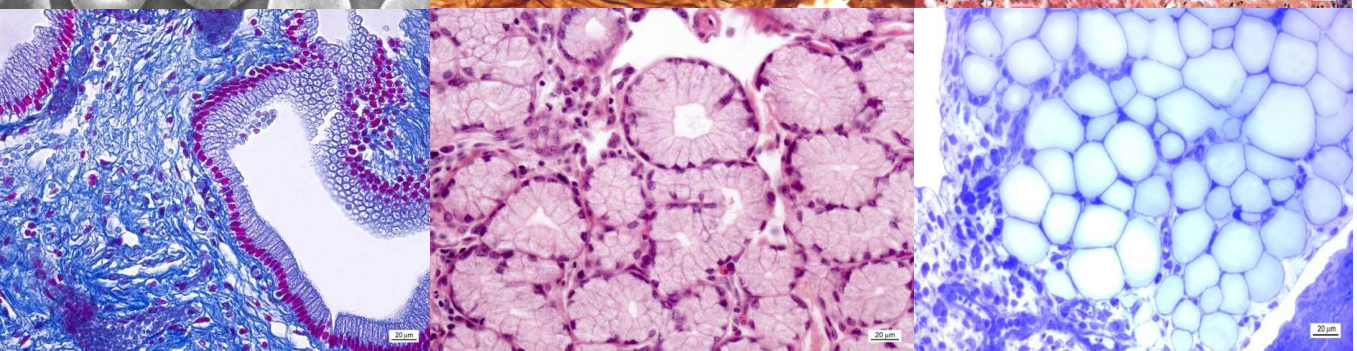
MUNI MED

Ústav histologie a embryologie



Tissue concept and classification



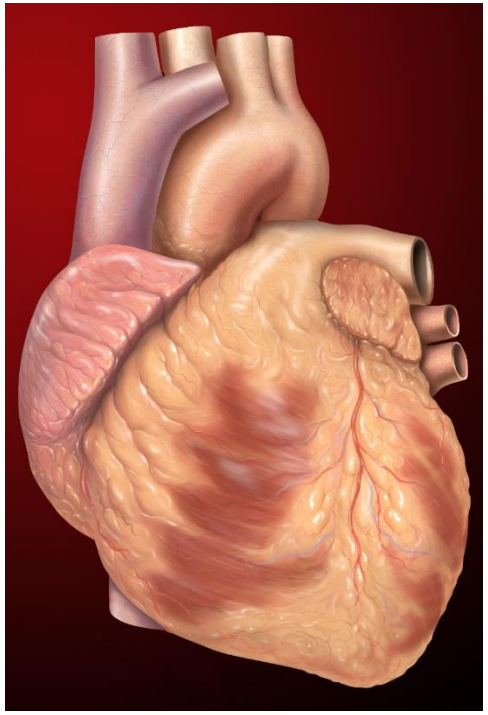


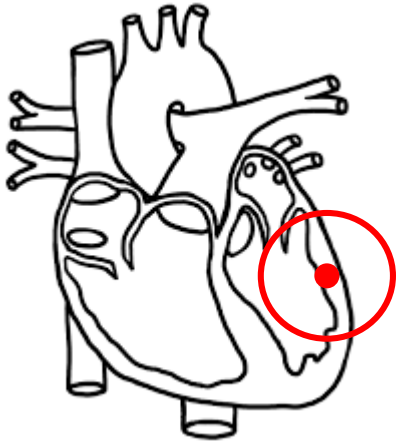
Petr Vaňhara

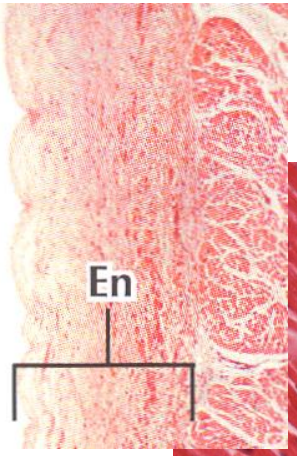
Tissues and organs

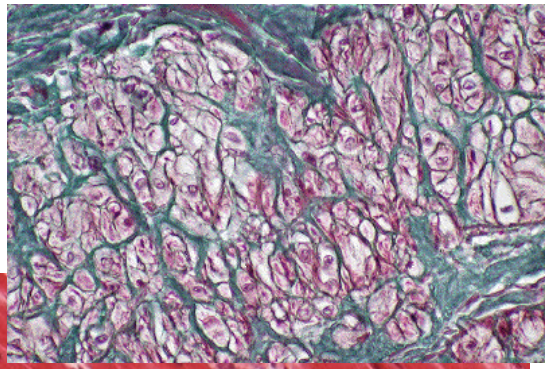
- **6** × **10^{13}** **CELLS** of **200** different types

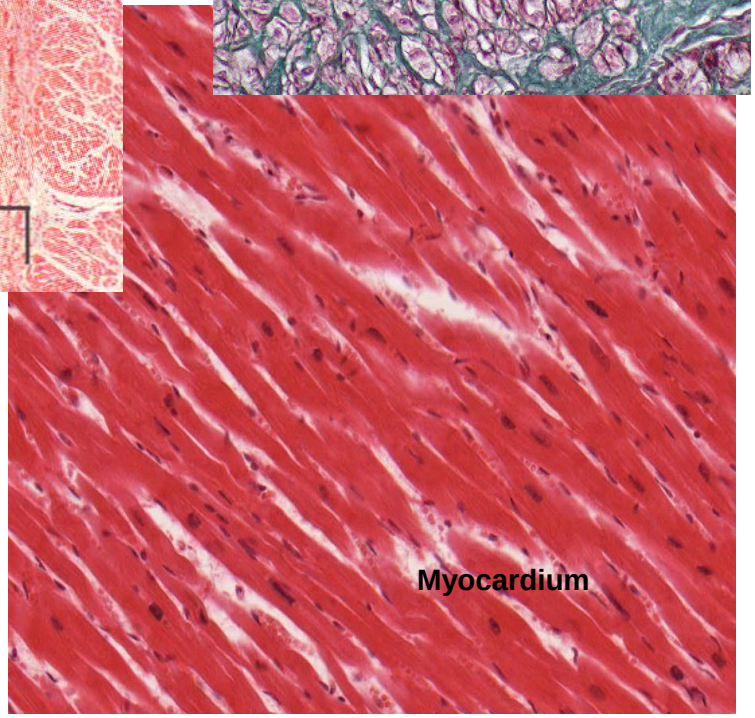
- cells form **functional**, **three-dimensional**, **organized** aggregations of morphologically similar cells and their products or derivatives - **TISSUES**
- tissues constitutes **ORGANS** and organ systems

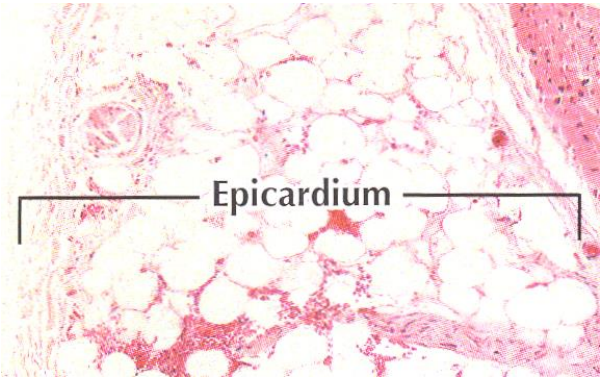








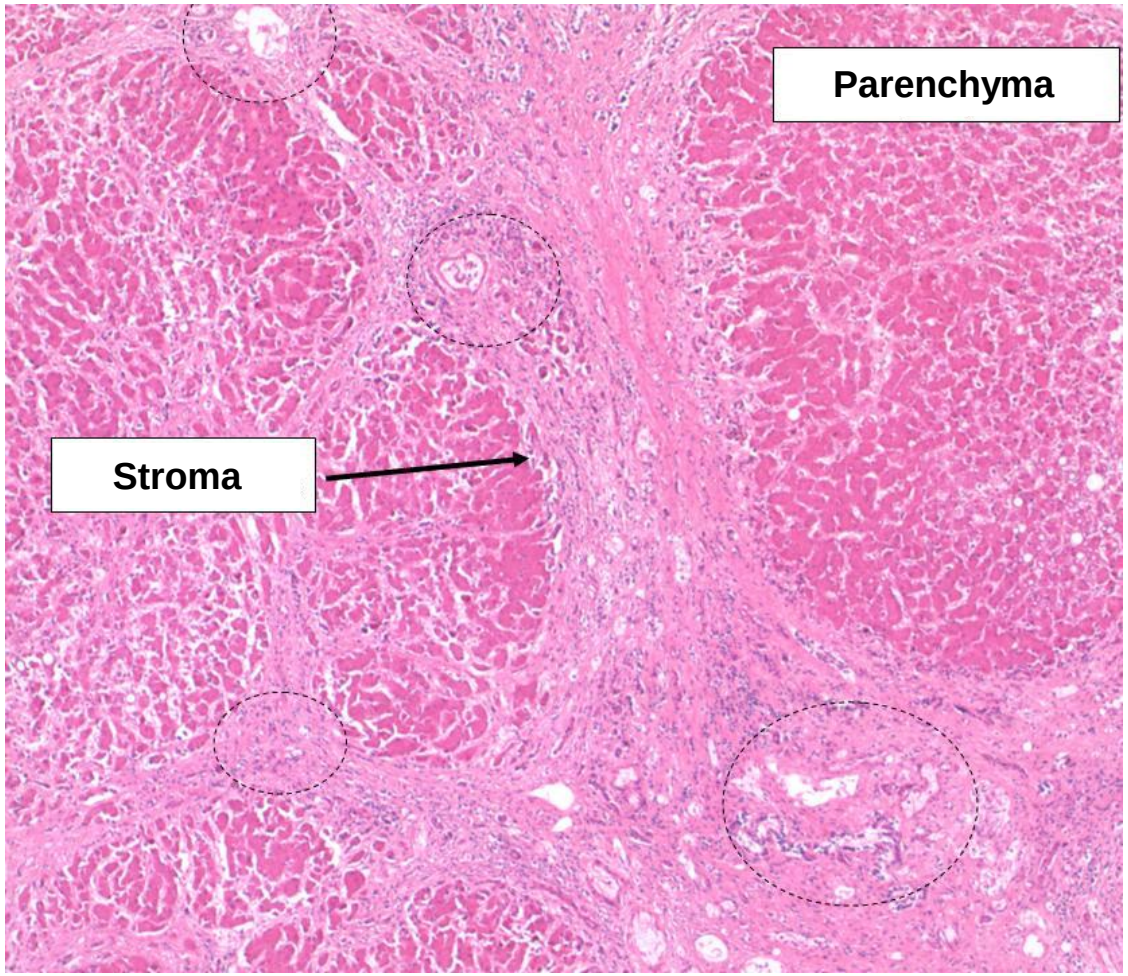




Tissues and organs

Parenchyma: functional component of a tissue (liver, lung, pancreatic, kidney parenchyma)

Stroma: surrounding, supportive tissue



LIVER

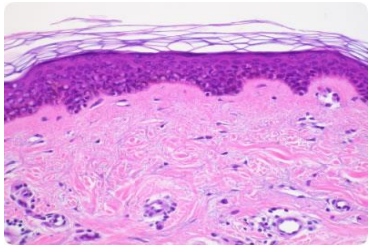
Parenchyma:
- Hepatocytes
- Sinusoids and adjacent structures

Stroma:
- Connective tissue and adjacent structures
- Vessels
- Nerves
- Bile ducts

Contemporary tissue classification

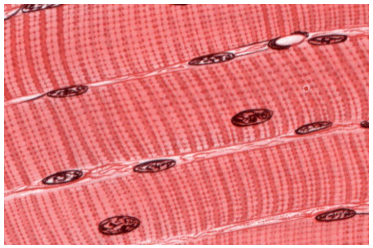
Based on **morphology** and **function**:

Epithelium



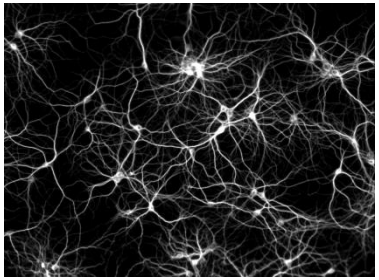
Continual, avascular layers of cells with different function, oriented to open space, with specific junctions and minimum of ECM and intercellular space.
Derivates of all three germ layers

Muscle



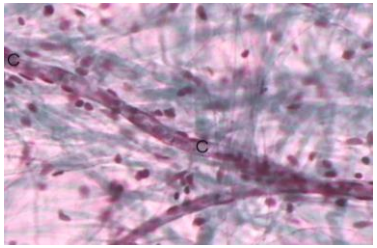
Myofibrils → contraction
Mesoderm – skeletal muscle, myocard, mesenchyme – smooth muscles
Rarely ectoderm (eg. m. sphincter a m. dilatator pupillae)

Nerve



Neurons and neuroglia
Reception and transmission of electric signals
Ectoderm, rarely mesoderm (microglia)

Connective



Dominant extracellular matrix
Connective tissue, cartilage, bone…
Mesenchyme

- Basic principles of histogenesis

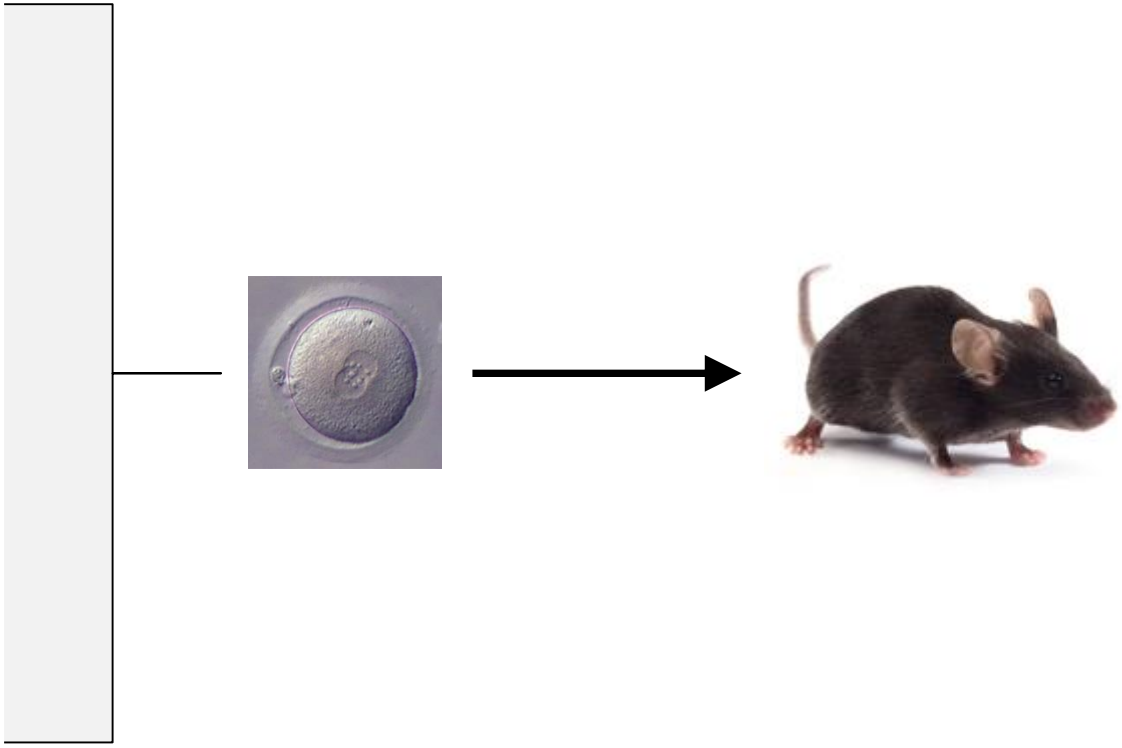
Proliferation

Differentation

Migration

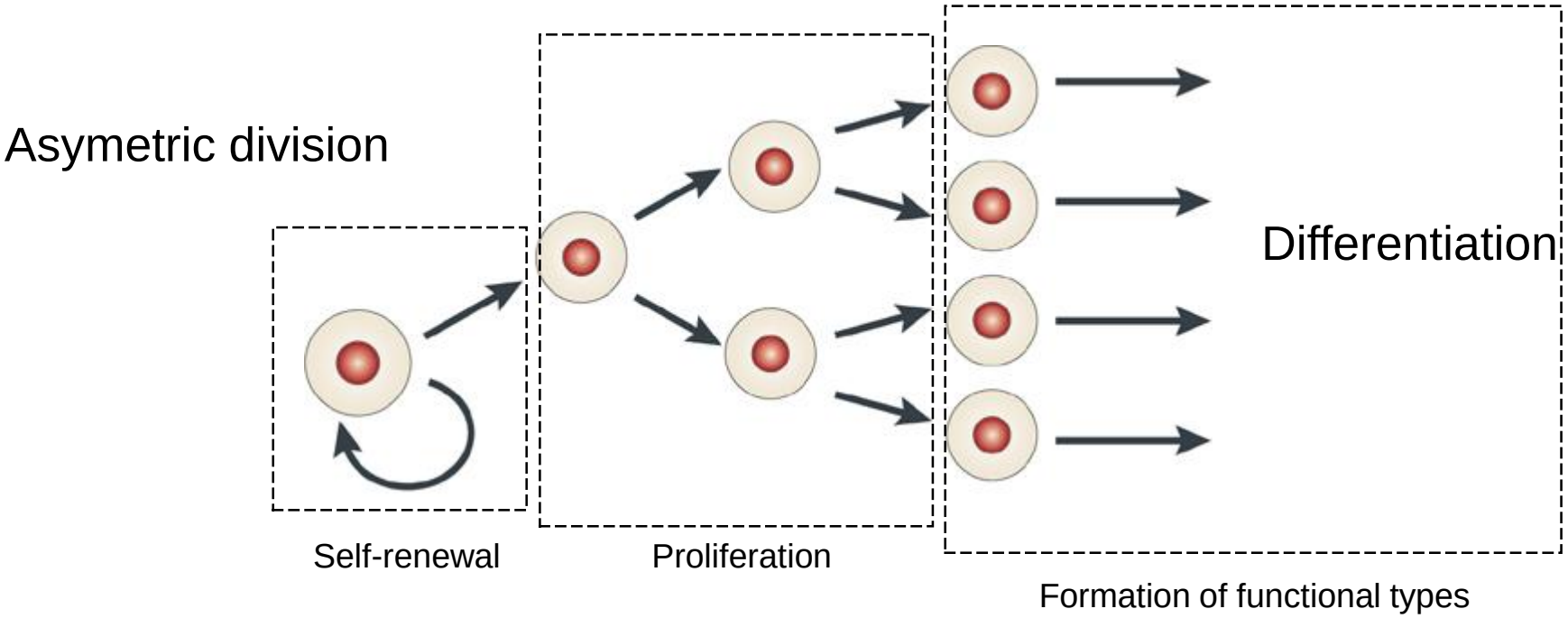
Apoptosis

Tissue patterns



- Functional cells of tissues differentiate from stem cells

Stem cells are capable of differentiation and self-renewal



Knoblich JA. Asymmetric cell division during animal development. 2001. Nat Rev Mol Cell Biol

Stem cells

Totipotent

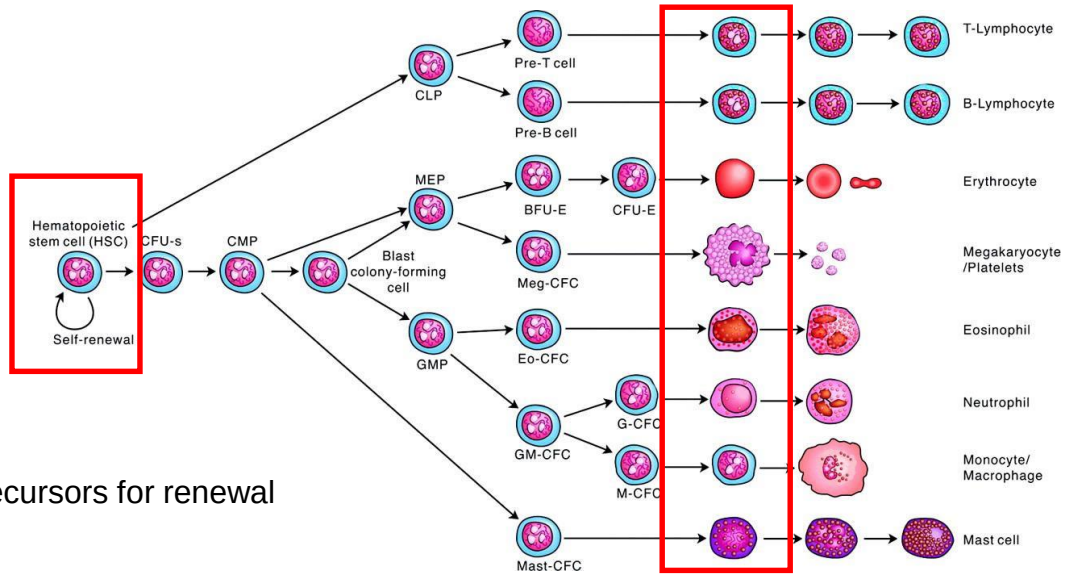
- Constitute all cells of the body incl. extraembryonic tissues
- Zygote and early stages

Pluripotent

- All cells in the body except for trophoblast
- Blastocyst – Inner cell mass - ICM (embryoblast)
- Embryonic stem cells

Multipotent

- Give rise to various cell types of a particular tissue
- Mesenchymal SC, hematopoietic SC

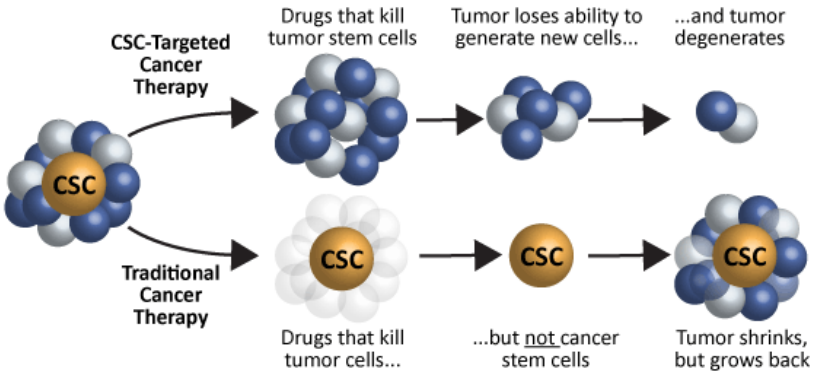


Oligo- a unipotent

- One or several cell types – hematopoietic, tissue precursors for renewal of intestinal epithelia, etc.

http://www.embryology.ch/anglais/evorimplantation/furchung01.html

Stem cells as a foe



Cancer stem cells

- solid tumor is always heterogeneous

- small population of cells with stem cell character can repopulate tumor tissue after cytotoxic therapy

Tissue stem cells

Renewal

Quiescence

Multipotency

Low frequency (<1%)

Long life

Resistence

Tumorigenicity

Proliferation capacity

Cancer stem cells

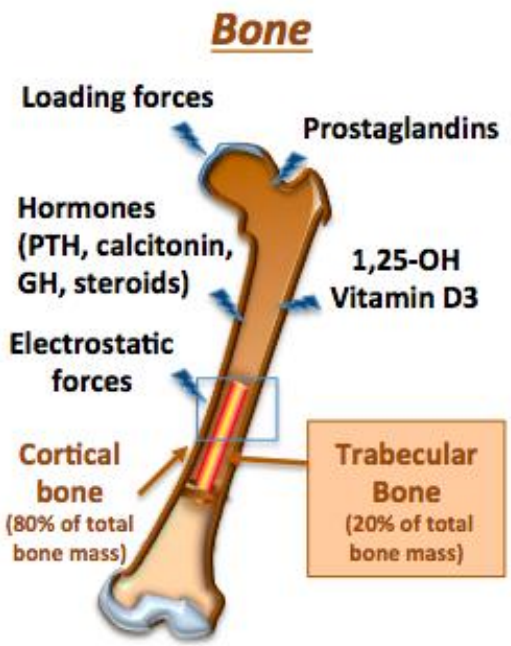
- Microenvironment regulates tissue function and reflects its tissue composition

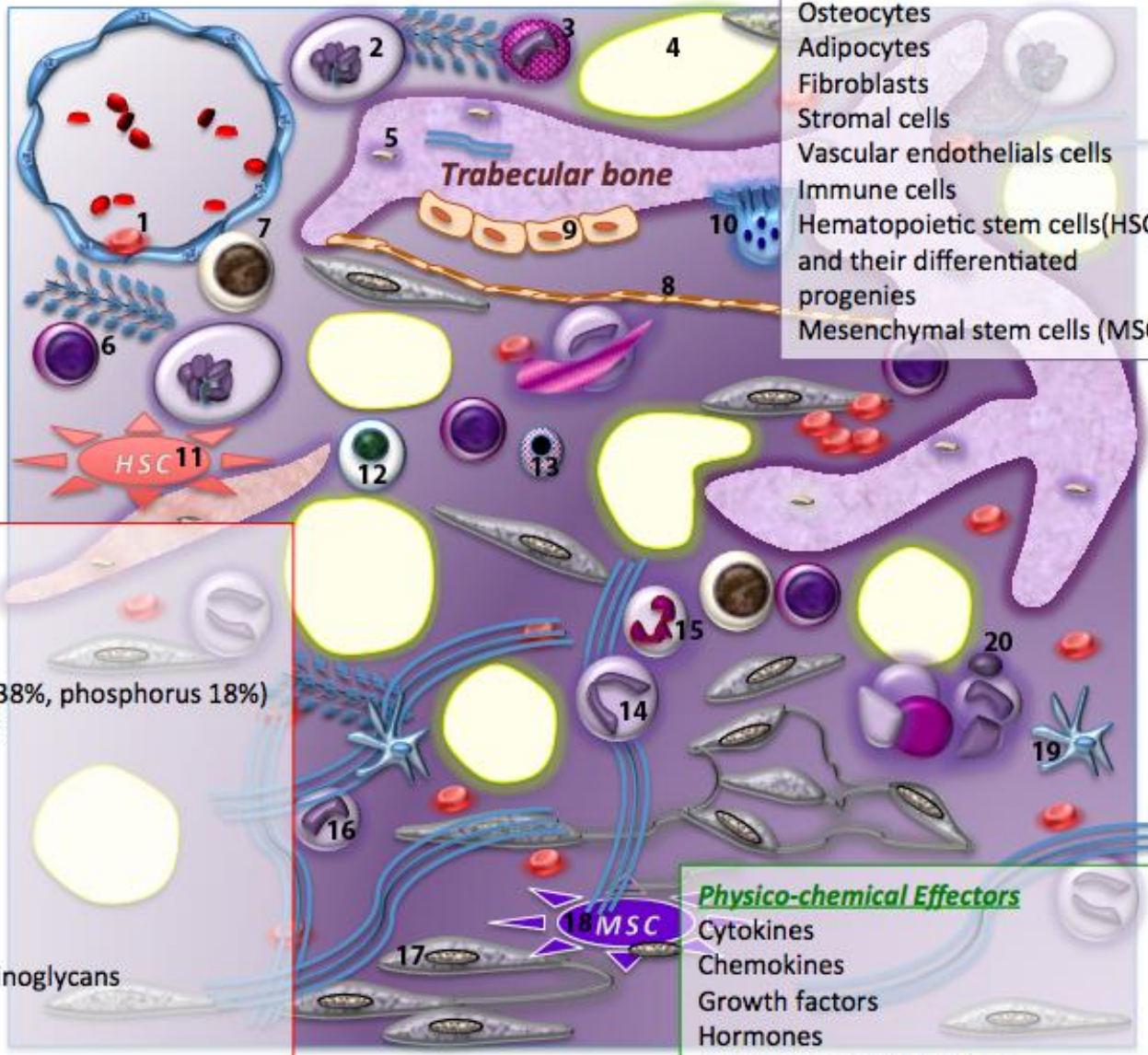
Huge number of **biological** and **physically-chemical** parameters

Stem cell niche

- Embryonic development
- Intercellular interaction
- Space organization (dimensionality)
- Gradient of morphogenes
- Epigenetic profile
- Gene expression dynamics
- Partial pressure of gases
- ECM composition
- Mechanical stimulation
- Perfusion and interstitial flows
- Local immunity response
- Metabolites

Stem cell niche?





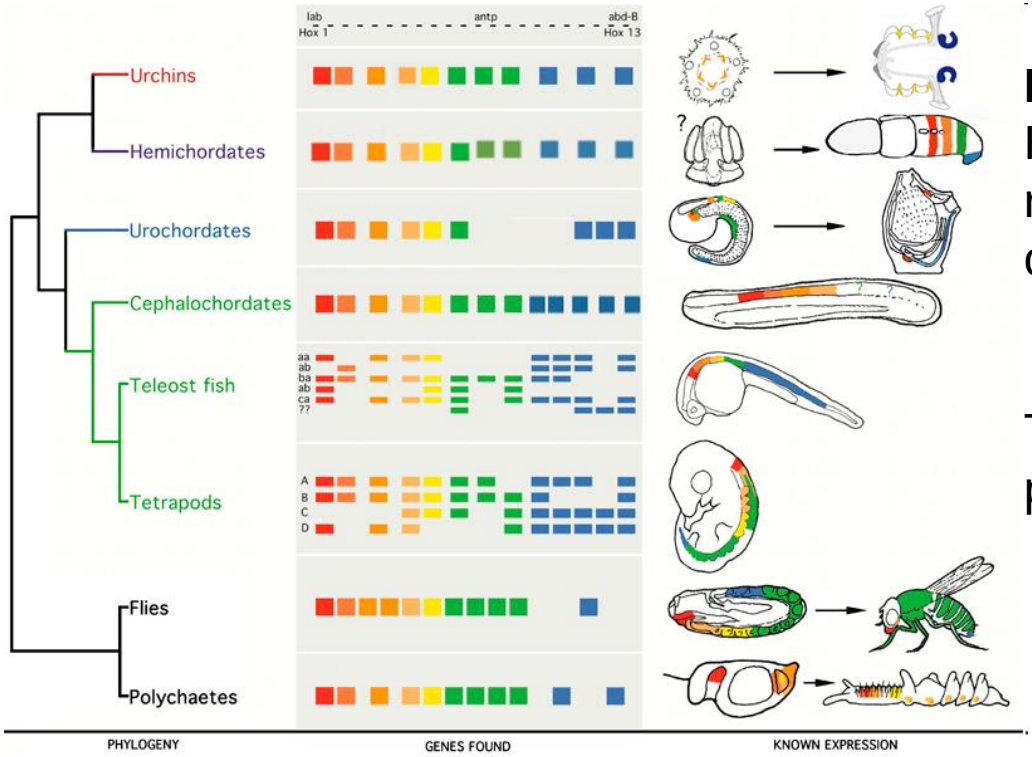
Bone & Bone Marrow cells
Osteoblasts
Osteoclasts
Osteocytes
Adipocytes
Fibroblasts
Stromal cells
Vascular endothelials cells
Immune cells
Hematopoietic stem cells(HSC) and their differentiated progenies
Mesenchymal stem cells (MSC)

ECM components
Fibronectin
Laminin
Collagens
Apatite crystals (calcium 38%, phosphorus 18%)
Bone promoting proteins
Bone sialoproteins
Osteonectin
Osteoprotegerin
Osteocalcin
Integrins
Alcaline Phosphatase
Proteoglycans, Glycosaminoglycans
Osteopontin
MMPs & TIMPs
Receptors
Adhesion molecules

Physico-chemical Effectors
Cytokines
Chemokines
Growth factors
Hormones
Physico-mechanical forces
Biochemical regulators (pH, oxygen concentration, nutrients…)

Molecular principles of histogenesis

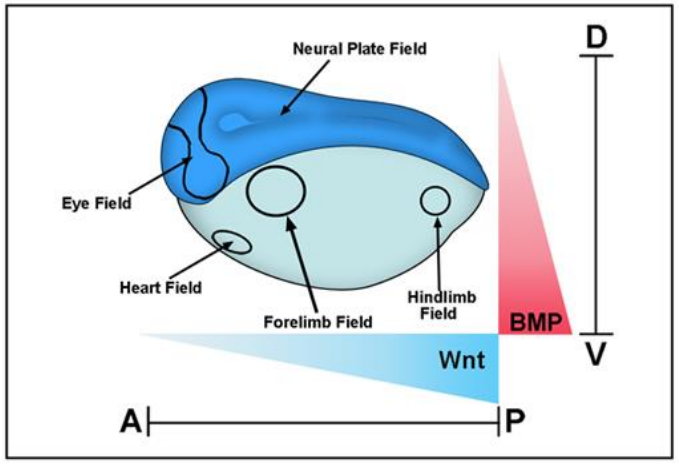
Hox complex



Hox genes
Highly conserved family of transcription regulators that determine body polarity, orientation and axis

Tissue differentiation along anterio-posterior axis

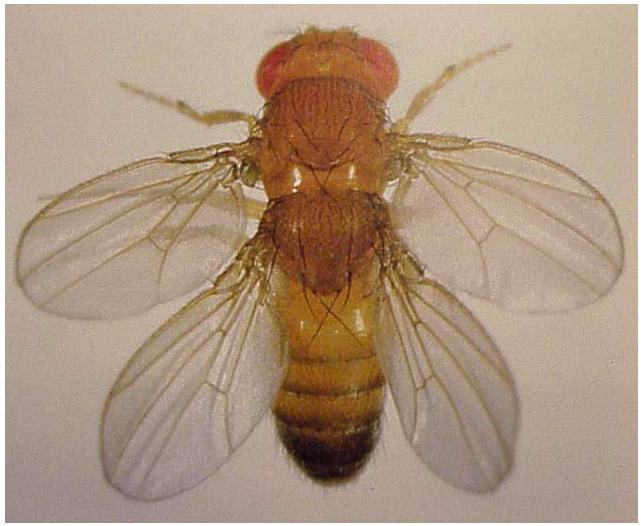
doi:10.1038/sj.hdy.6800872

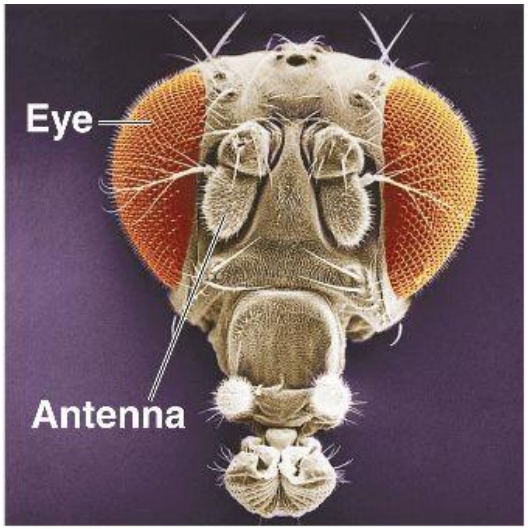


Human (39 genes)

Cluster	Chromosome	# Hox genes
HoxA	7	11
HoxB	17	10
HoxC	12	9
HoxD	2	9

- Lessons from fruitflies



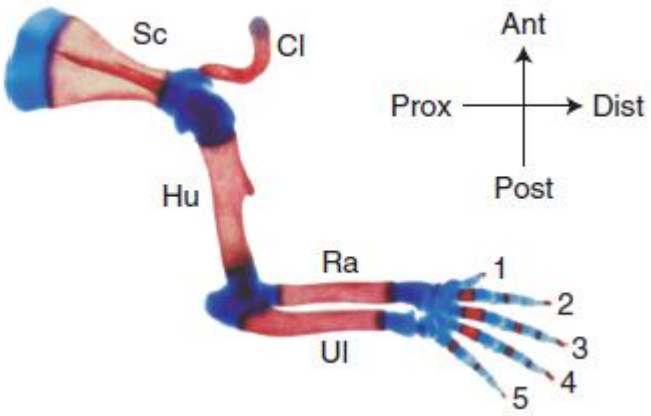


Wild type

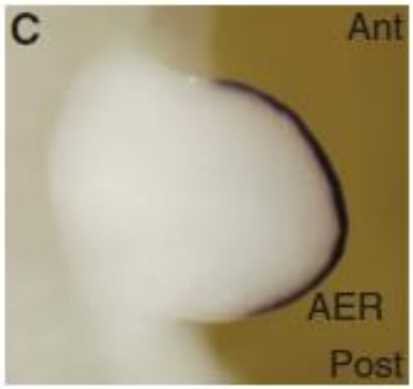
Mutant

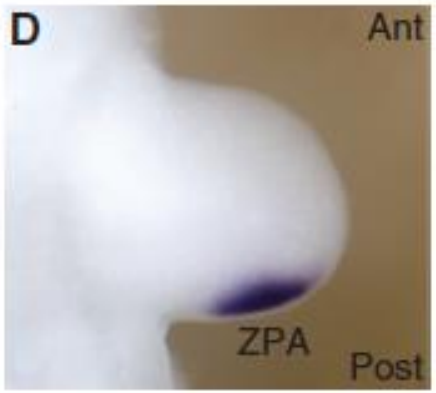
- French flag model

Microenvironment controls embryonic organogenesis

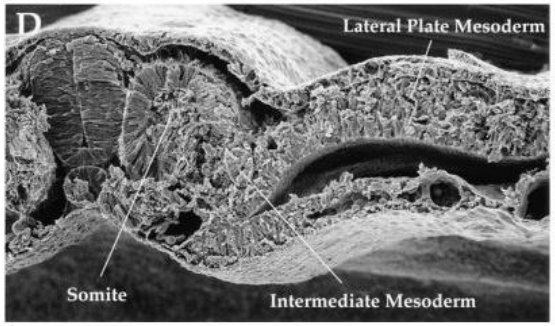


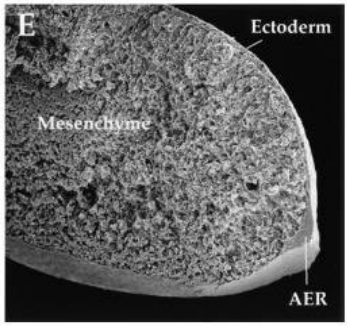
Apical ectodermal ridge (AER)



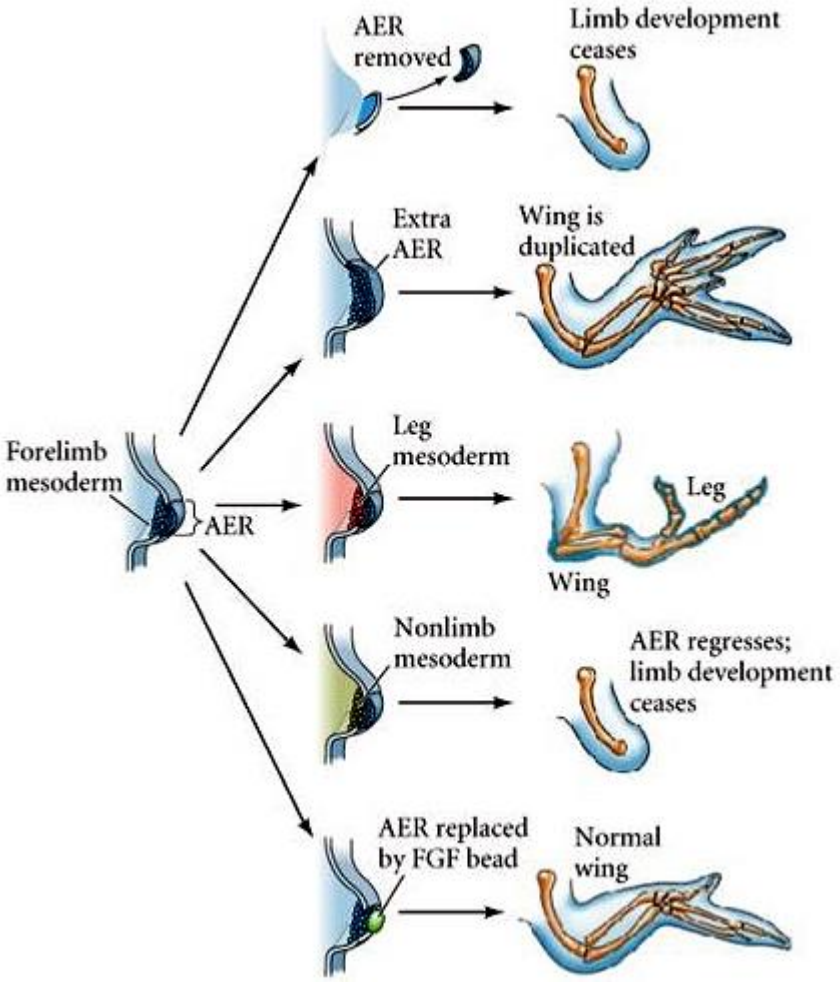


Zone of polarizing activity (ZPA)

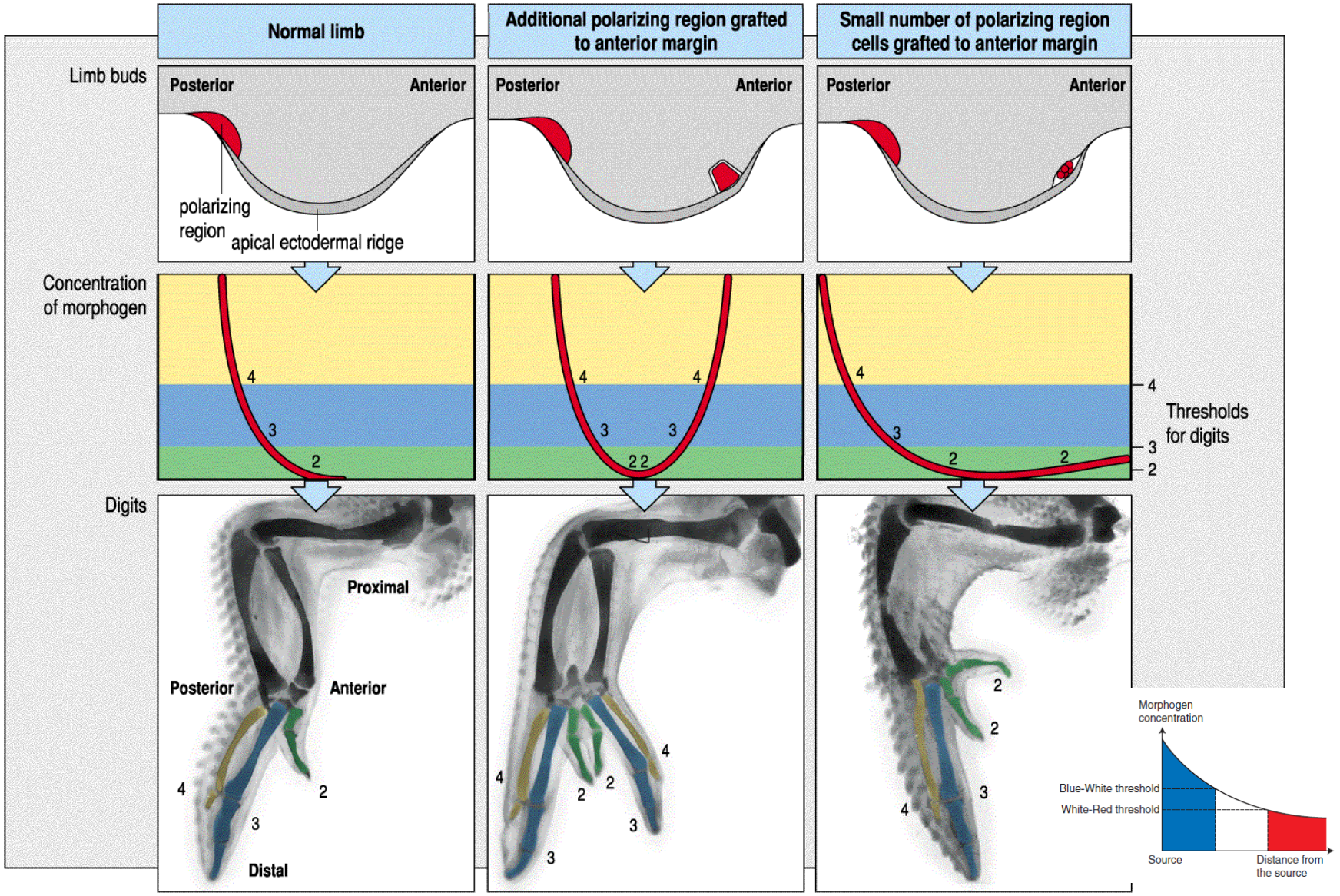




Manipulation with AER changes the instructions for limb development

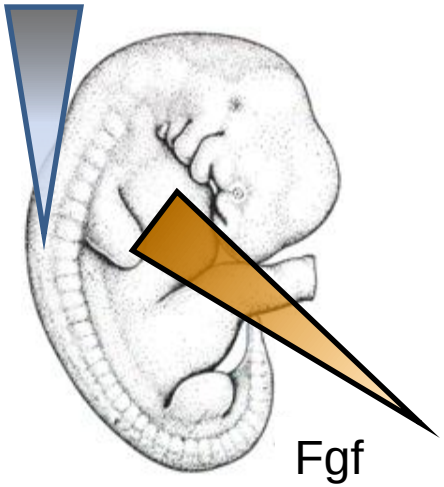


Gradients of morphogenes from AER and ZPA defines limb formation

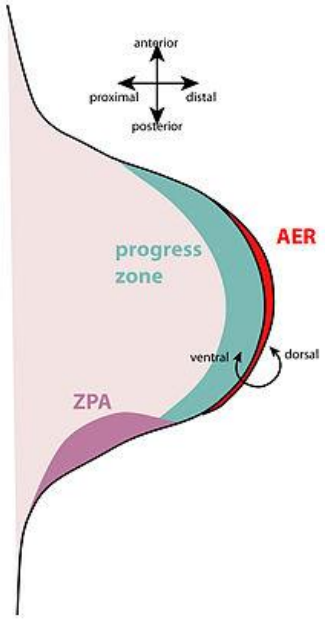


Thalidomid

HOX



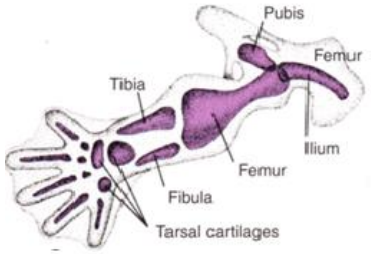
Fgf
Shh
…

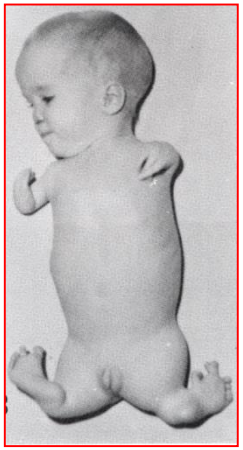


Proliferation

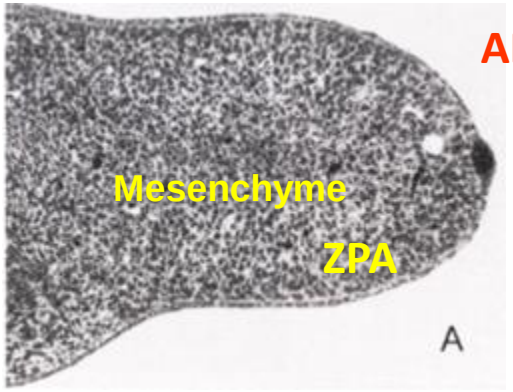
Vascularisation

Thalidomid





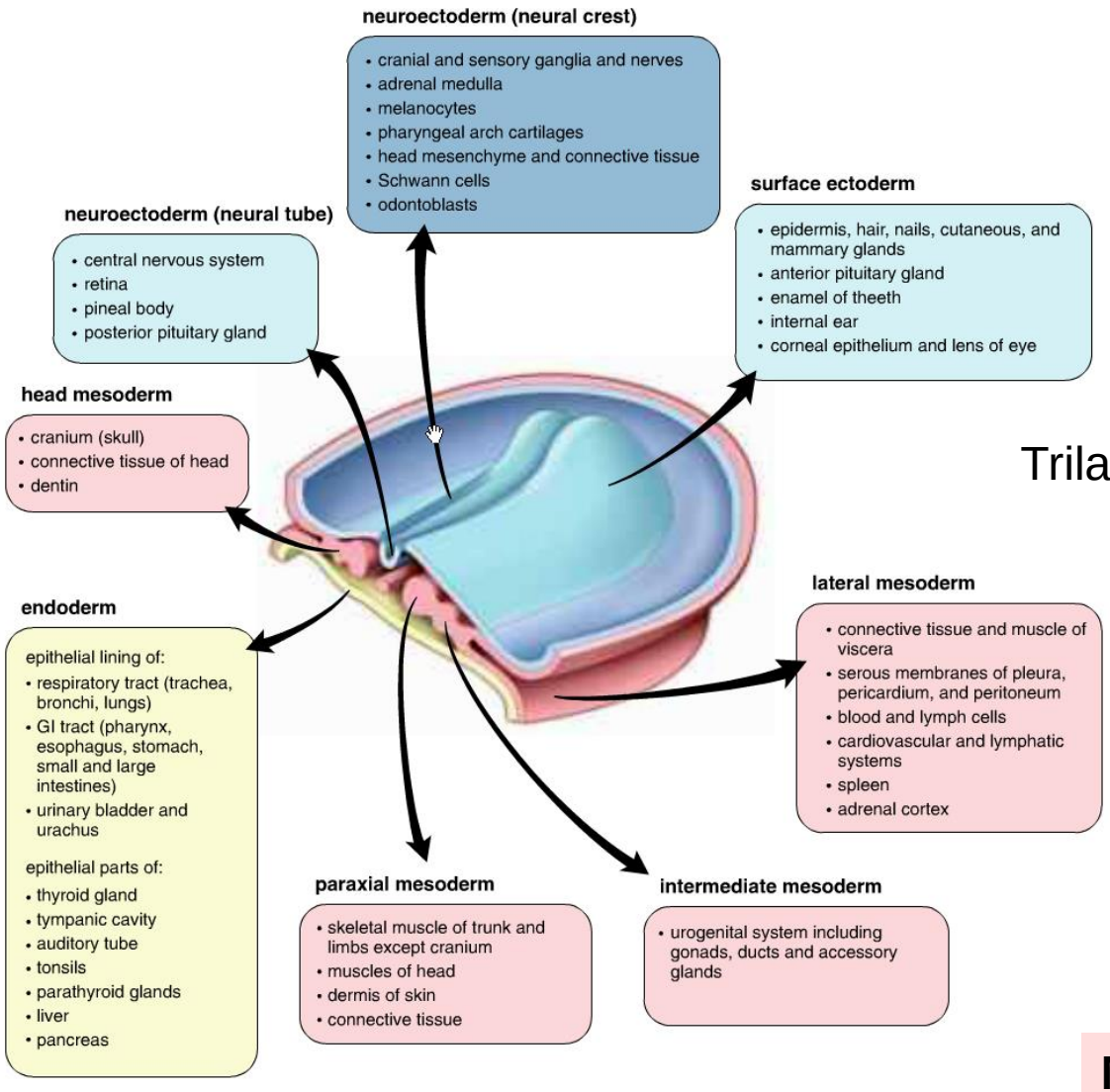
Ectoderm



AER

Histogenesis and organogenesis

Ectoderm



Trilaminar germ disc

(3rd week)

Entoderm

Mesoderm

Embryonic development

Ectoderm

Surface ectoderm

- Epidermis, hair nails, cutaneous and mammary glands
- Corneal epithelium and lens of eye
- Enamel of teeth
- Internal ear
- Anterior pituitary gland
- Epithelium of oral cavity and part of anal canal

Neuroectoderm

- **Neural tube** and derivatives
  - CNS
  - Retina
  - Posterior pituitary gland
  - Pineal body
- **Neural crest** and derivatives:
  - Cranial and sensory ganglia and nerves
  - Schwann cells
  - adrenal medulla
  - Enteroendocrinne cells
  - Melanocytes
  - Head mesenchyme and connective tissue
  - Odontoblasts

Mesoderm

head

- Connective tissue of head
- Cranium, dentin

Paraxial

- Skeletal muscle of trunk and limbs except cranium
- Dermis of skin
- Muscles of head

Intermediate

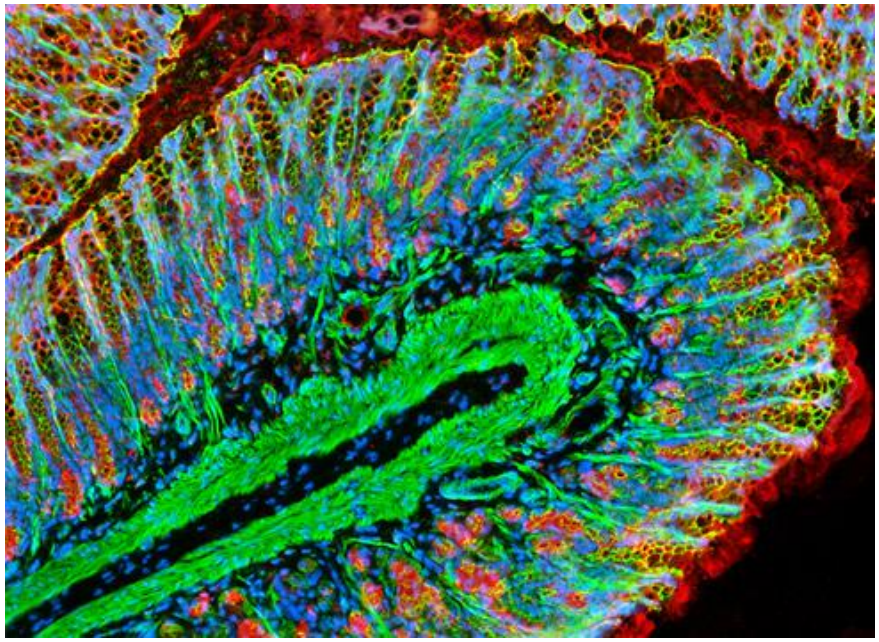
- Urogenital system + ducts, glands and gonads

Lateral

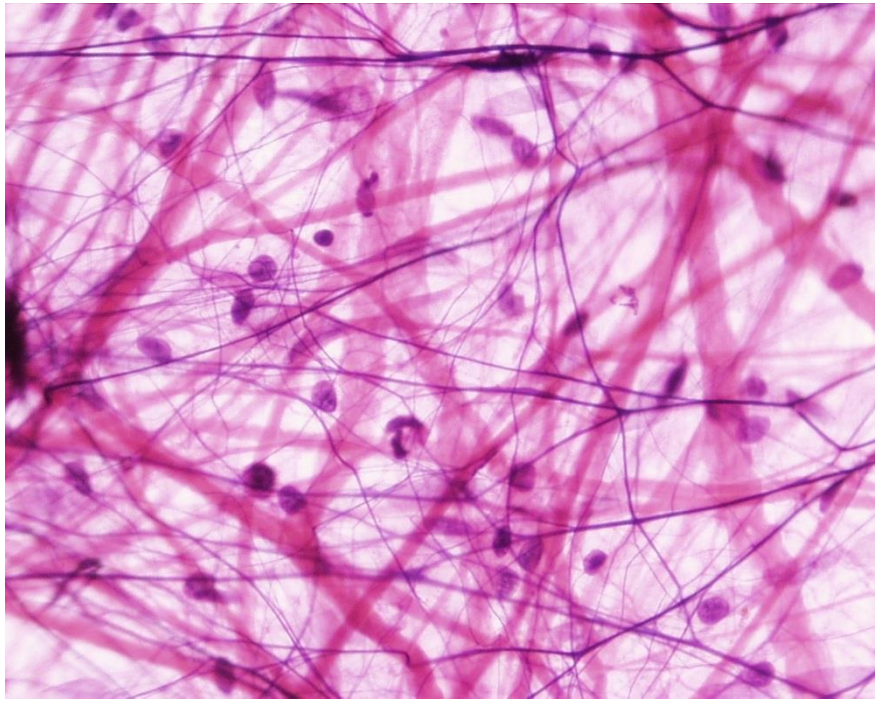
- Visceral muscle and connective tissue
- Serous membranes of pleura, peritoneum and pericardium
- Blood cells, leukocytes
- Cardiovascular and lymphatic system
- Spleen
- Adrenal cortex

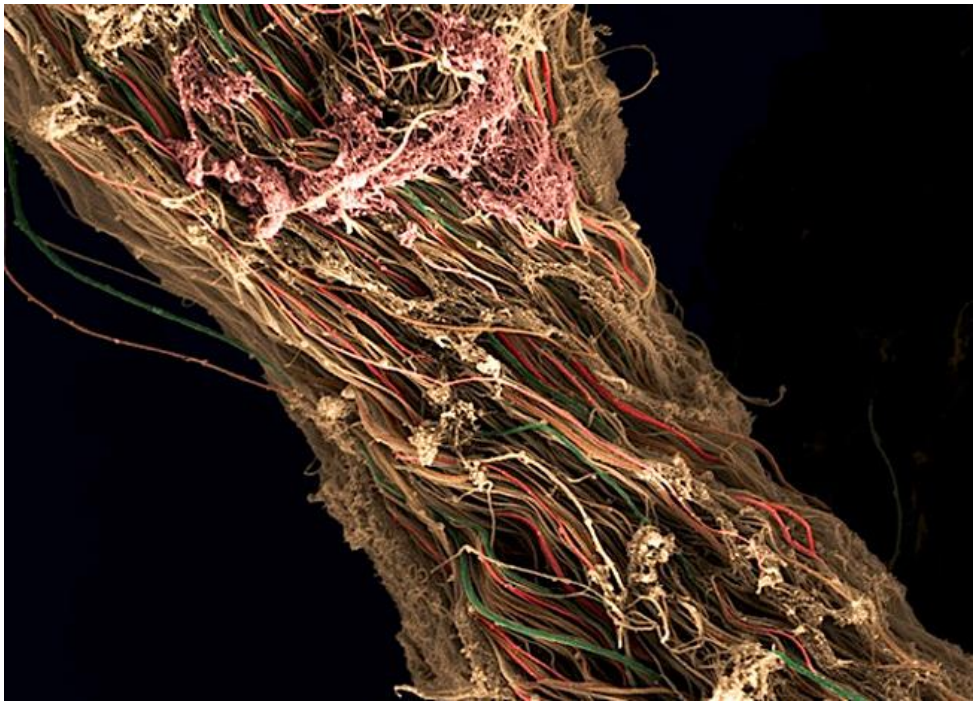
Endoderm

- GIT epithelium except oral cavity and part of anal canal
- Extramural glands of GIT
- Epithelium of bladder
- Epithelium of respiratory system
- Thyroid gland, parathyroid glands, thymus
- Tonsils
- Epithelium of cavum tympani and Eustachian tube



Connective tissue

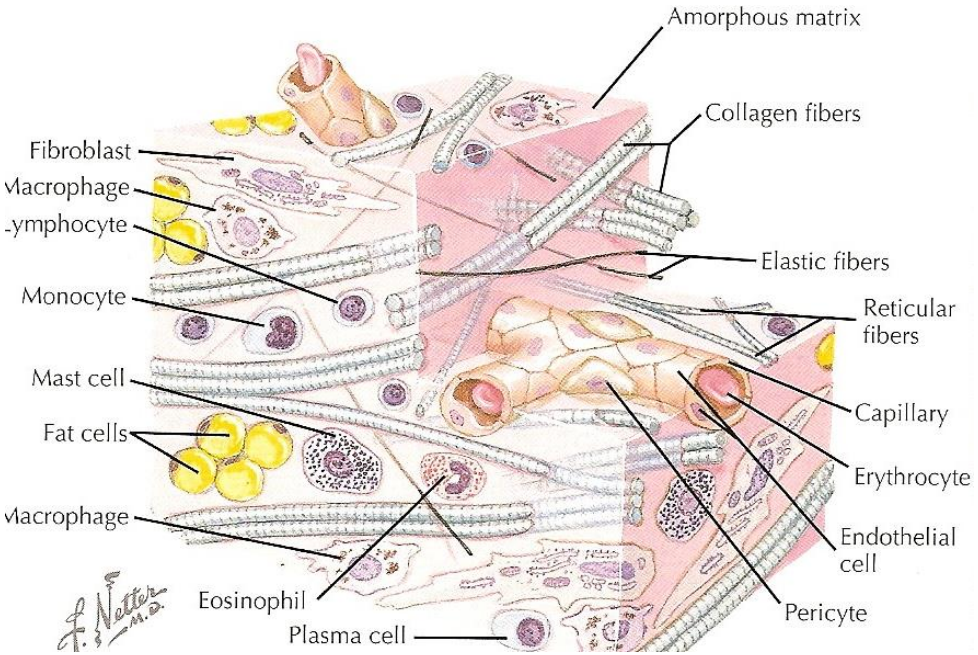




Connective tissue

Mechanical and biological properties

⟶ surrounds other tissues, compartmentalization, support, physico-chemical environment, immunological support, storage

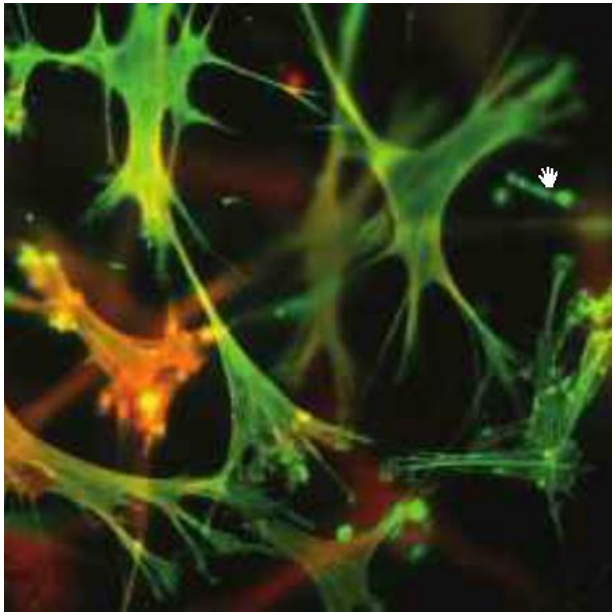


General composition of connective tissue (CT)

Cells and extracellular matrix

- **Cells**

Connective tissue – permanent and transient cell populations (fibroblasts/myofibroblasts, immune cells, adipocytes, adult stem cells)
Cartilage – chondroblasts/chondrocytes
Bone – osteoblasts/osteocytes/osteoclasts



- **Matrix** – fibrous and amorphous

Fibrous component
- collagen
- reticular
- elastic

Amorphous component (amorphous ground substance)
- Complex matrix consisting of glycosaminoglycans, glycoproteins and proteoglycans,

depending on tissue type (connective × ligament × cartilage × bone)

Classification of CT

Embryonic CT
- Mesenchyme
- Jelly-like CT (Wharton jelly, dental pulp, stroma of iris)

Adult CT
- Areolar (loose, interstitial) CT
- Dense collagen irregular CT

CT

- Dense collagen regular CT
- Fat (adipose tissue)
- Cartilage
- Bone

Specialized CT

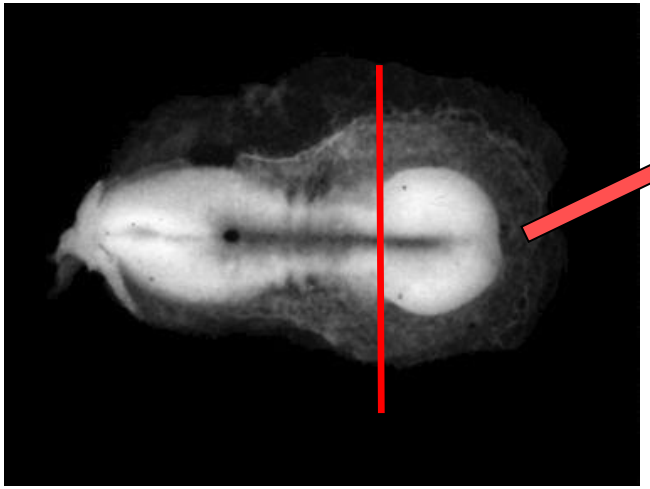
- Blood and hematopoietic tissue
- Lymphatic tissue

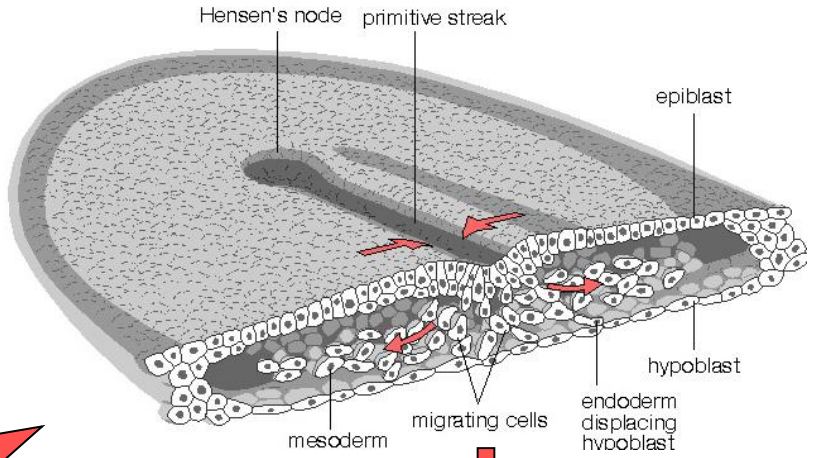
Trophic CT (body liquids)

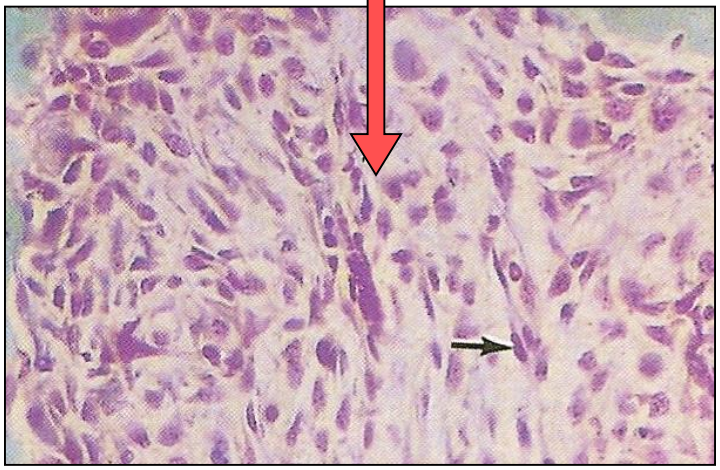
Embryonic origin of CT

- Mesenchyme = loose tissue between germ layers
- Complex network of star- or spindle-shaped cells
- Jelly-like amorphous ground substance

Week 3 of embryonic development

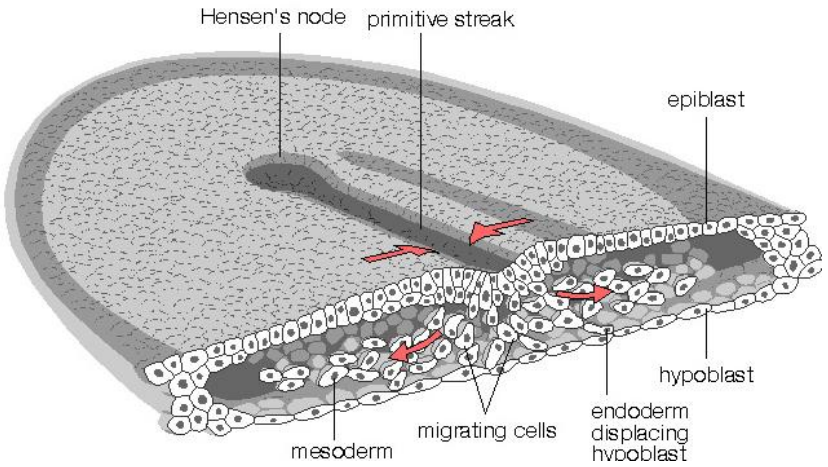


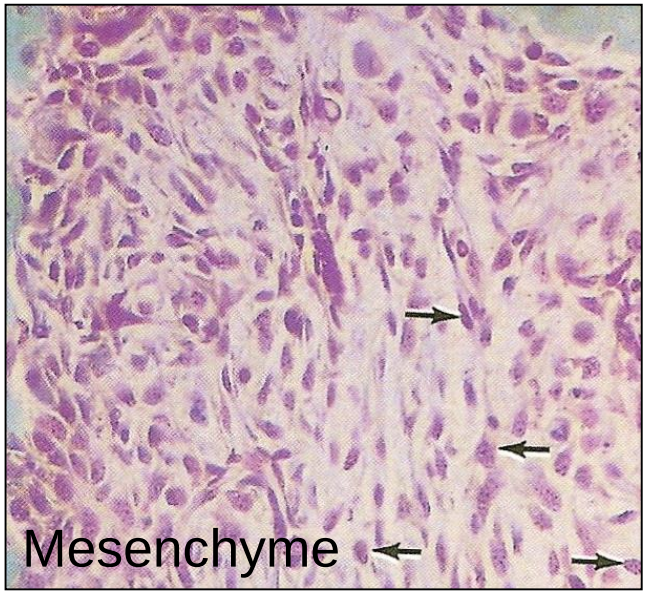


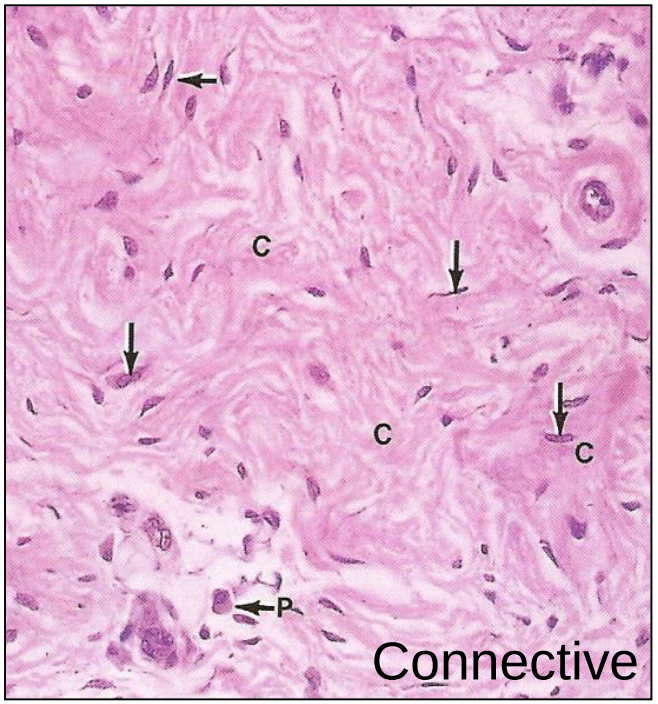


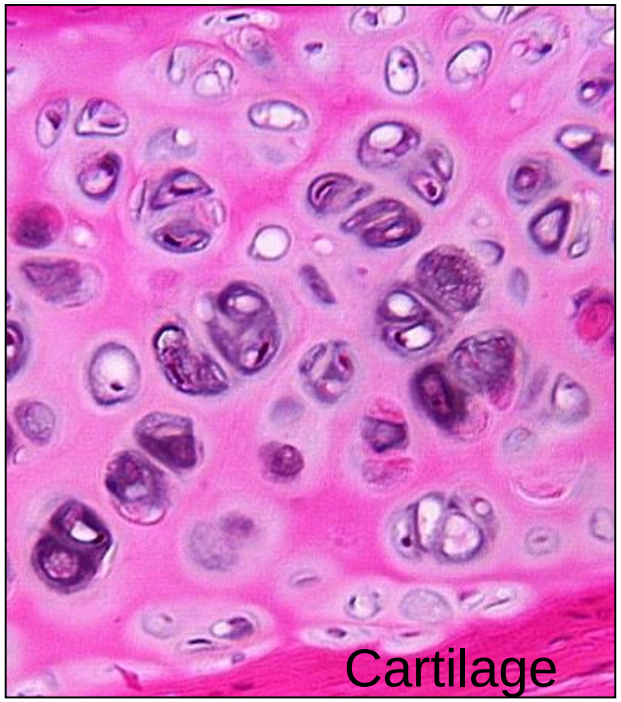
http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_Ch02/DBNModel.html

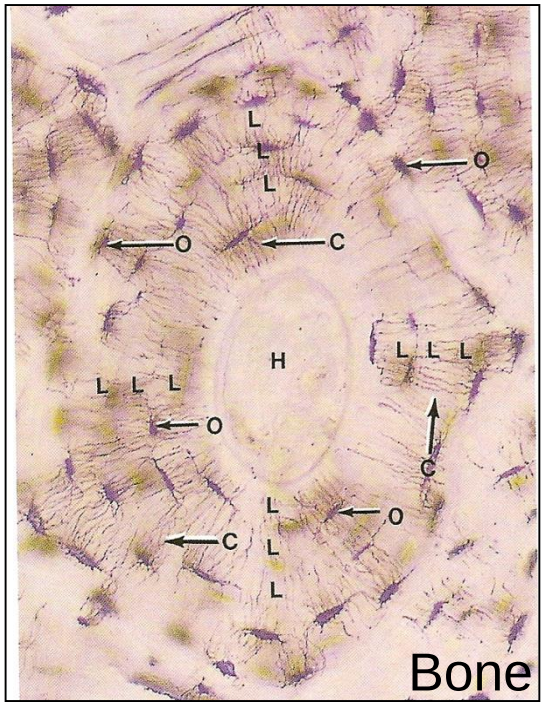
- Basic derivatives of CT







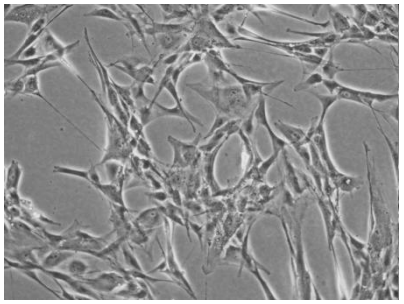


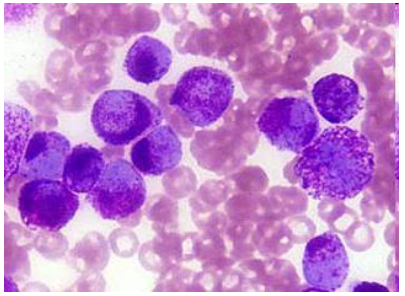


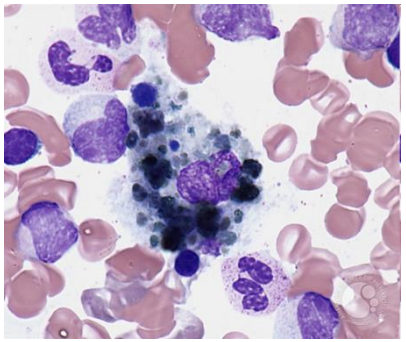
Cells of connective tissue

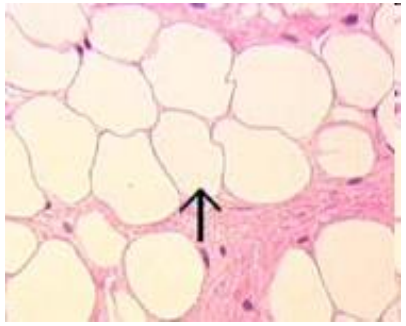
Cells

- Fibroblasts/fibrocytes/myofibroblasts
- Heparinocytes
- Macrophages of CT = histiocytes
- Plasma cells
- Lymphocytes
- Adipocytes
- Adult stem cells



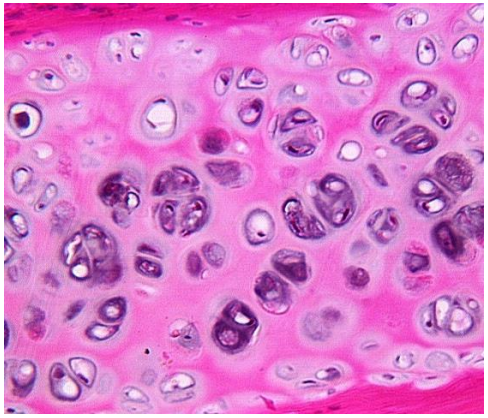


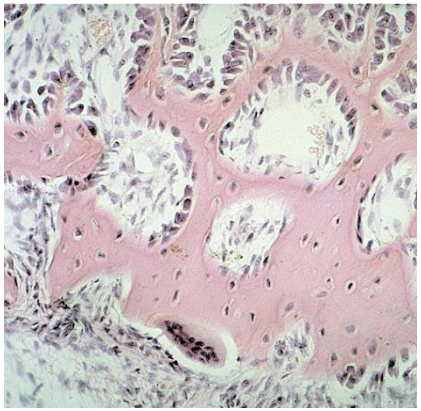


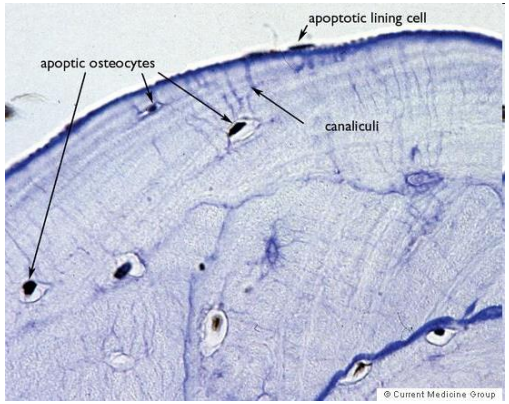


Extracellular matrix

- Fibrous compound
- Amorphous ground substance

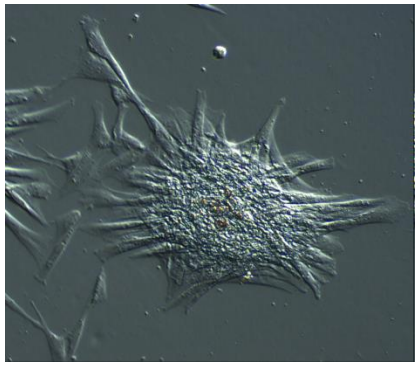


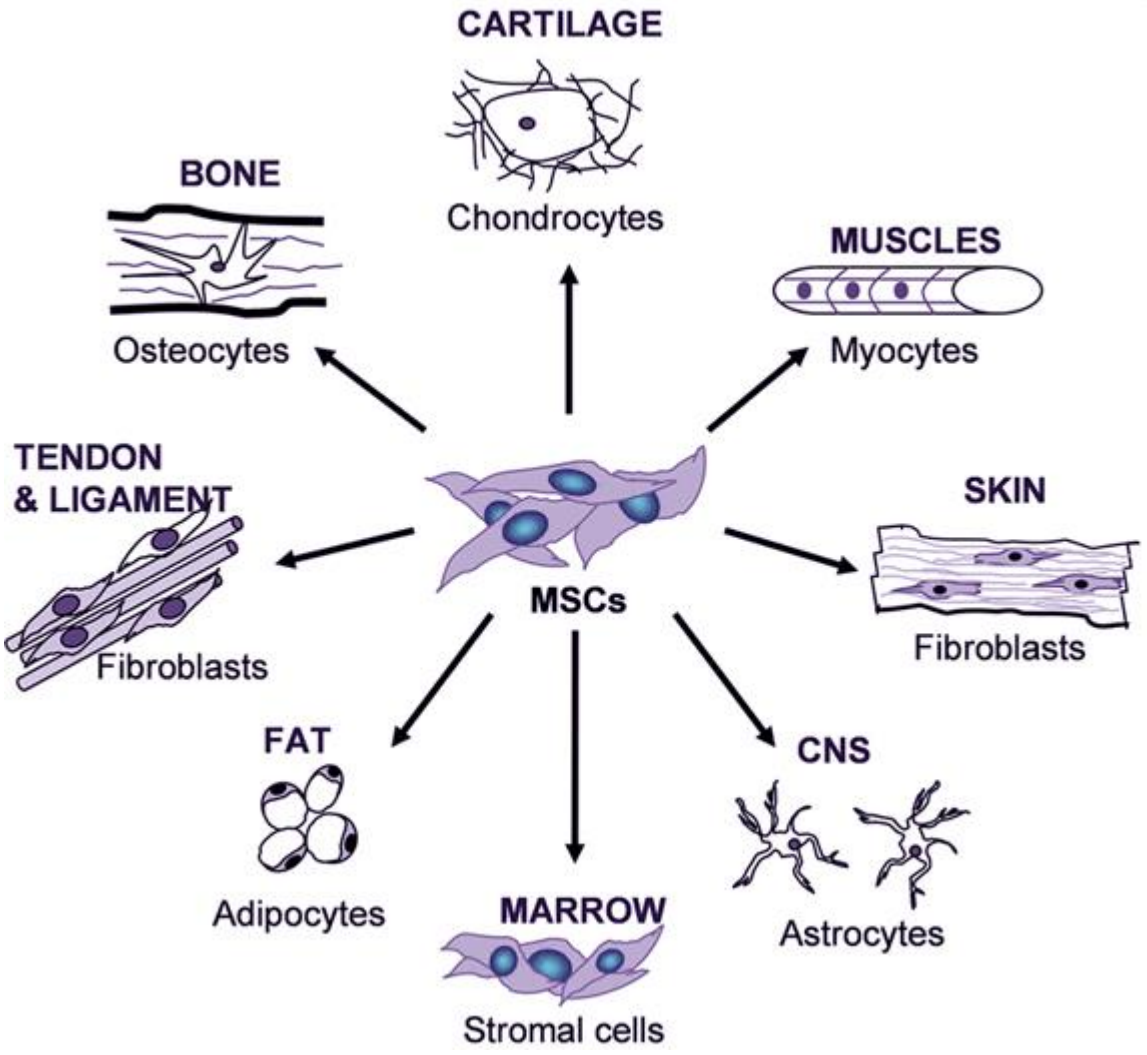




Cells of connective tissue

Mesenchymal (adult) stem cells



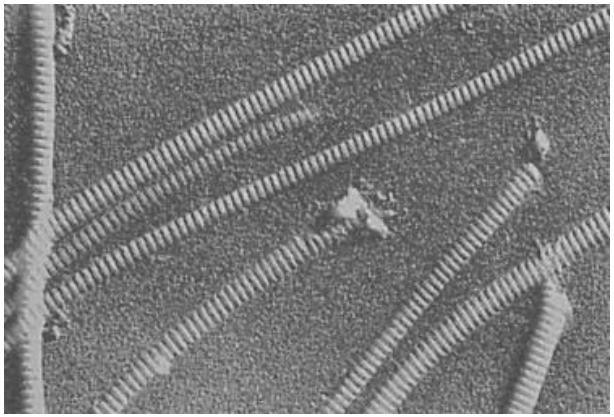


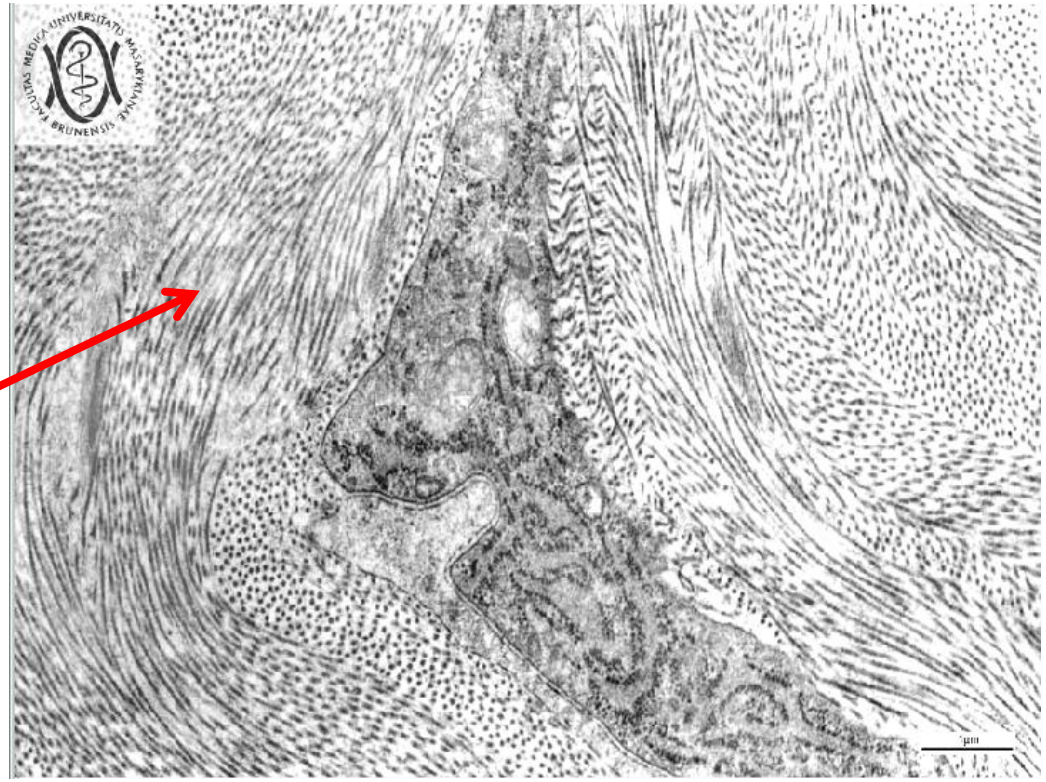
Koch *et al. BMC Biotechnology* 2007 7:26 doi:10.1186/1472-6750-7-26

Extracellular matrix – fibrous component

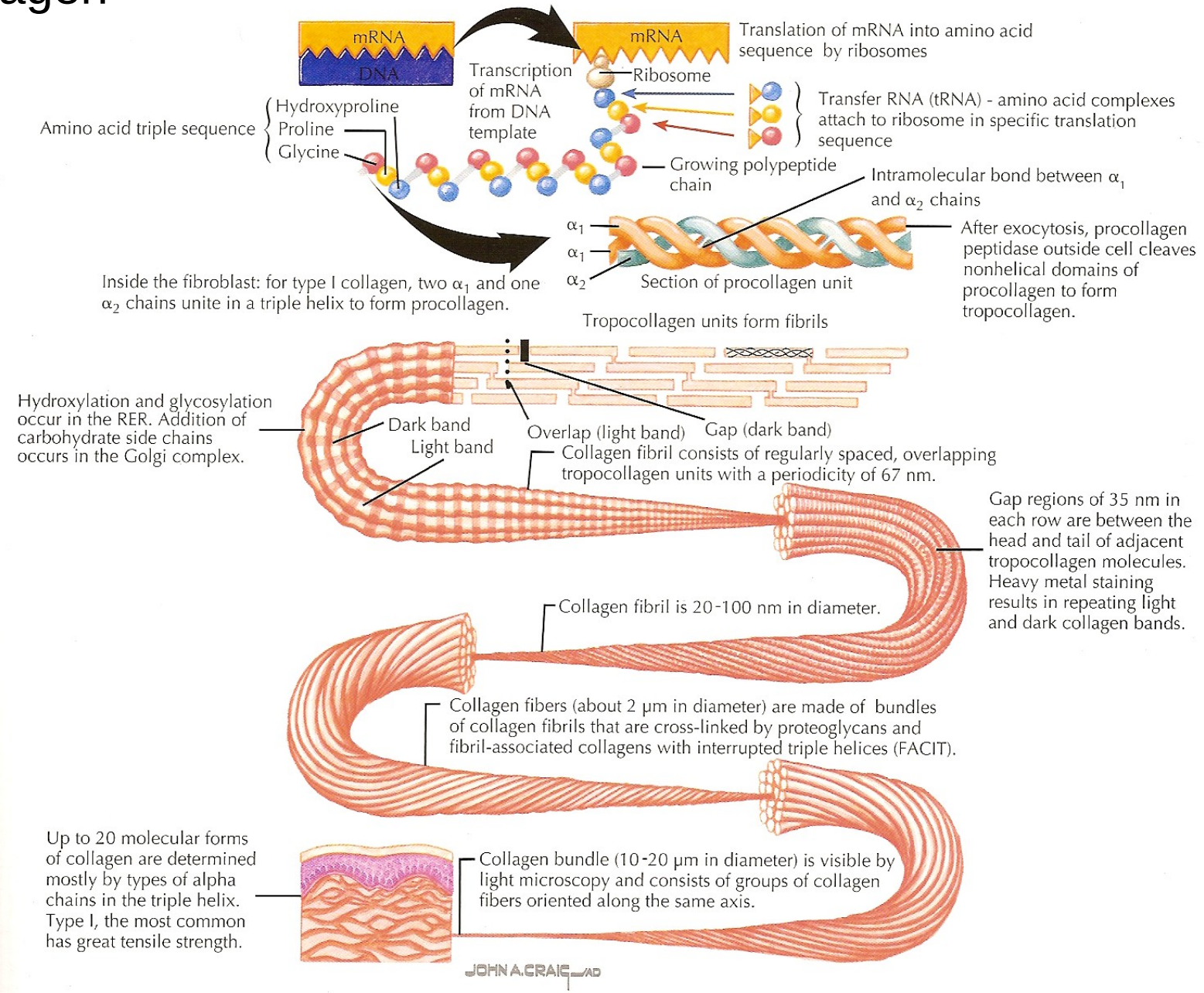
Collagen fibers

- family of fibrous proteins encoded by >35 genes (2013)
- polymer – subunit = tropocollagen; triple helix
- different structural and mechanical properties (strength, elasticity, pliability…)
- most abundant protein in human body (30% dry weight)





- Collagen


mRNA
DNA
Transcription of mRNA from DNA template
mRNA
Ribosome
Translation of mRNA into amino acid sequence by ribosomes
Transfer RNA (tRNA) - amino acid complexes attach to ribosome in specific translation sequence
Amino acid triple sequence
Hydroxyproline
Proline
Glycine
Growing polypeptide chain
Intramolecular bond between α_1 and α_2 chains
α_1
α_1
α_2
Section of procollagen unit
After exocytosis, procollagen peptidase outside cell cleaves nonhelical domains of procollagen to form tropocollagen.
Inside the fibroblast: for type I collagen, two α_1 and one α_2 chains unite in a triple helix to form procollagen.
Tropocollagen units form fibrils
Hydroxylation and glycosylation occur in the RER. Addition of carbohydrate side chains occurs in the Golgi complex.
Dark band
Light band
Overlap (light band)
Gap (dark band)
Collagen fibril consists of regularly spaced, overlapping tropocollagen units with a periodicity of 67 nm.
Gap regions of 35 nm in each row are between the head and tail of adjacent tropocollagen molecules. Heavy metal staining results in repeating light and dark collagen bands.
Collagen fibril is 20-100 nm in diameter.
Collagen fibers (about 2 μm in diameter) are made of bundles of collagen fibrils that are cross-linked by proteoglycans and fibril-associated collagens with interrupted triple helices (FACIT).
Up to 20 molecular forms of collagen are determined mostly by types of alpha chains in the triple helix. Type I, the most common has great tensile strength.
Collagen bundle (10-20 μm in diameter) is visible by light microscopy and consists of groups of collagen fibers oriented along the same axis.
JOHN A. CRAIG, MD

- Collagen

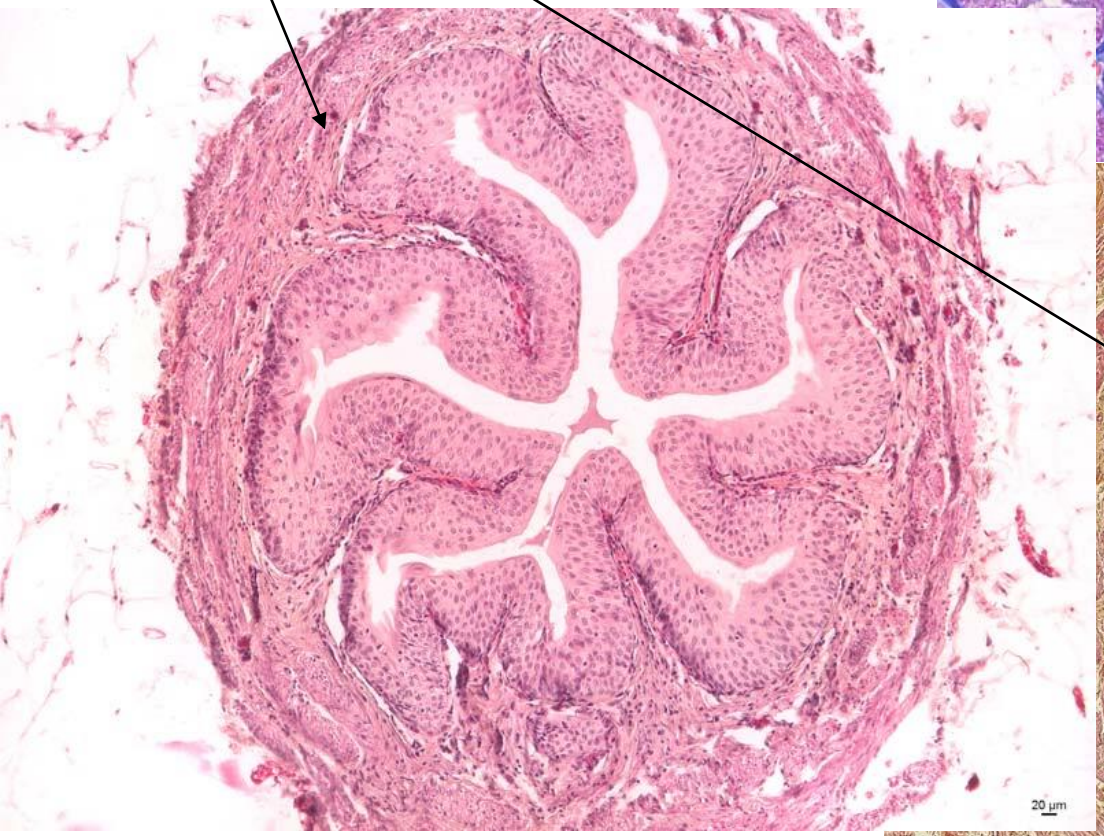
Type	Localization	Structure	Main function
I	Bone, tendons, meniscus, dentin, dermis, capsules of organs, loose CT 90% of type I	Fibrils (75nm) – fibers (1-20μm)	Resilience in pull
II	Hyaline and elastic cartilage	Fibrils (20nm)	Resilience in pressure
III	Skin, veins, smooth muscles, uterus, liver, spleen, 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)		
X	Growth plate, mineralized cartilage		Growth of bones, mineralization

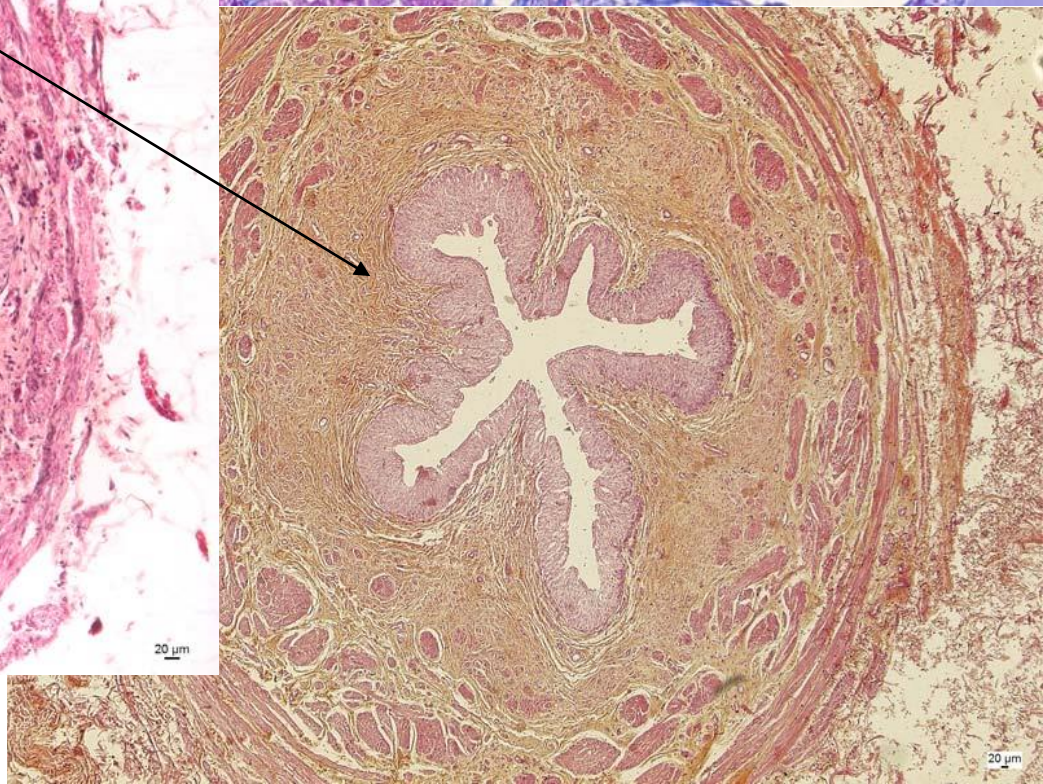
- Collagen in LM

AZAN

HE

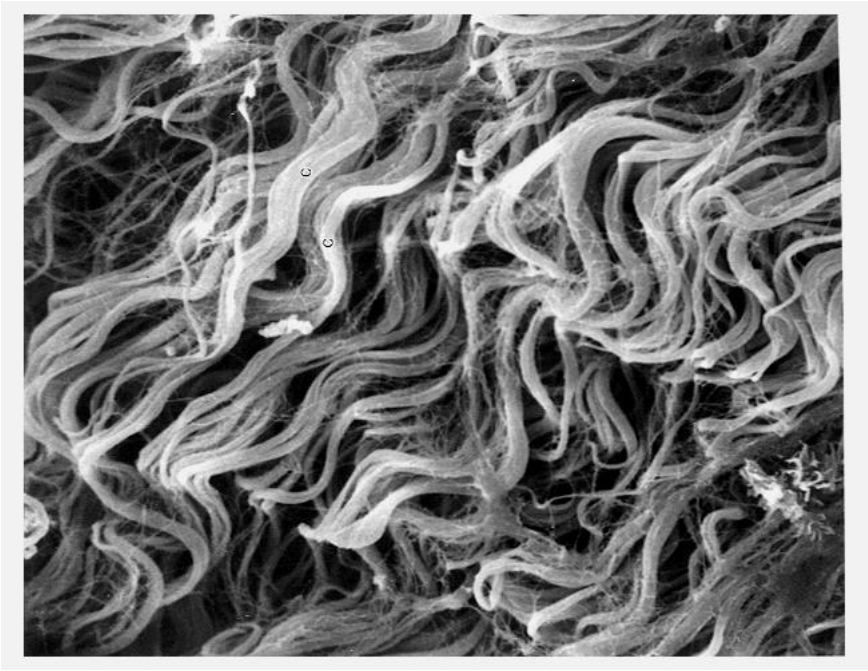
HES

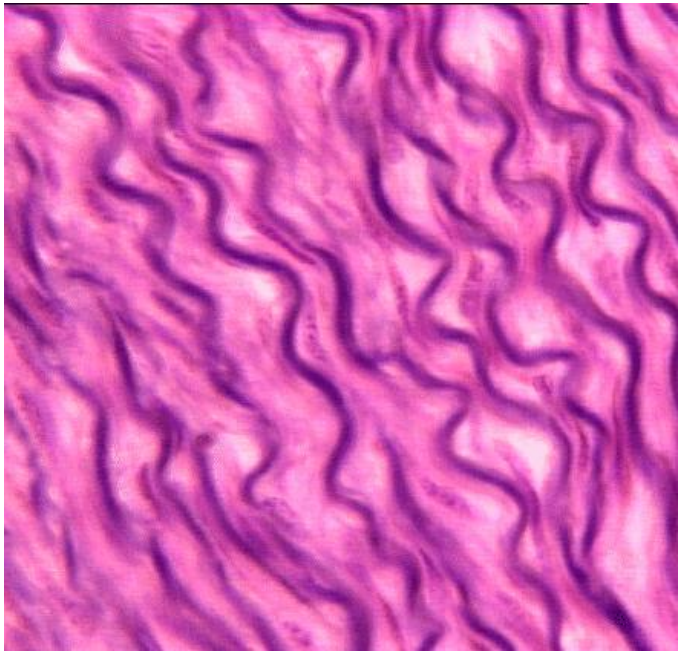




Elastic fibers

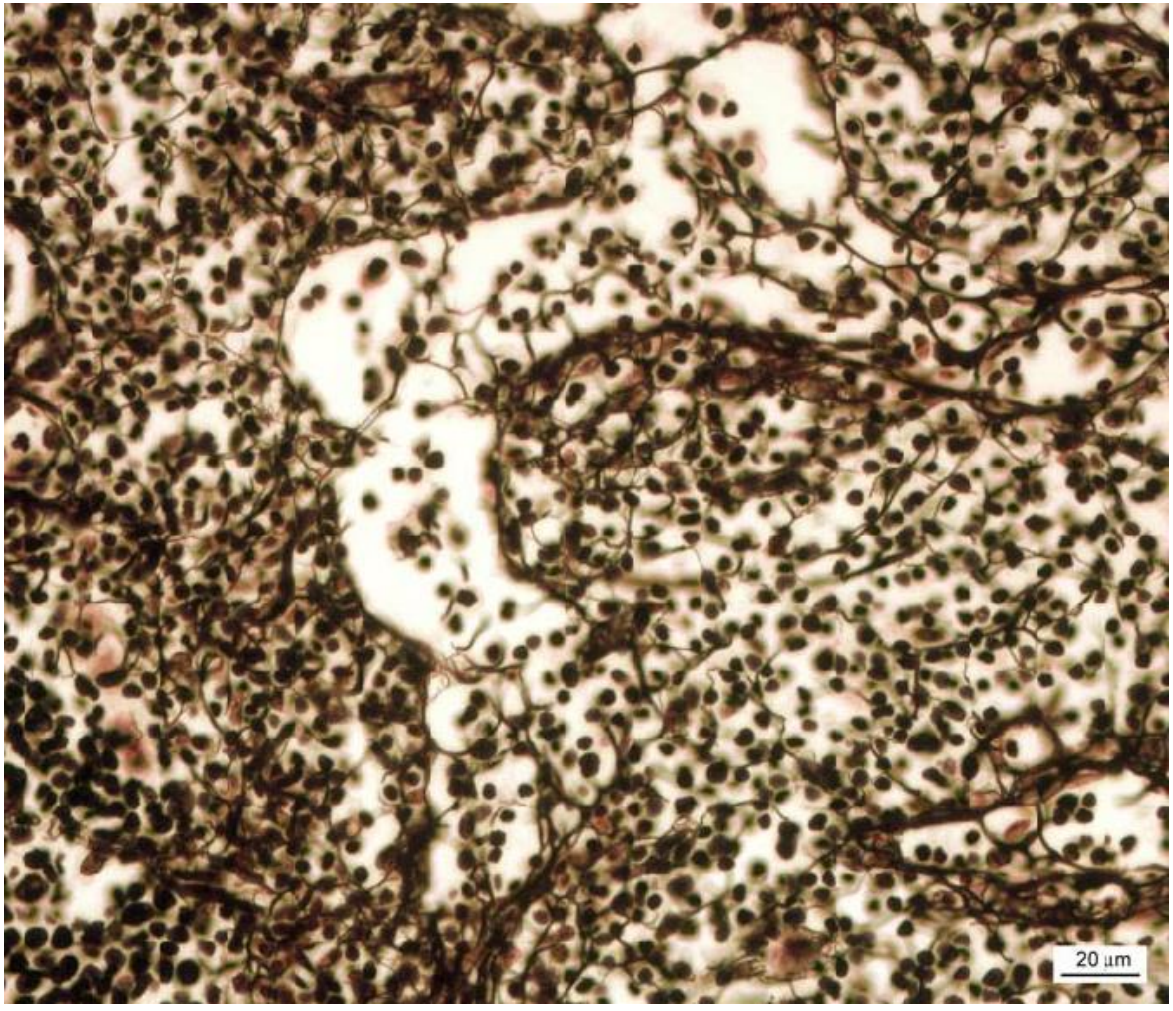
- less abundant than collagen
- polymer – tropoelastin
- minimal tensile resistance, loss of elasticity if overstretched
- reduction of hysteresis = allow return back to original state after mechanic change





Reticular fibers

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

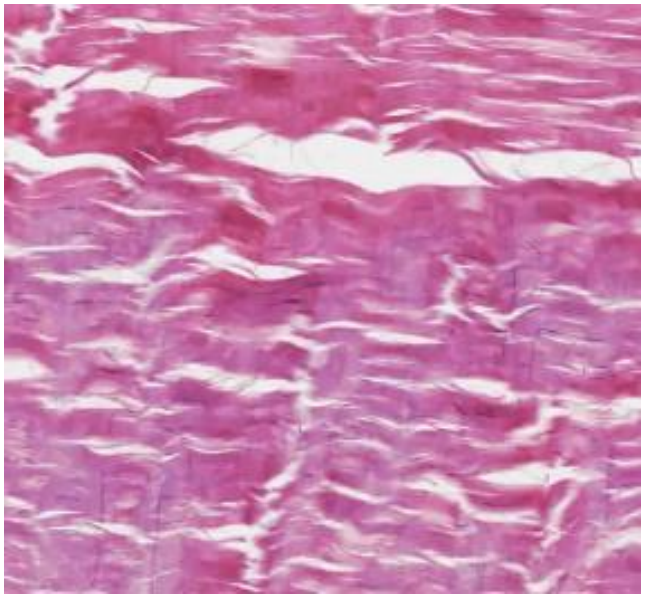


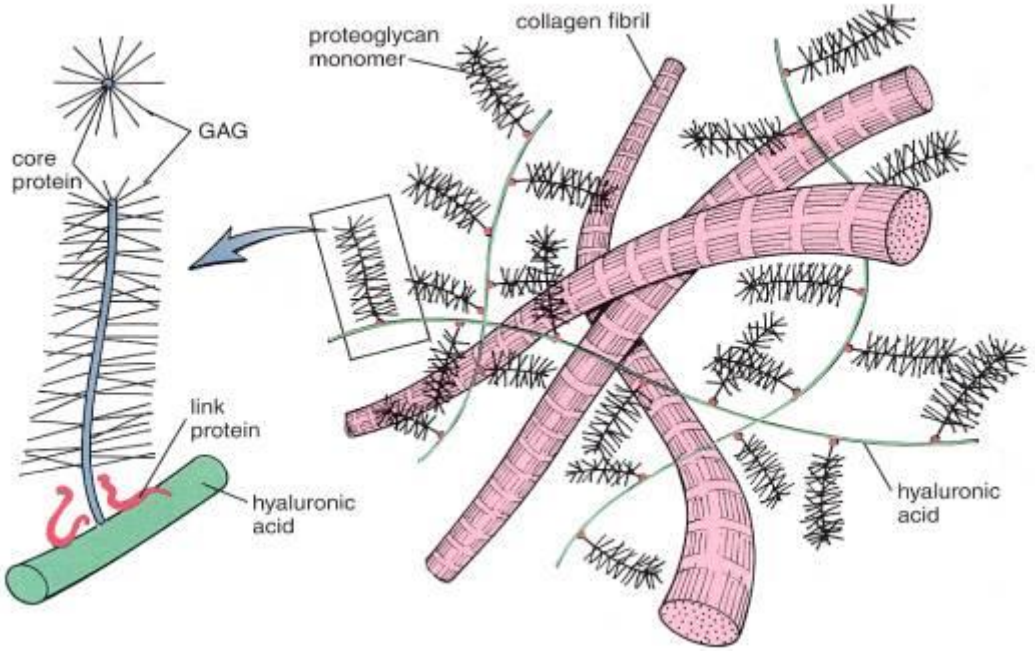

M
Rt
N
N
P
M
P

Extracellular matrix – ground matrix

Amorphous extracellular matrix

Colorless, transparent, homogenous substance consisting of glycosaminglycans, proteoglycans and structural glycoproteins



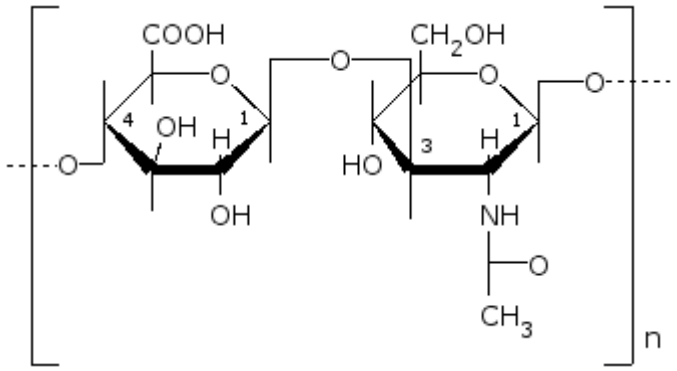


- Glycosaminoglycans

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

polysaccharides rich in hexosamines = acid mukopolysaccharides

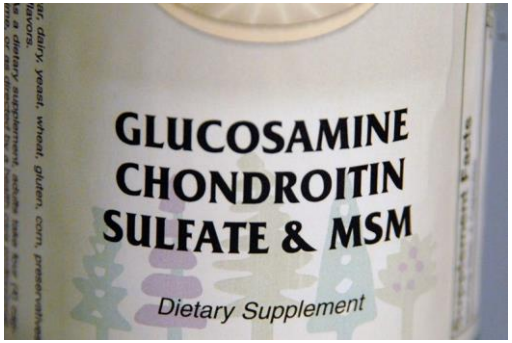
glucuronic or iduronic acid



glucosamin or galactosamin

- Glycosaminoglycans

They bind to protein structures (except for hyaluronic acid)



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

Proteoglycans

— protein + dominant <u>linear</u> saccharide component

— proteoglycan aggregates

— water-binding, volume dependent of hydratation

— aggrecan (cartilage)
— syndecan
— fibroglycan

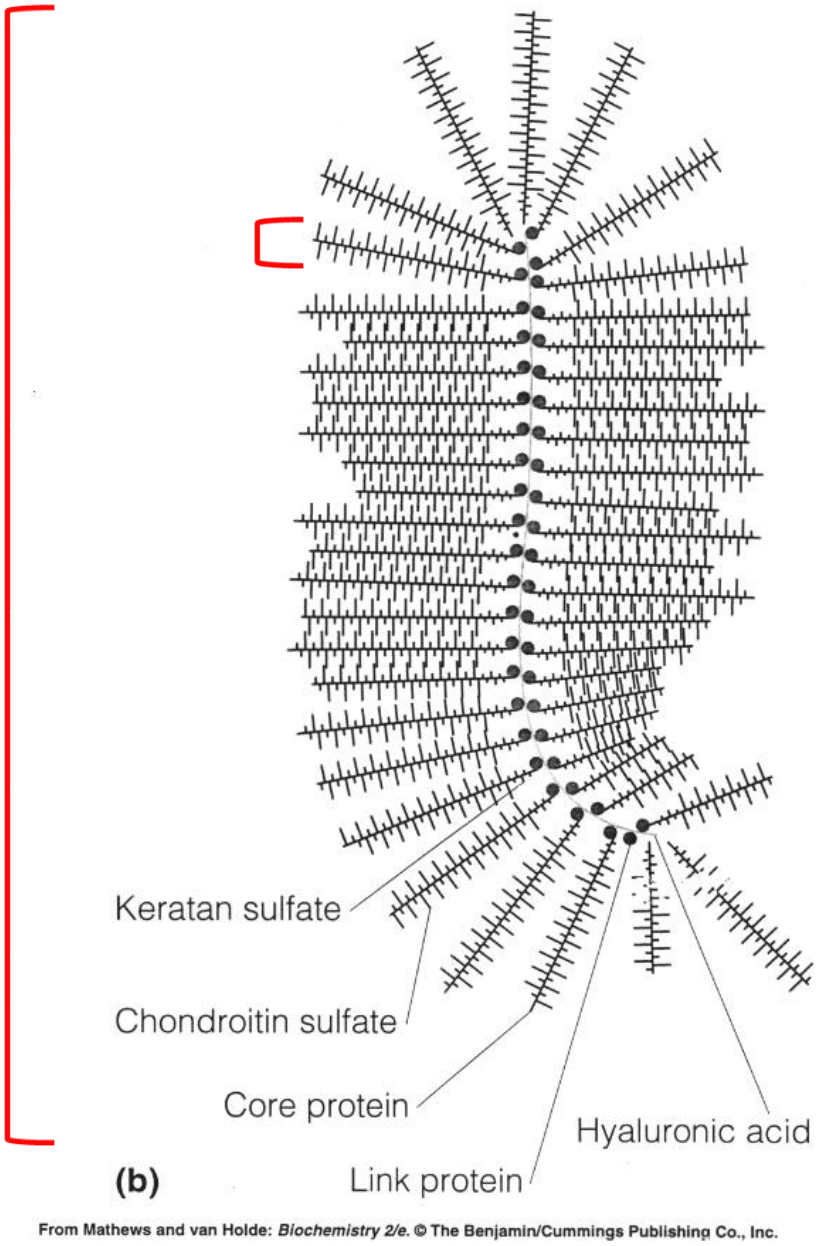
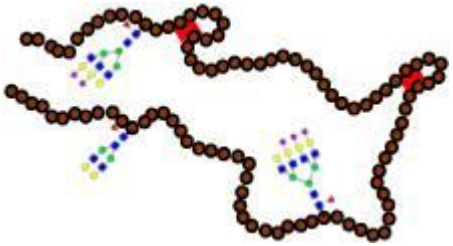


Figure 9.25b Proteoglycan structure in bovine cartilage

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

Structural glycoproteins

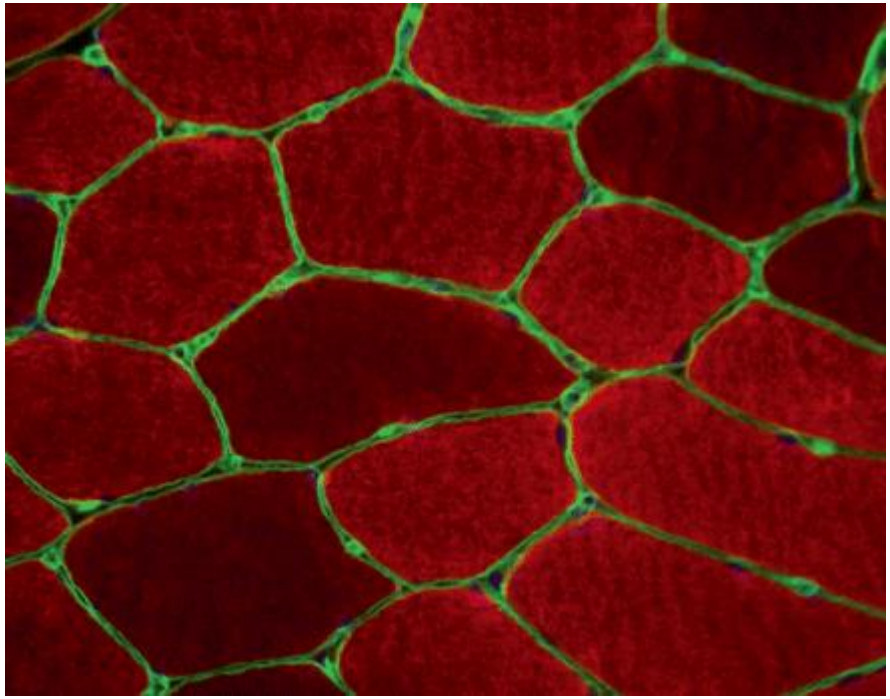


- dominant protein + branched saccharide component
- interaction between cells and ECM

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

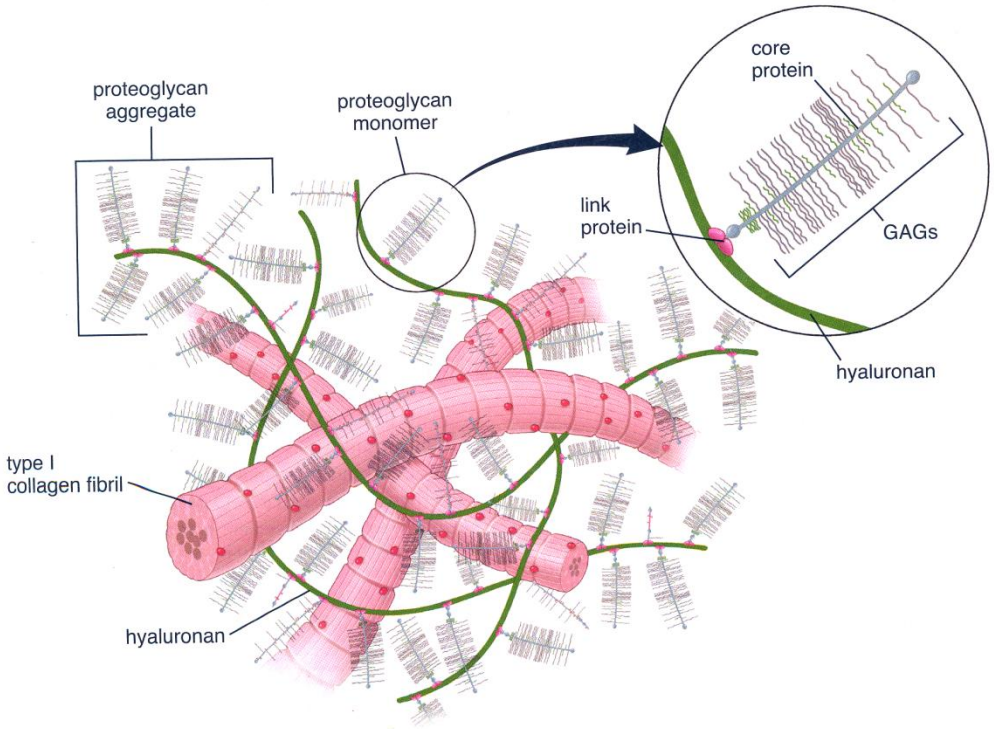
— **laminin** – basal lamina – epithelial integrity

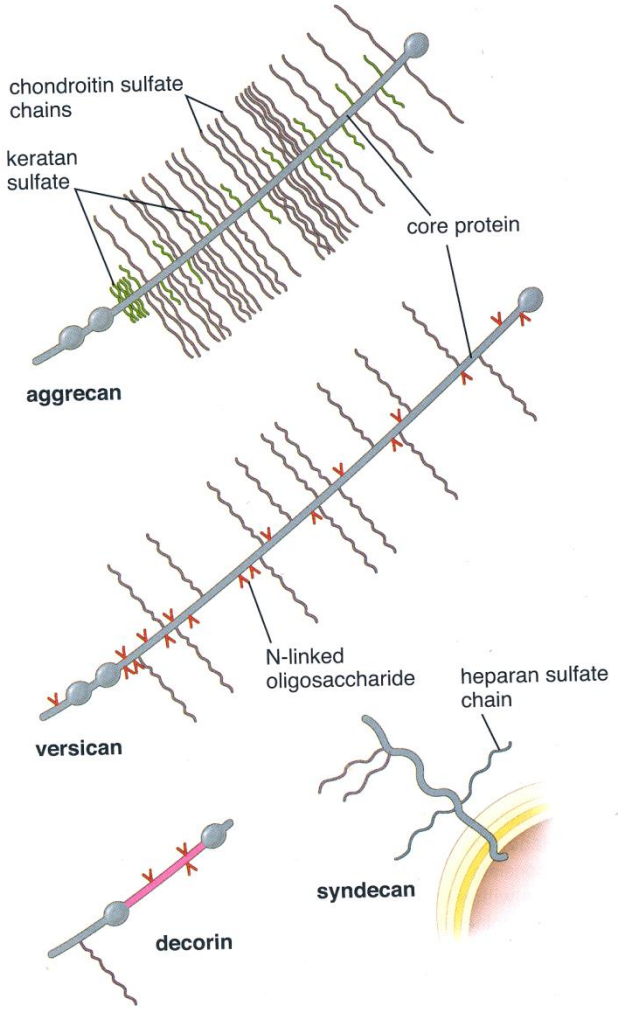
— **chondronectin** – cartilage – adhesion of chondrocytes to collagen



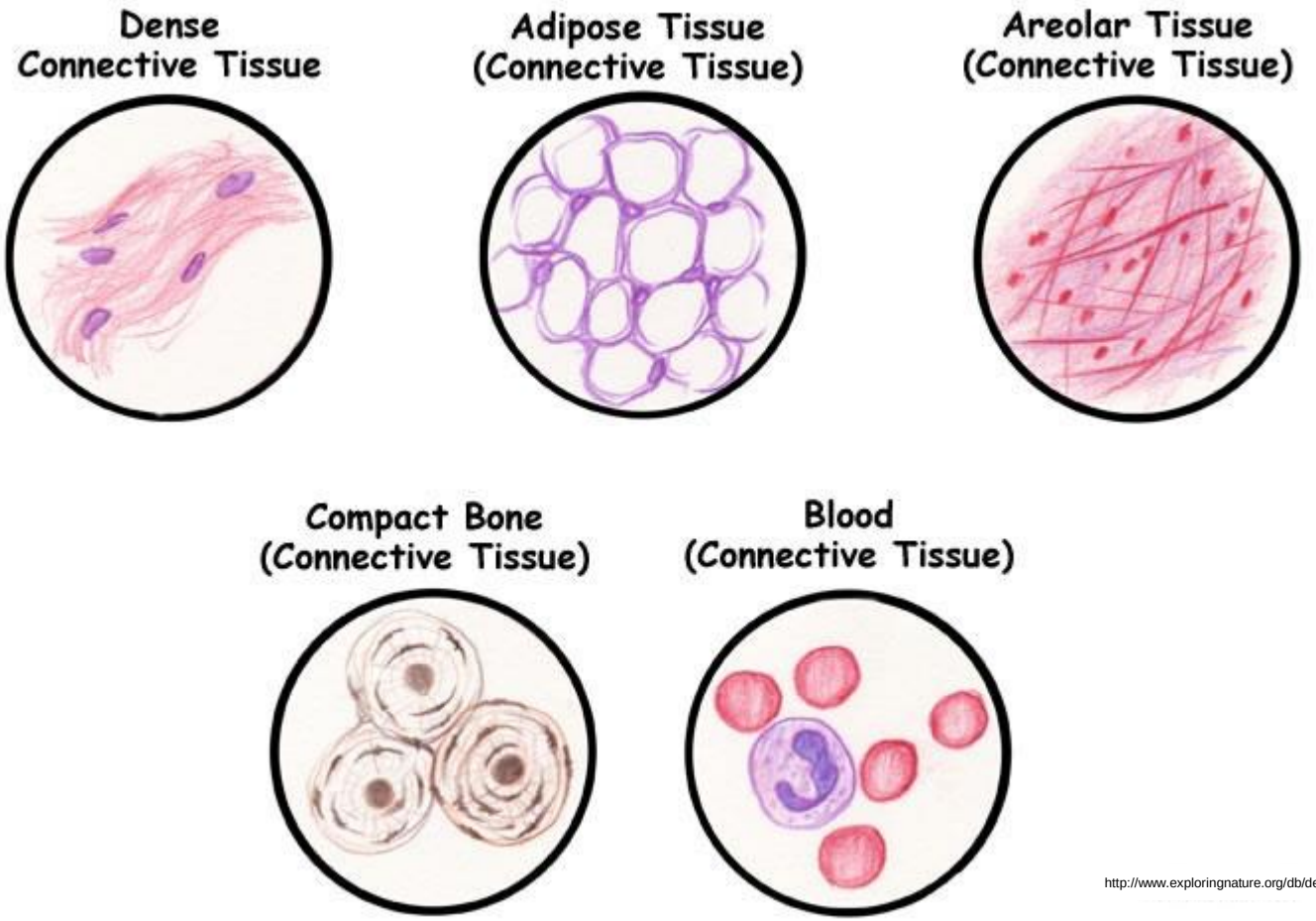
(J. Nutr. 136:2123-2126, 2006)

- Composition of amorphous ground matrix





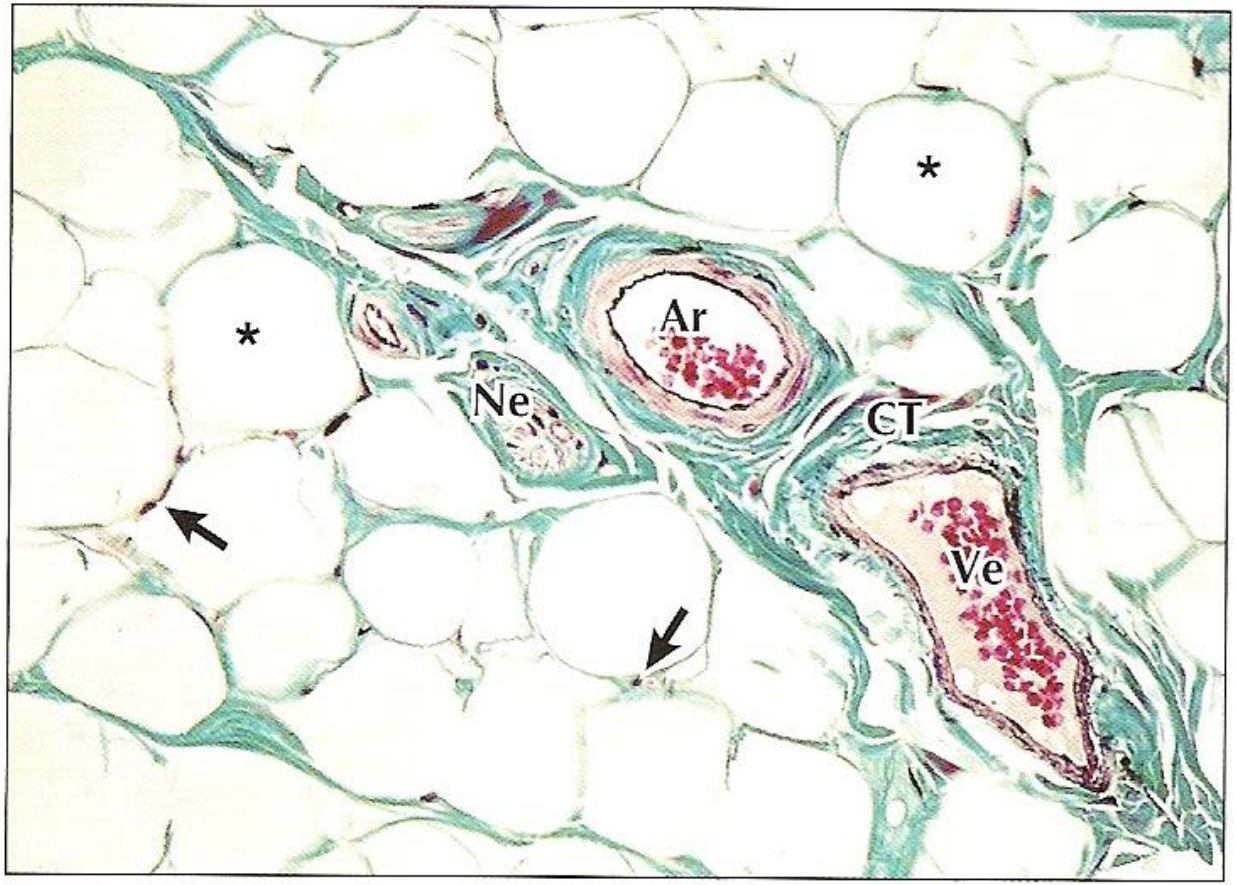
- **Classification of specialized connective tissue**



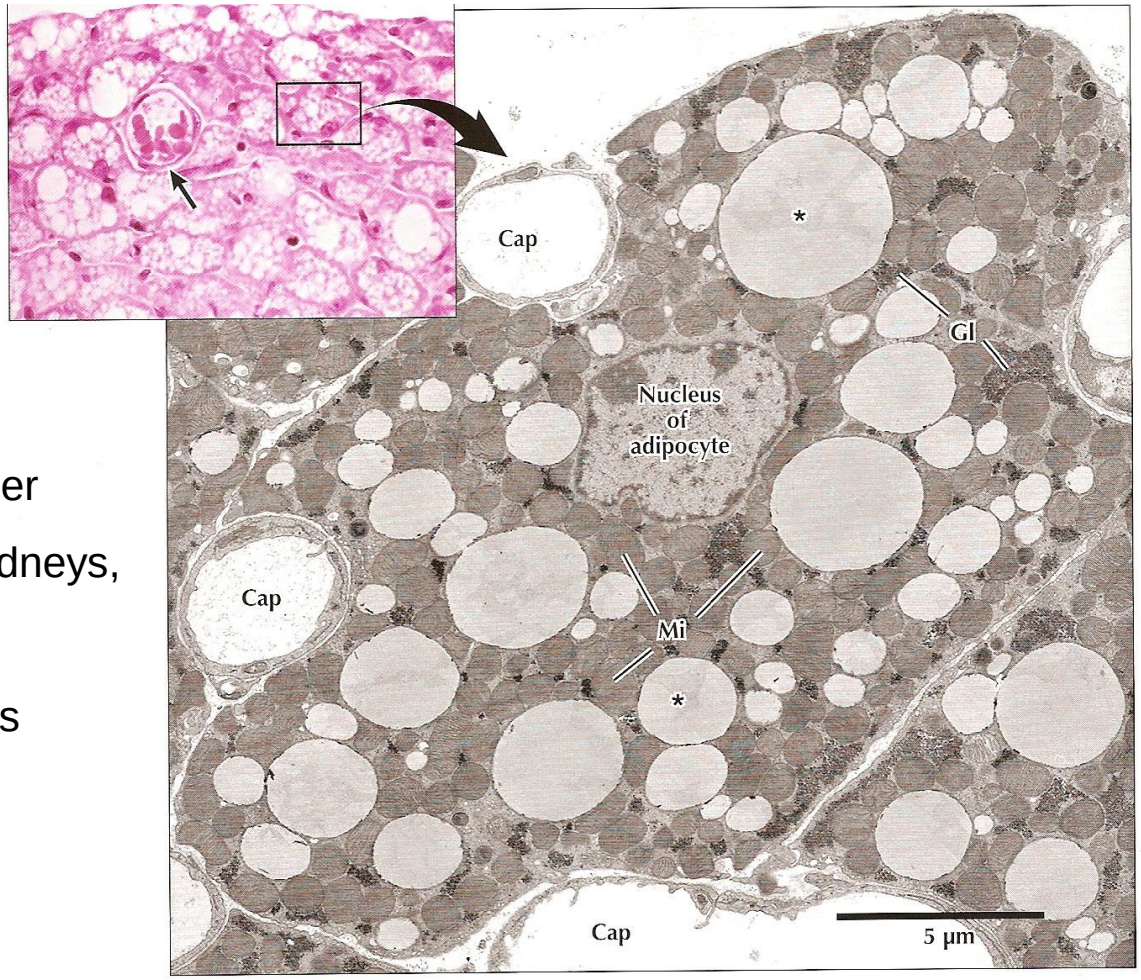
http://www.exploringnature.org/db/detail.php?dbID=21&detID=691

Adipose tissue

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



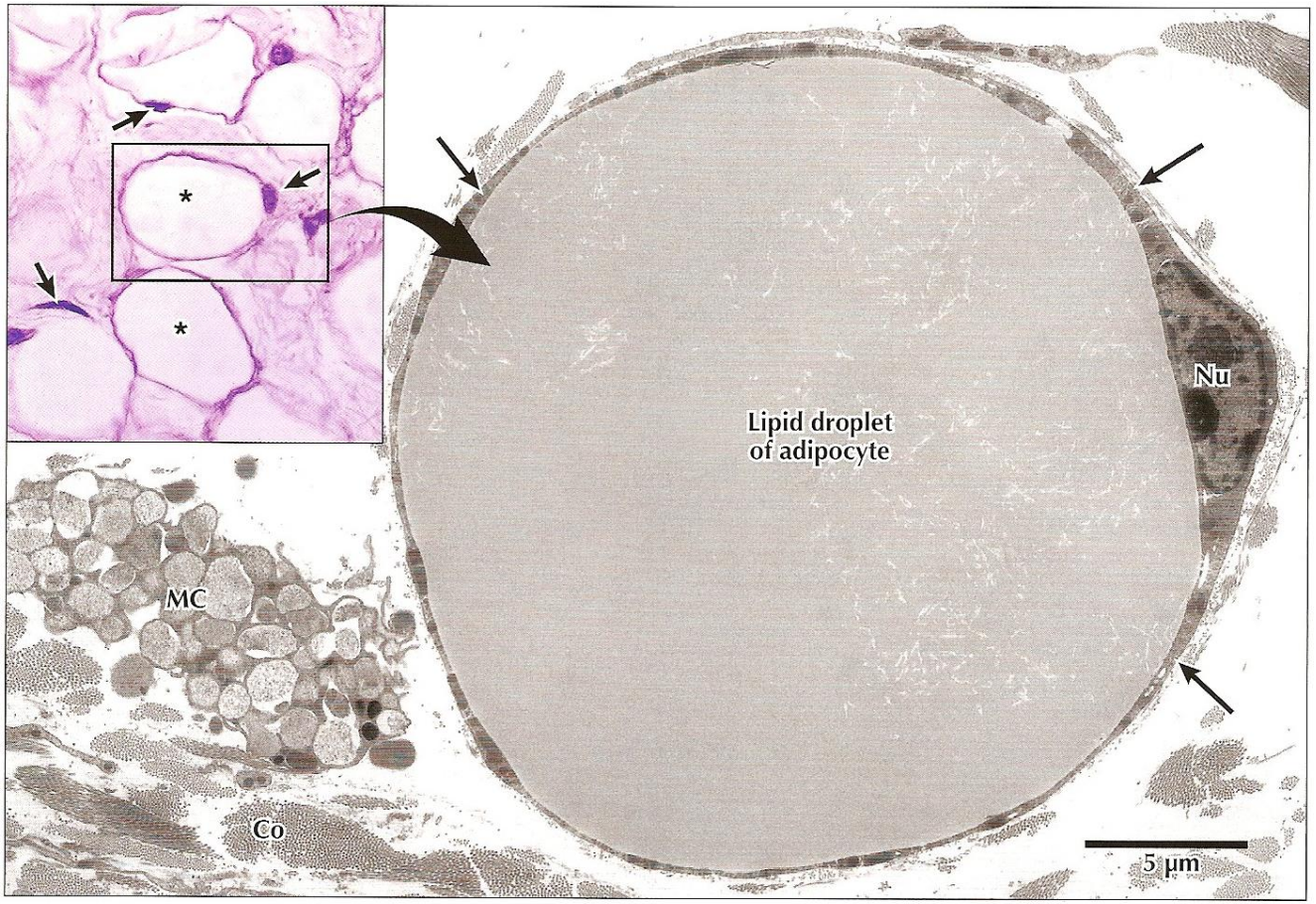
Brown adipose tissue



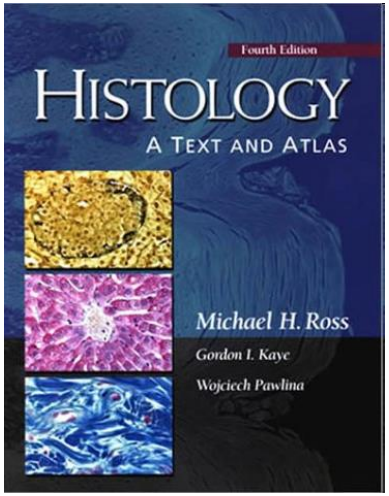
- fetus and child to 1st year of life
- fast source of energy
- typical localization – between shoulder blades, axilla, mediastinum, around kidneys, pancreas, small intestine
- small cells with numerous fat droplets

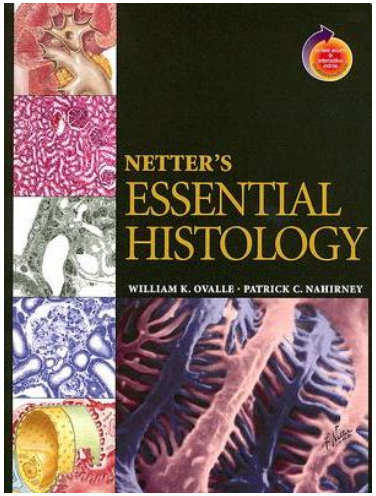
White adipose tissue

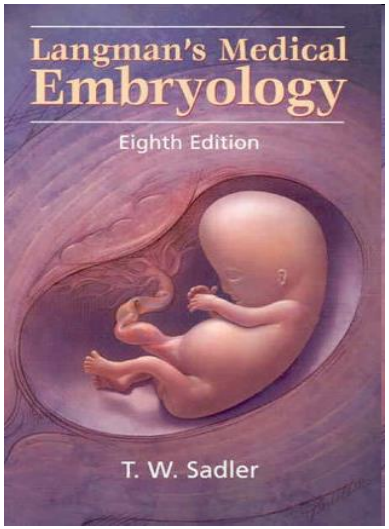
- adipocytes are actively form until 2nd year of life
- no innervations, but rich vascularisation
- adipocytes with only one lipid droplet
- leptin (adipokinins)

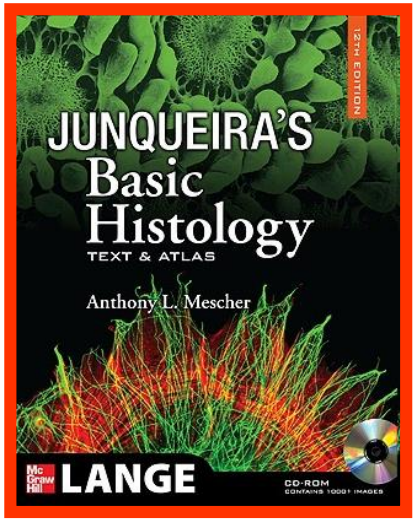


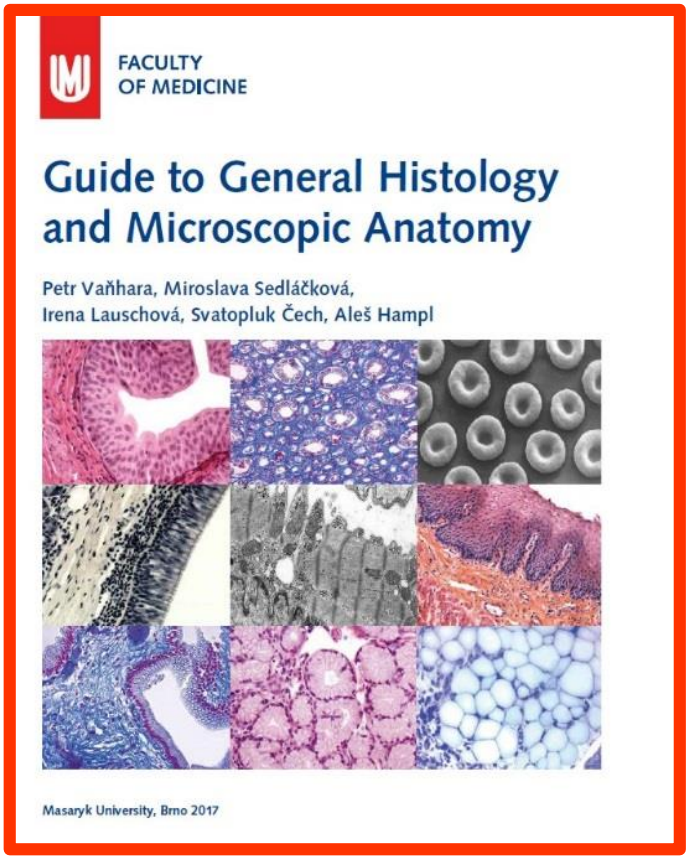
- Further study











http://www.med.muni.cz/histology

Thank you for attention

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