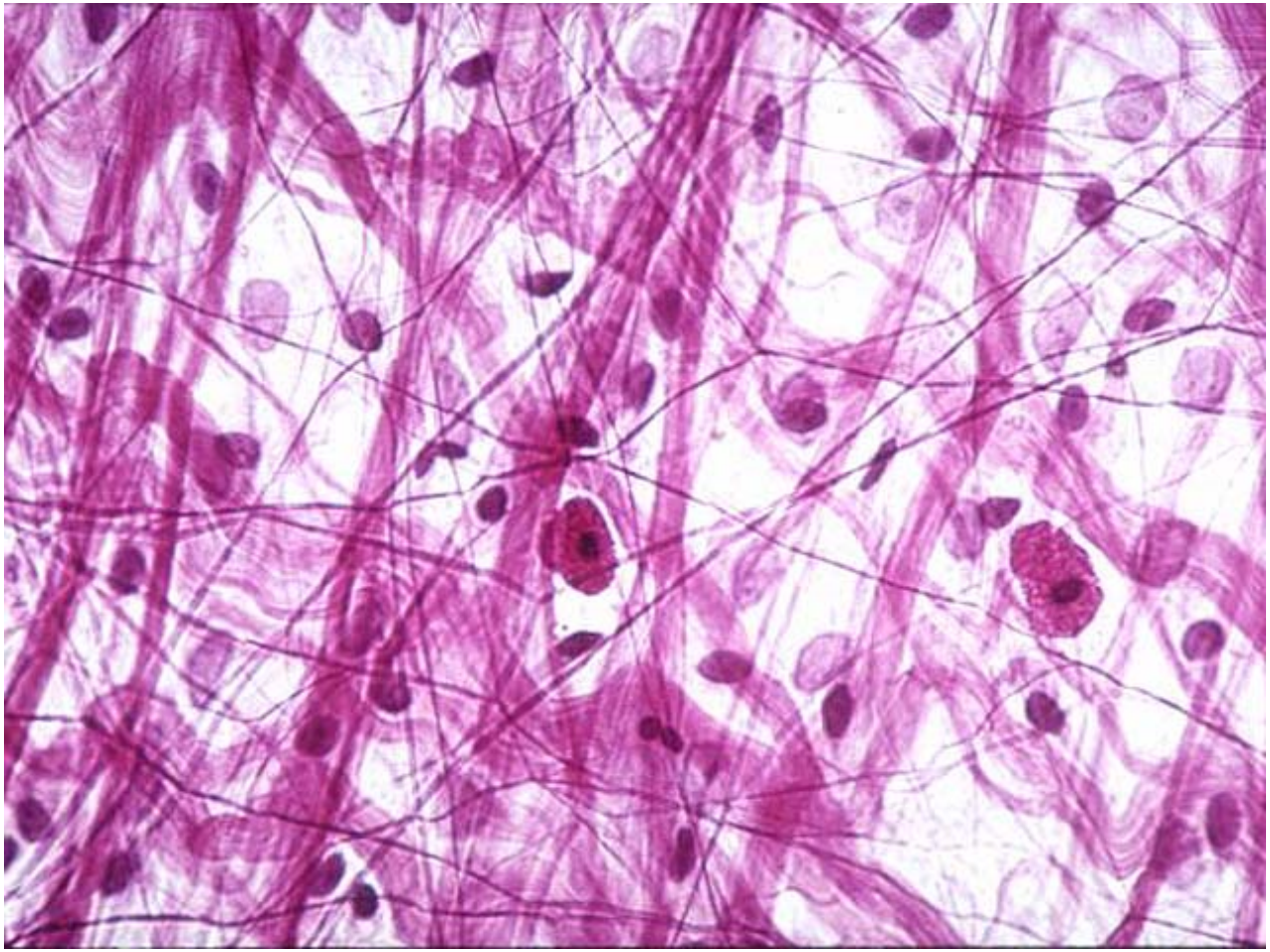
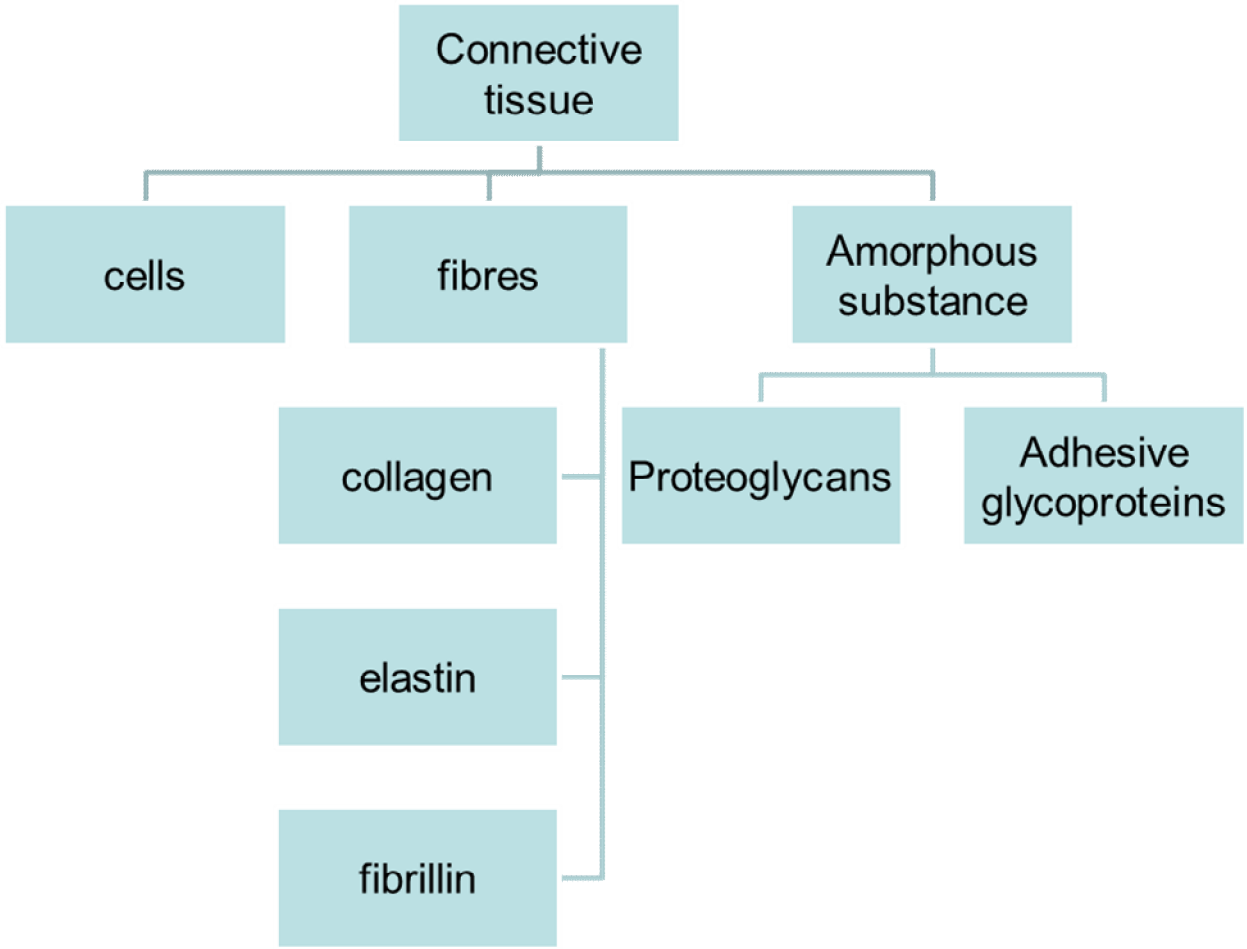
Connective tissue



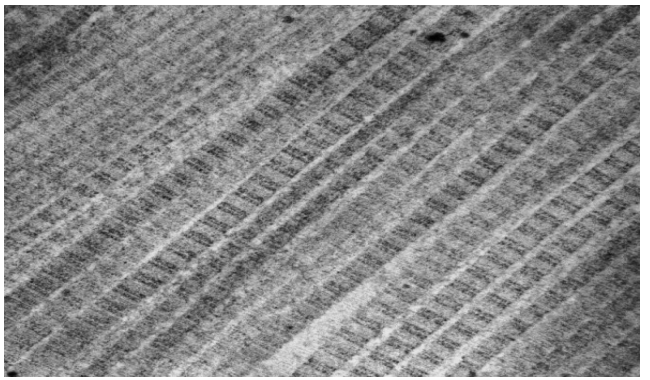

Connective tissue
cells
fibres
Amorphous substance
collagen
elastin
fibrillin
Proteoglycans
Adhesive glycoproteins

Collagen

Most abundant protein of our body

Role:

- *Framework*– tendons, articular capsules, basal lamina, skin, vascular wall etc.
- extrinsic pathway of hemostasis

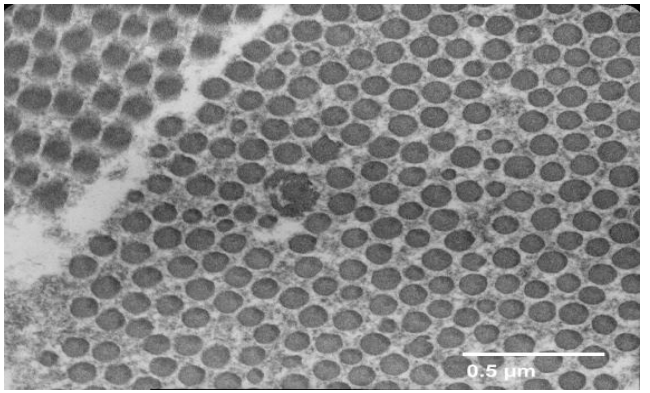


Structure: tropocollagen subunits bind to each other in a shifted construction

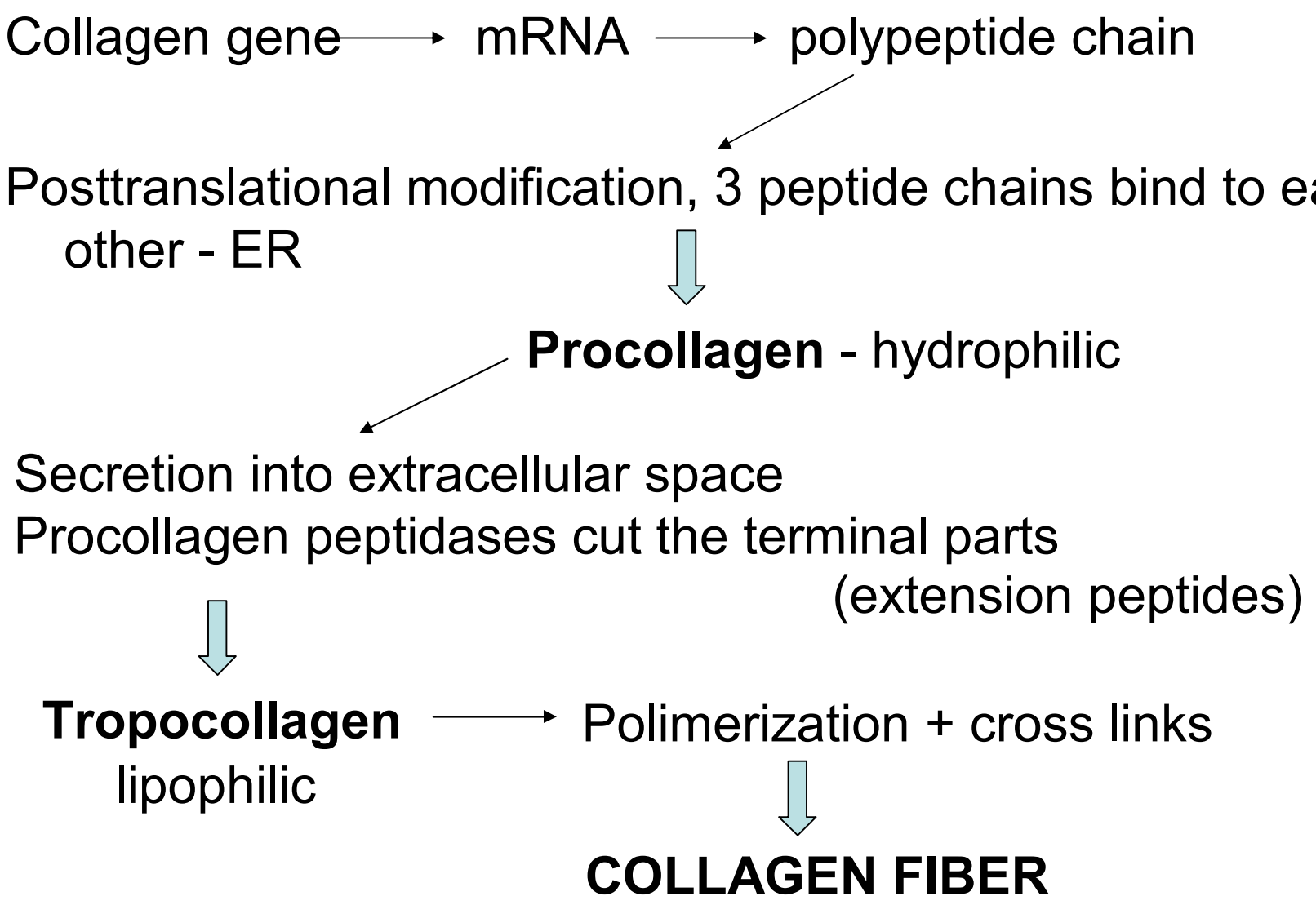
↓

Striped pattern

Forms tufts, fibrils



Synthesis of collagen



Characteristics of synthesis

- **Sequence:** repeated parts, approx. 30% of aminoacids is Gly, there's also much Pro

- **Posttranslational modification**
  1. Hydroxilation – on Lys & Pro, dioxygenase enzymes catalysate it, with vitamin C cofactor
  2. Glycosylation – glucose-galactose disaccharide units

- **CROSS-LINKING**

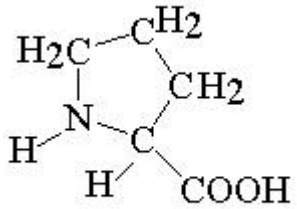
  Lys-aldehyde + Lys → lysinorleucyn (Schiff-base)

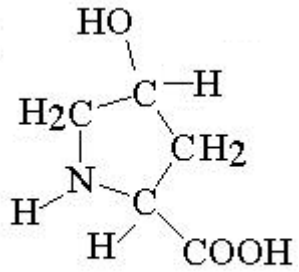
  → 2 lysinaldehyde → aldole crosslinks

  2 OH-Lys + Lys → hydroxi-pyridin crosslinks

Proline hydroxilase

(+ vitamin C)





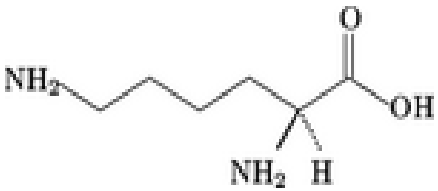
alpha-keto-glutarate

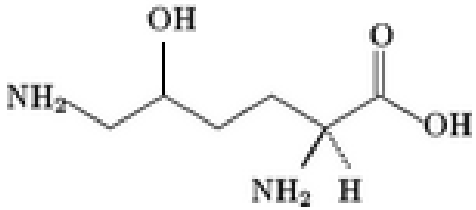
succinate

O_2 CO_2

Lysin hydroxilase

(+ vitamin C)

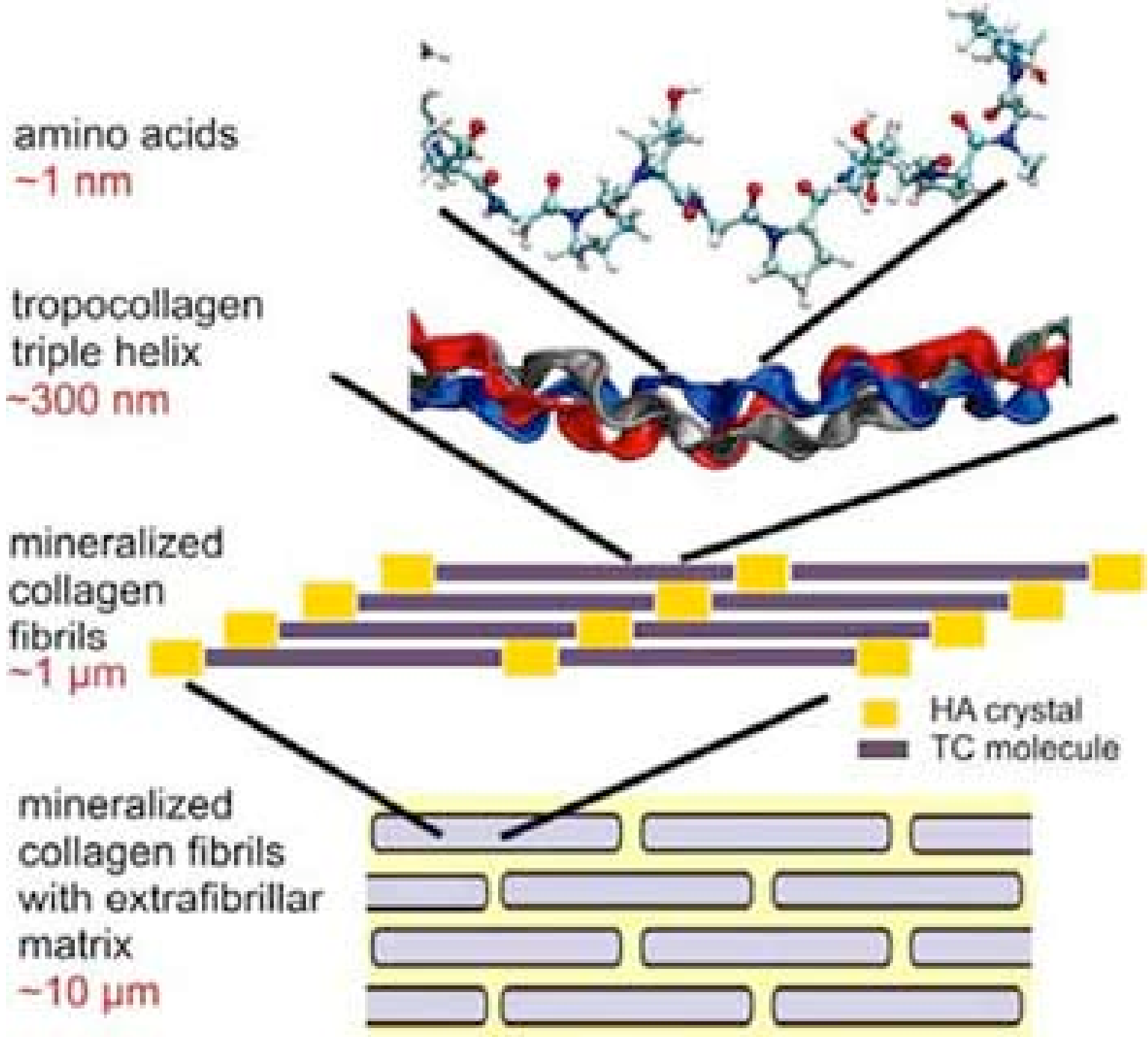




alpha-keto-glutarate

succinate

O_2 CO_2


amino acids
~1 nm
tropocollagen
triple helix
~300 nm
mineralized
collagen
fibrils
~1 µm
HA crystal
TC molecule
mineralized
collagen fibrils
with extrafibrillar
matrix
~10 µm

Collagen types

12 types of tropocollagen ⟶ 12 types of collagen

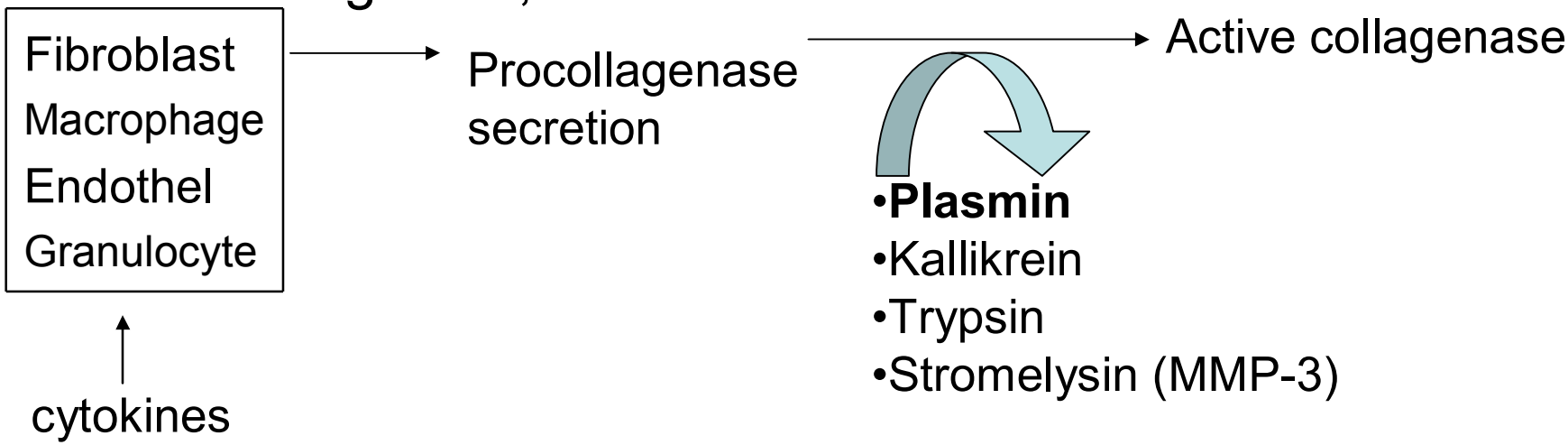
appearance	**Type (eg.)**	**occurence (eg.)**
Fibre forming	I	Most abundant – tendons, skin…
	II	cartilage, corpus vitreum
	III	
Reticulum forming	IV	Lamina basalis
Associated to other collagens	V	Associated to I
	XII	Associated to I, II

Degradation of collagen

- Stable molecules – degradation: tissue collagenase (MMP-1)
- Reassembly needed: wound healing, uterine cycle
- Pathologic degradation:

  Clostridium histolyticum

  Tumor growth, metastasis



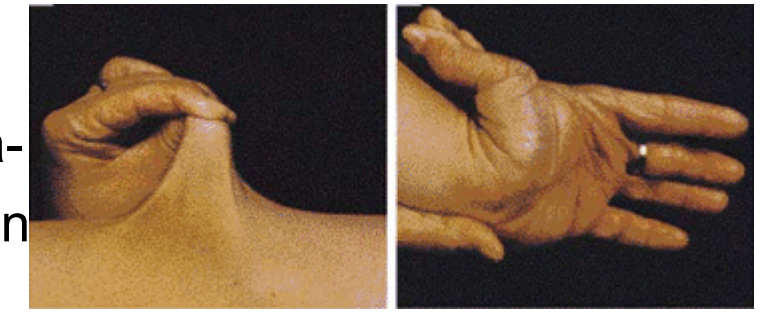
Collagen defects

Secondary

- **Vitamin C deficiency**– decreased hydroxilation ⇒ more vulnerable (gingiva bleeding when tooth brushing, poor woundhealing)

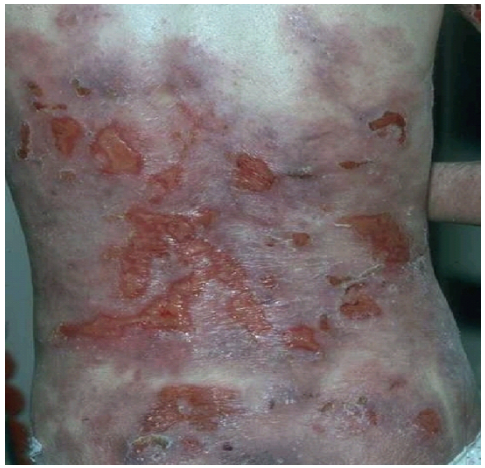
Primary

- **Ehlers-Danlos syndrome** – ⇓ procolla-genase activity, procollagen accumulation tensile skin, flexible joints



- **Osteogenesis imperfecta**

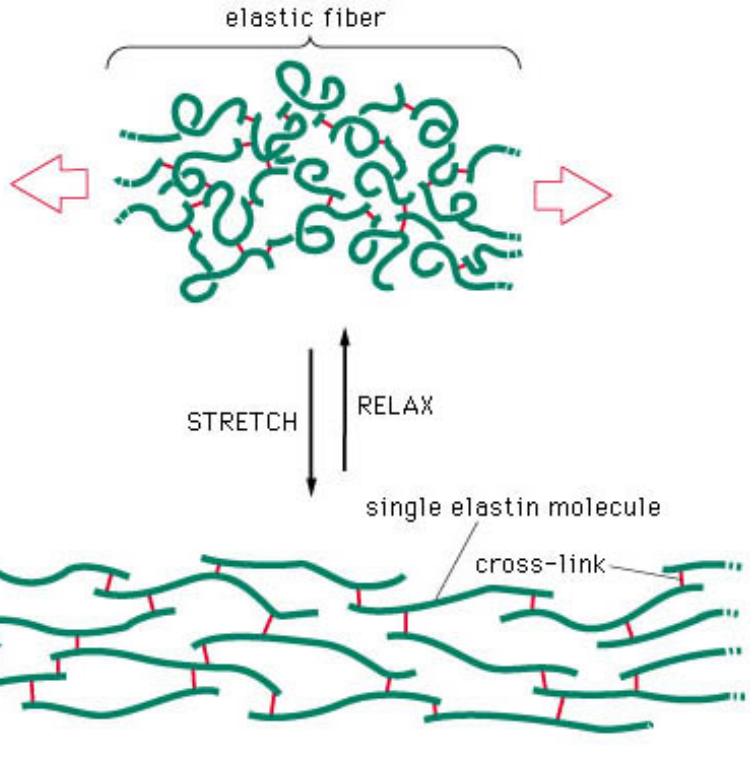
  Gly ⇒ Cys substitution →

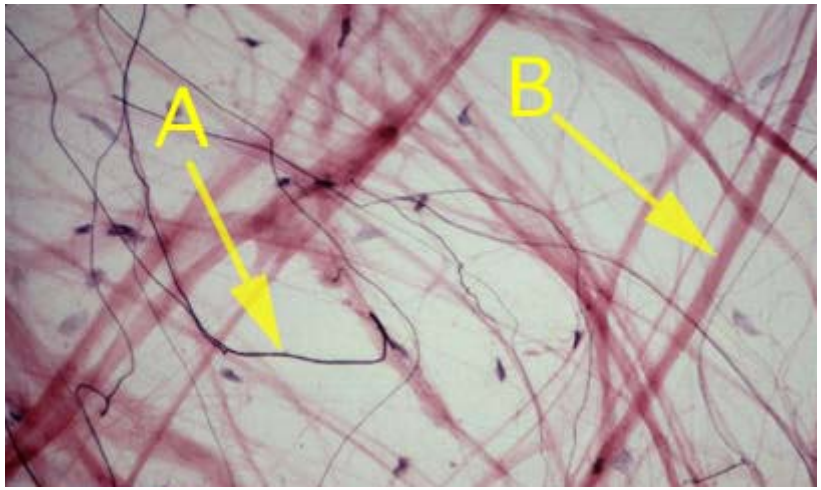


- **Epodermolysis bullosa**
- **Alport syndrome**
- **Chondrodysplasias**

Elastic fibres

- tensile, gives flexibility to tissues
- occurence: aorta, wall of arteries, lungs,.
- Not commono: skin, loose conn. tissues
- Cross-links stabilizing it



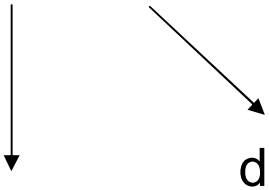


A – elastic B – collagen

Synthesis of elastin

- hydrophilic
- Val-Pro-Gly-Val sequences are common
- A lot of Gly, Ala
- Special helical parts
- Between them: Ala rich not helical parts

- lipophilic
- Contains cross-links



lysinorleucyn

desmosin

Elastin degradation - diseases

ELASTIN

Elastase

Pancreas
Leukocytes

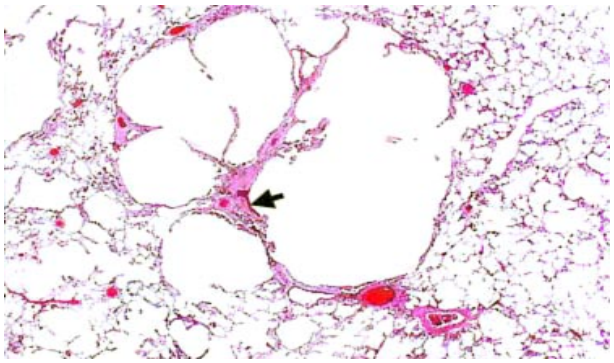
Alpha$_1$-antitripsin

When missing:
unlimited elastase activity

Enzyme defect

SMOKING

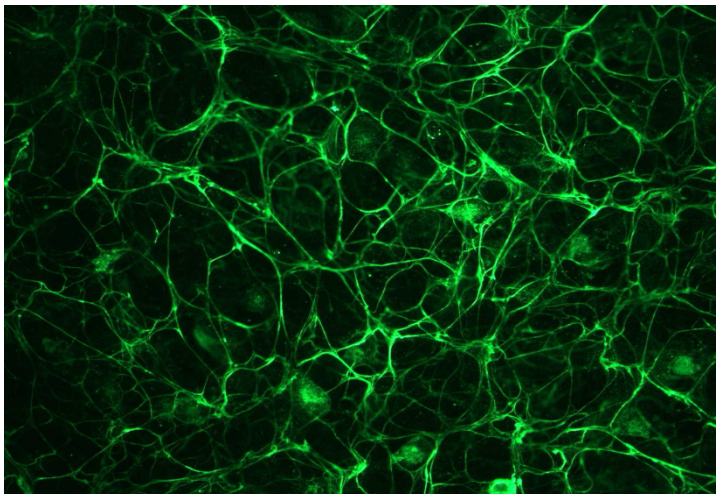
Emphysema of the lungs



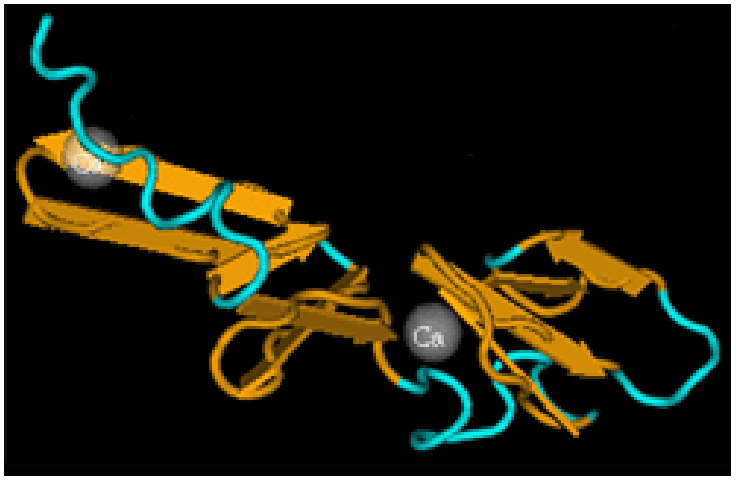
Fibrillin

- Thin fibrils bound to elastin,
- „framework” maintaining elastic fibres
- Synthetized by fibroblasts
- abundant:

  bones, tendons, vessel wall, lens-suspeding fibres, heart valves
- When missing: damage to these organs– **Marfan syndrome**



Fibrillin with immunhistochemistry

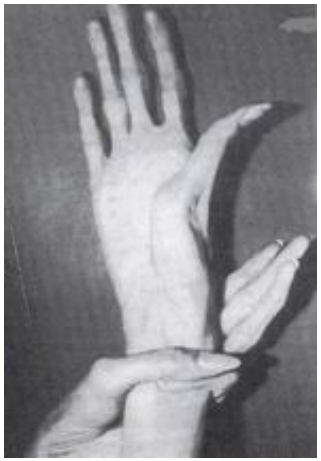


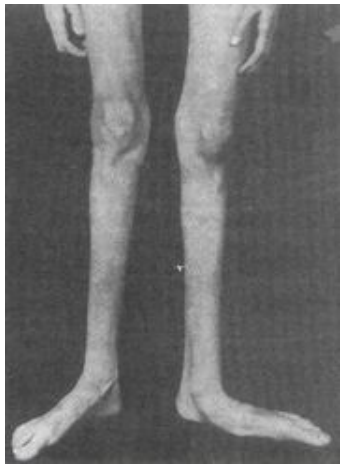
Fibrillin monomer

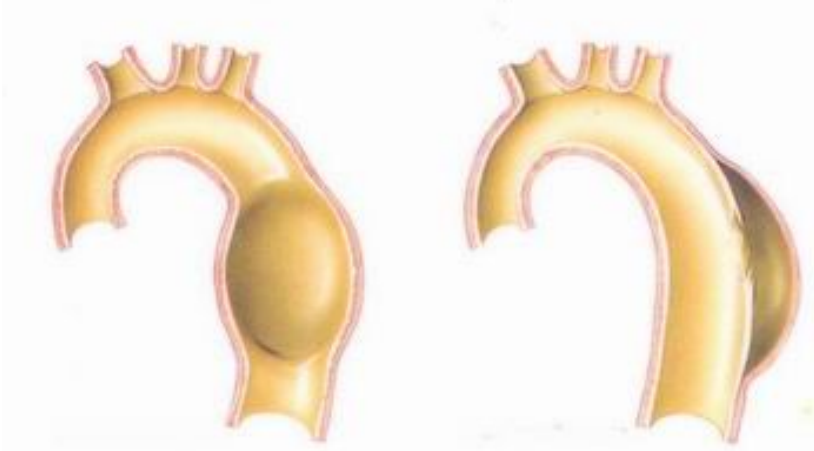
Marfan syndrome

Fibrillin gene defect

Symptoms: tall, thin, long limbs, fingers (arachnodactylia), common scoliosis, subluxation of the eye lens, aneurysm and dissection of the aorta, heart valve insufficiencies





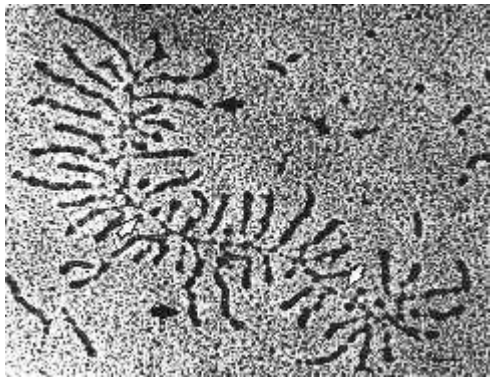


Proteoglycans

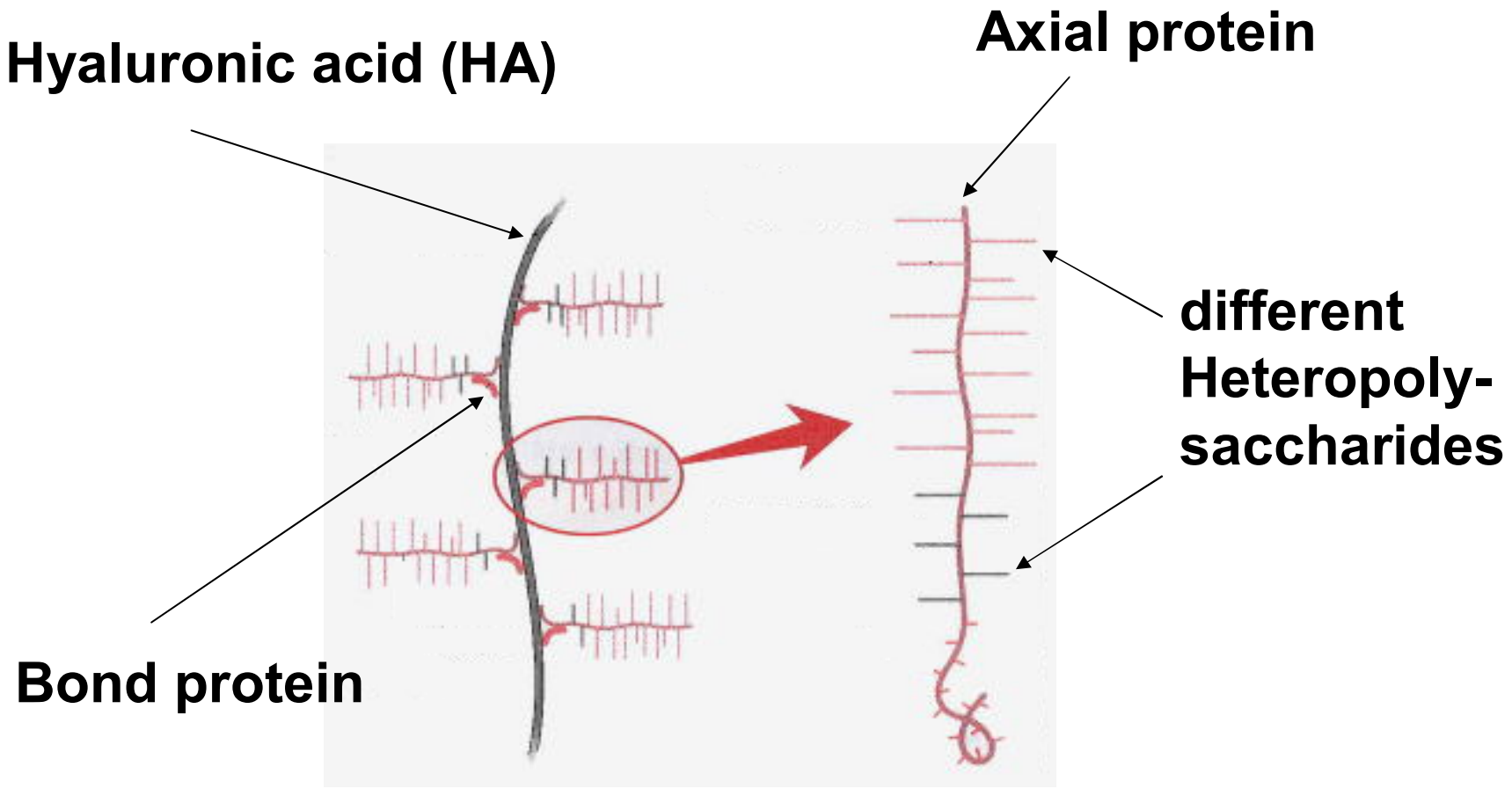
- Different amount but in all connective tissues

  Muc eg. Cartilage Less eg. tendon
- Seems homogenous by light microscopy
- Polyanions, binds much water, solidification (eg cartilagineous disc)
- Gel-like substance: diffusion, cell wandering
- Functional role

  eg. Heparine – hemostasis
- Compounds:
  - Polysaccharides: 95%
  - Proteins: 5%



Structure


Hyaluronic acid (HA)
Axial protein
different
Heteropoly-
saccharides
Bond protein

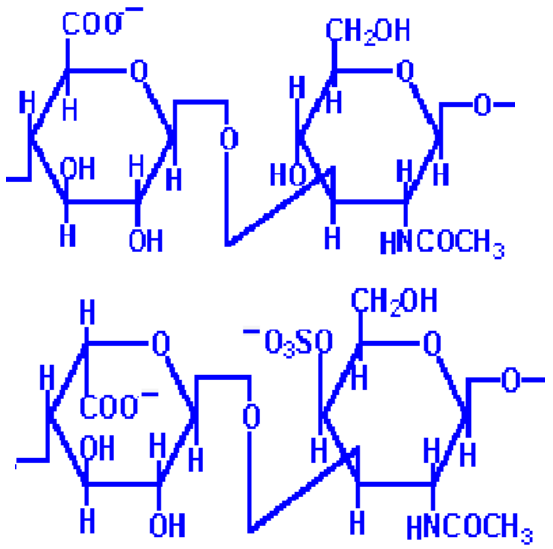
Polysaccharides

Name: mucopolysaccharides/glucose aminogycanes (GAG)

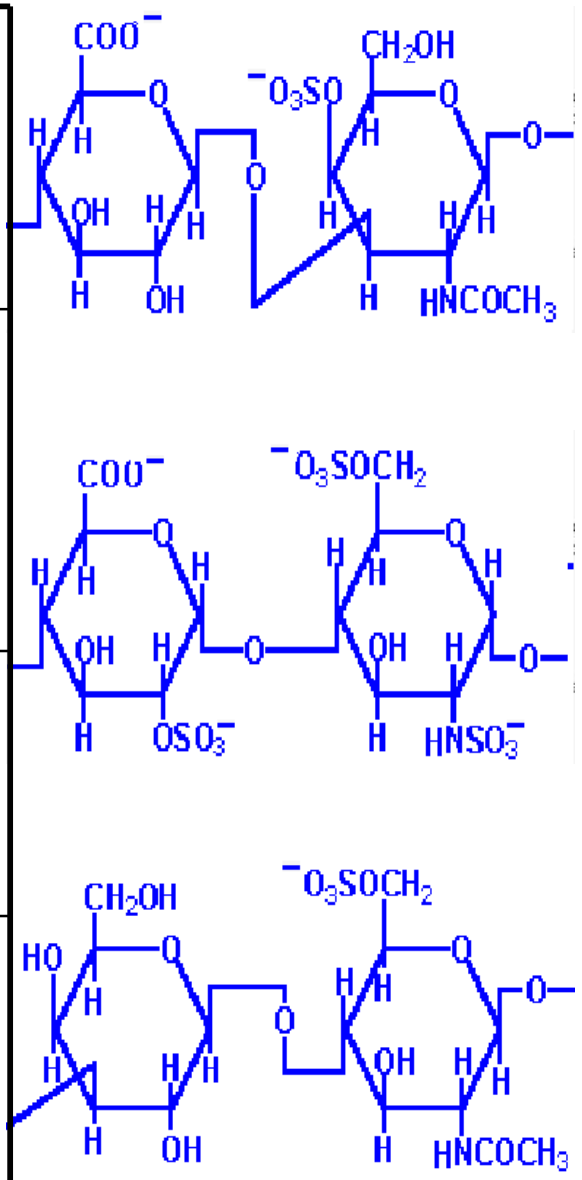
Disaccharide monomers

Sulfated on certain OH-groups except for HA

Type	Occurence eg.
Hyaluronic acid Iduronate N-Ac-glucoseamin	Corpus vitreum, synovia Embryonal ECM Helps proliferation
Dermatan-sulfate Iduronate N-Ac-galactose-amine	Skin, vessels



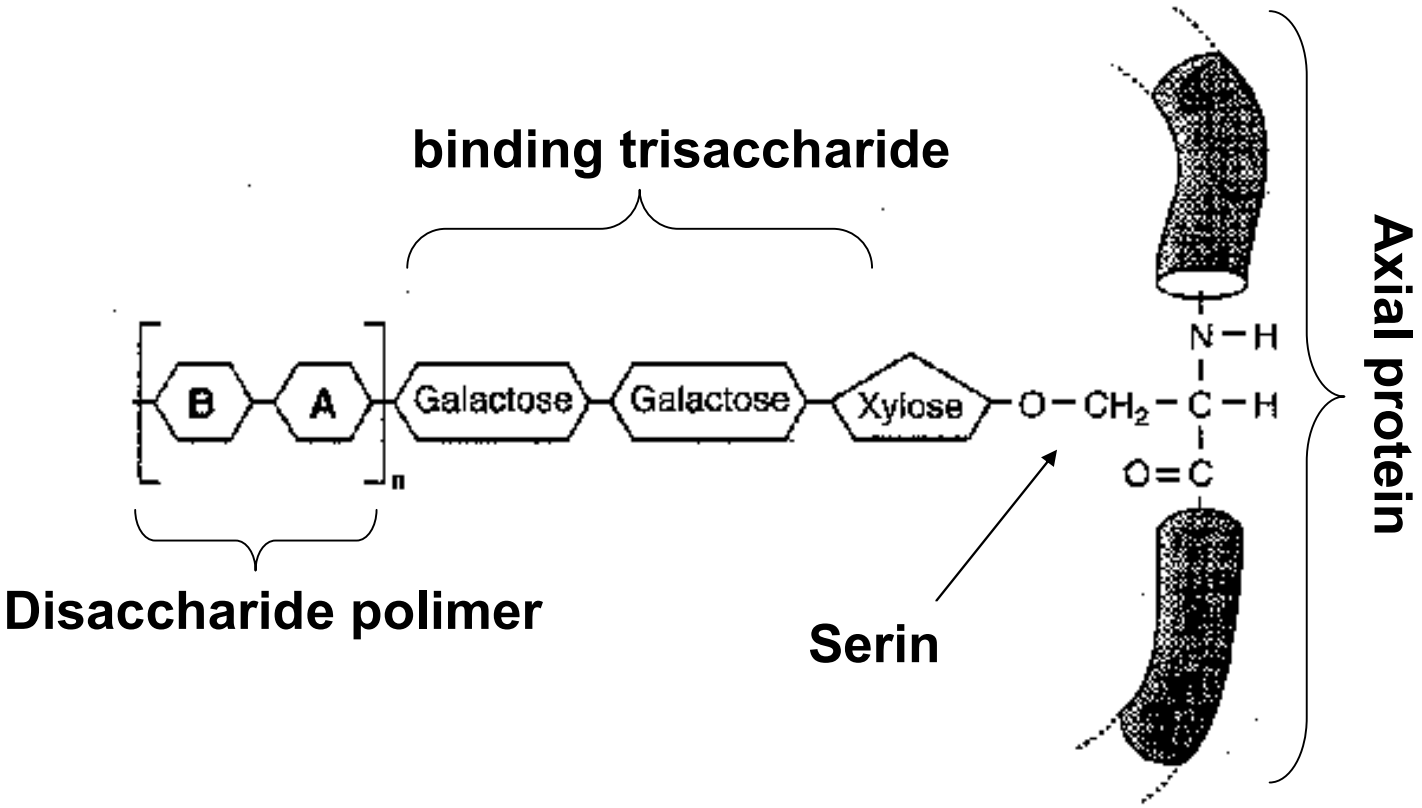
chondroitin-sulfate glucuronate N-Ac-galactose-amin	Cartilage, bone Most abundant proteglycan
Heparin glucuronate/iduronate N-sulfo-glucoseamin	Granules of mast cells endothel antithrombotic
Heparan-sulfate Same but less sulfated	basement membrane bound to inner surface of cells
Keratan-sulfate Galactose N-Ac-glucoseamin	Cornea, bone, cartilage



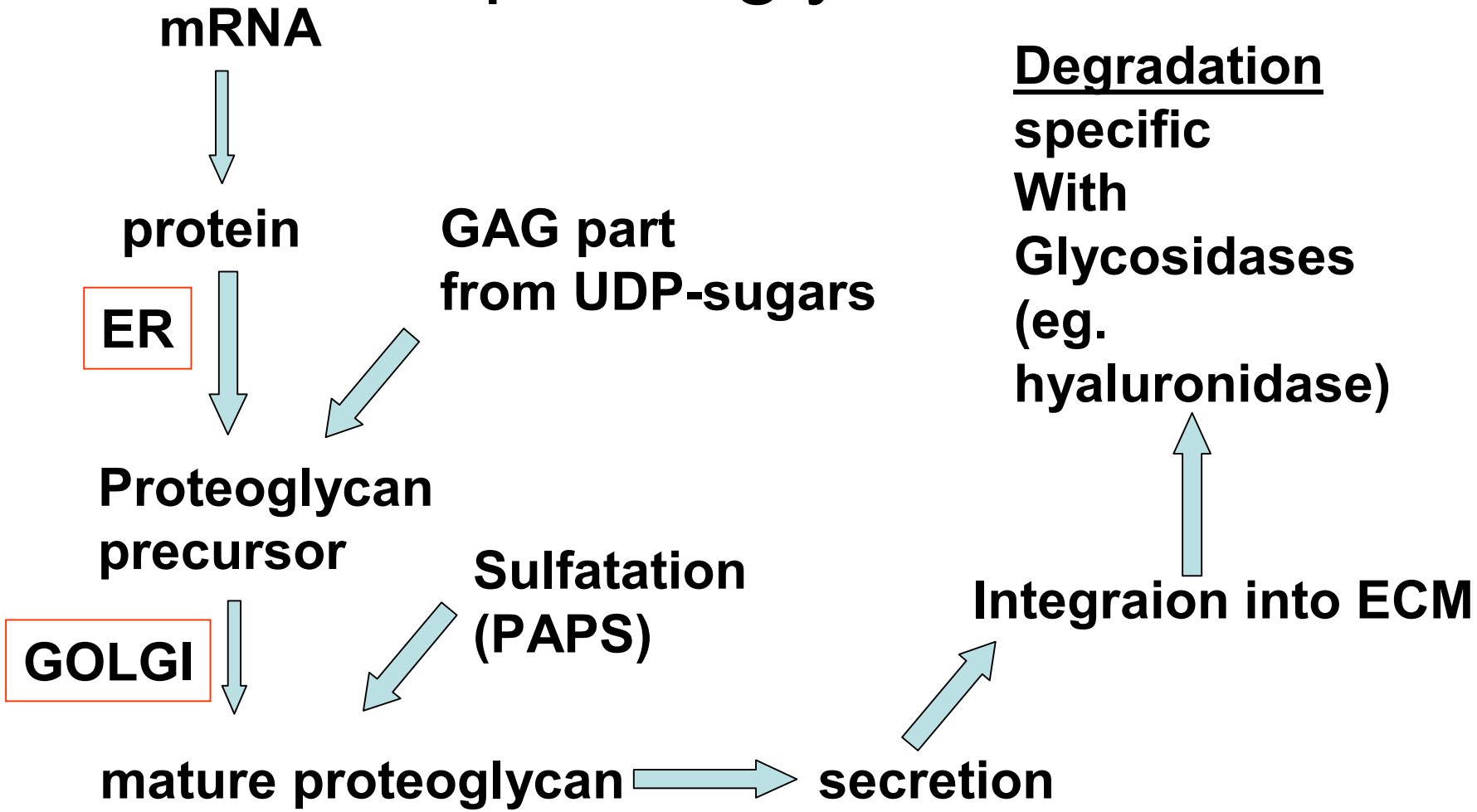
Protein-carbohydrate binding

CS, HS, DS, KS – covalent binding

HA – secondary binding



Synthesis and degradation of proteoglycans



Mucopolisaccharidoses

Defect of the degrading *glycosidases*

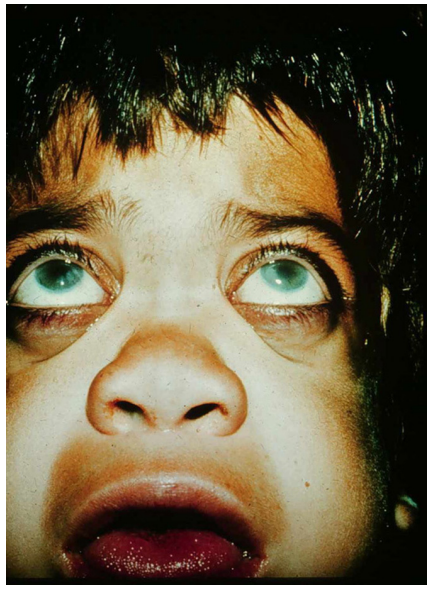
accumulation of substrates

- **Hurler's disease** – alpha-L-iduronidase defect
- **Hunter's disease** – iduronate-sulfate-sulfatase defect

Mental retardation,

Distorted face, body

Cause of death usually coronary occlusion

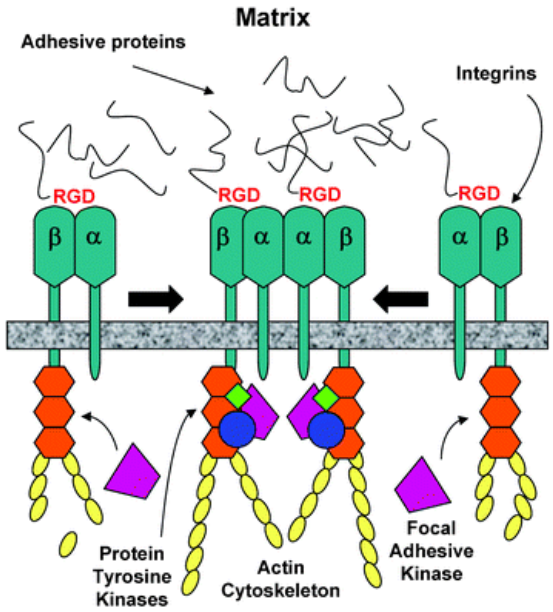


Proteoglycan types

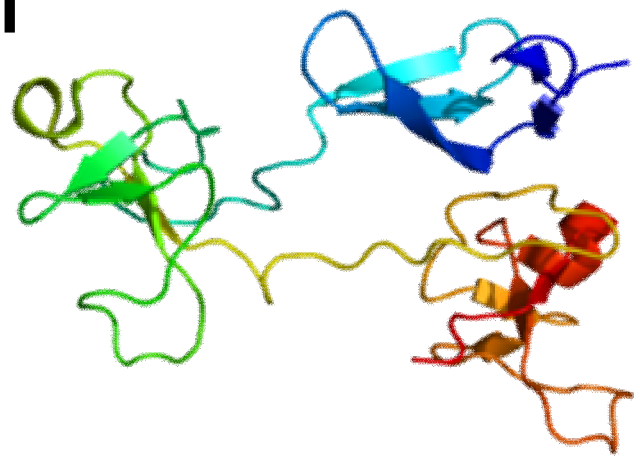
- huge, aggregating PGs
  - ✓ Aggrecan
  - ✓ Perlecan
- small, Leucin-rich PGs
  - ✓ Biglycan
  - ✓ Decorin
- Cell membrane PGs
  - ✓ Syndecan
  - ✓ Appican

Adhesive glycoproteins

- Contain often RGD sequence (Arg-Gly-Asp), which is recognized by specific receptors
- Groups:
- 1. „trace forming” eg.: fibronectin, tenascin
- 2. BasementMembrane components eg.: laminin, entaktin/nidogén
- 3. haemostasis eg.: von Willebrand factor
- 4. bone mineralisation eg.: osteopontin

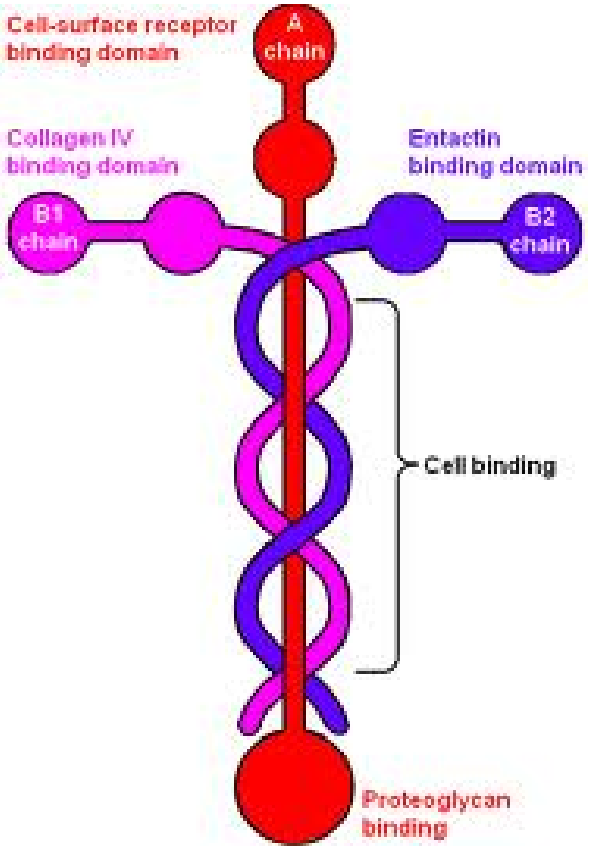


Fibronectin



- Multidomain structure
- Binds to fibrin and contains
  - Collagen binding site
  - Cell binding site
  - Binds to other fibronectin molecules - aggregates
- Functions:
  - Cell motion
  - Wound healing
  - Embryonic development
- Pathobiochemistry: fibrosis
  - too many fibroblasts activated, much collagen deposited at the damaged site

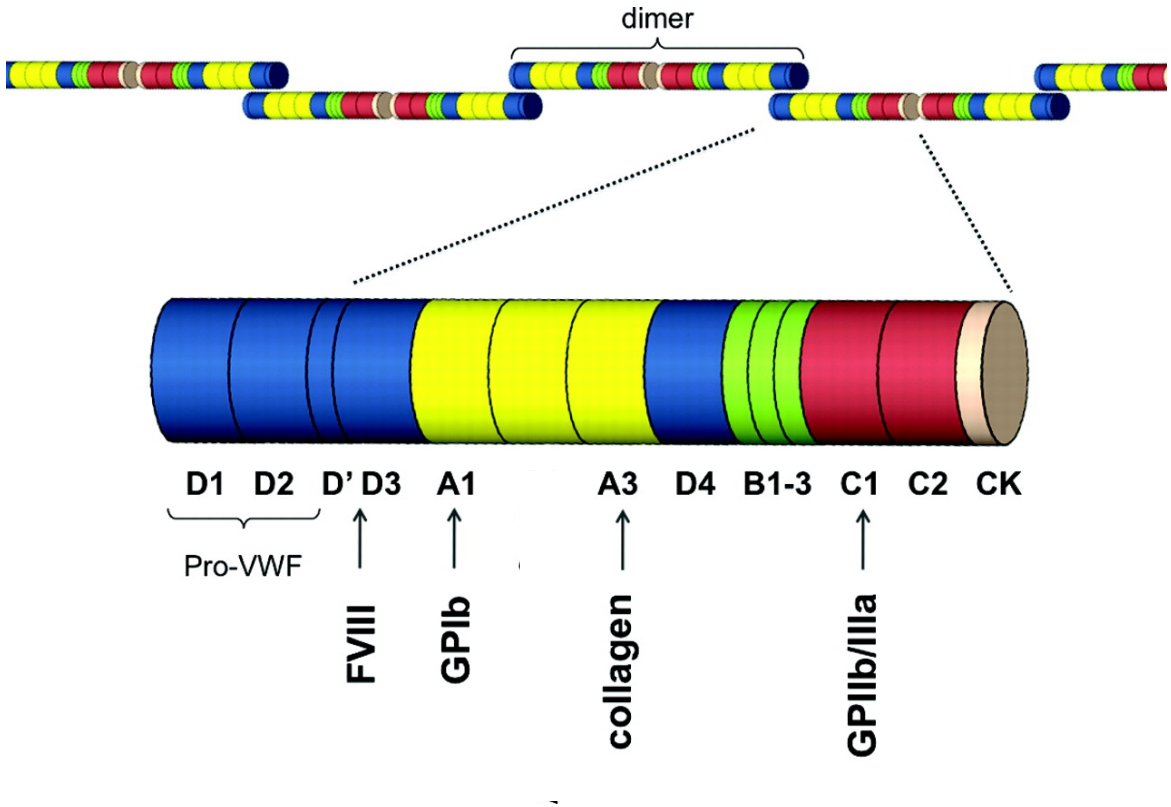
Laminin



- 3 subunits: α, β, γ
- Main component of BasementMembrane
- Several binding sites:
  - Several cell binding sites
  - Collagen binding site
  - Entactin/nidogen binding site
  - Laminin binding site (able to bind to each other at the end of the subunits)
- 10 laminin types, eg.:
  - I laminin: epithel, endothel, smooth muscle BasementMembrane
  - II laminin=merosin: nervous system, muscle, cardiac muscle; when missing: mental retardation, muscular dystrophy

von Willebrand factor (vWf)

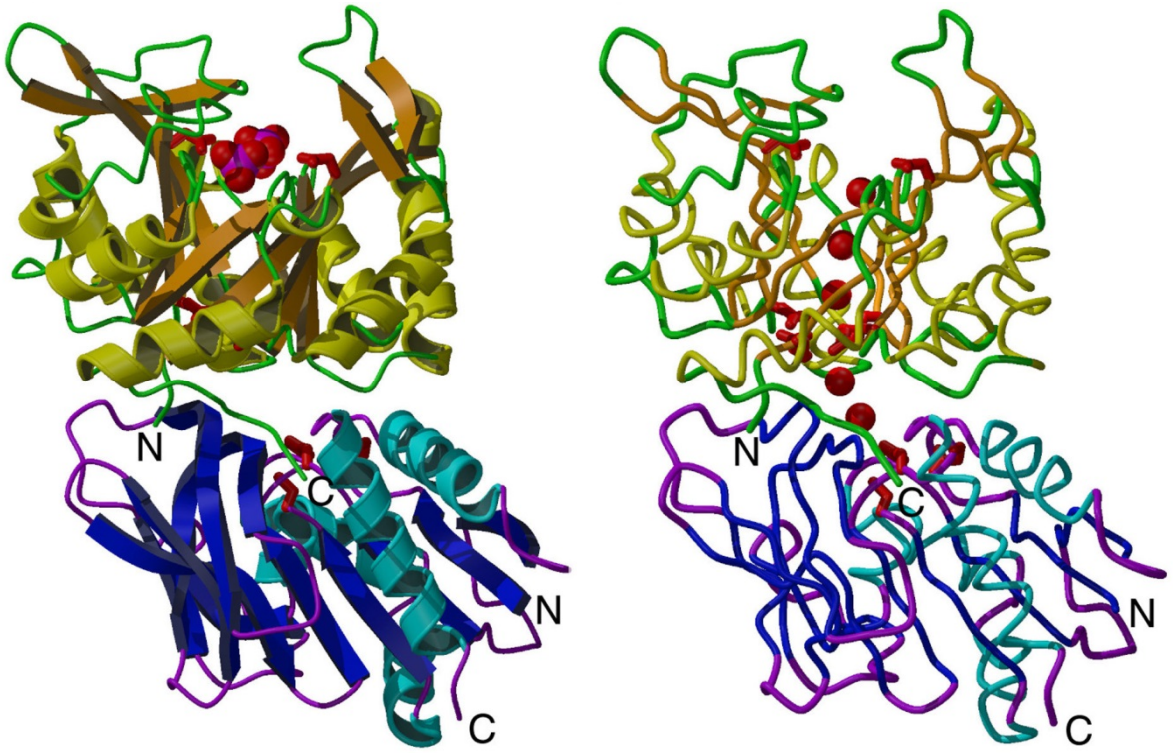
- Hugest known soluble protein, dimer



- plasm glycoprotein
- synthesis:
  limited proteolysis
- spec. receptor on
  thrombocyte for vWf
- Important for stable thrombocyte adhesion

Osteopontin

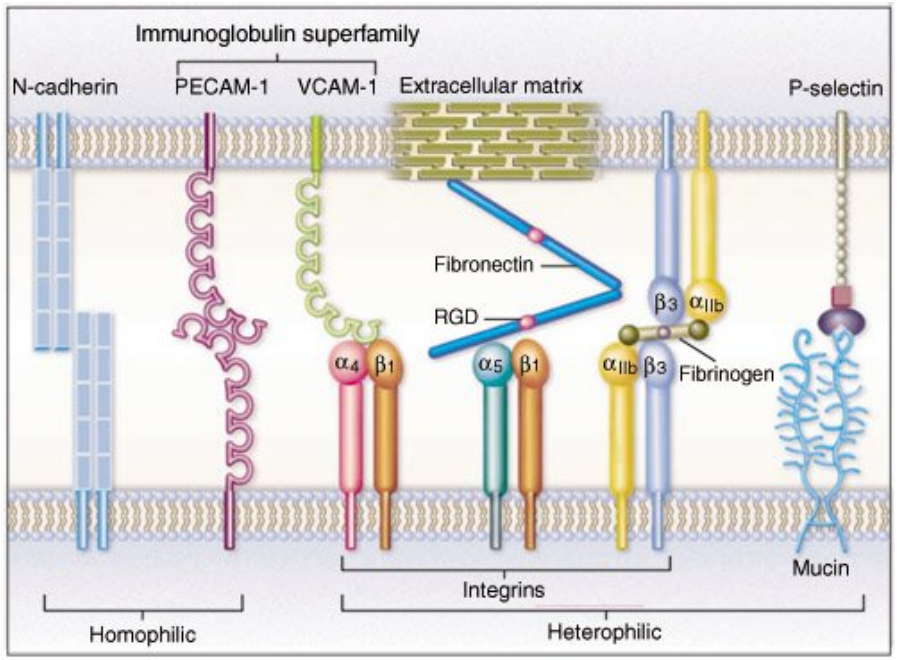
- Role: bone remodelling and degradation
- Cell binding (RGD)- synthetized by osteoclasts+early osteoblasts
- Heparin binding
- Hydroxiapatit binding
- Calcium binding



Adhesion receptors

- connection+signal recognition in the cell membrane
- **Groups:**
- Integrins → cell - extracell. matrix (ECM) adhesion
- Selectins
- Ig (immunoglobulin) superfamily
- Cadherins (bind to Ca ion)

} Cell-cell adhesion



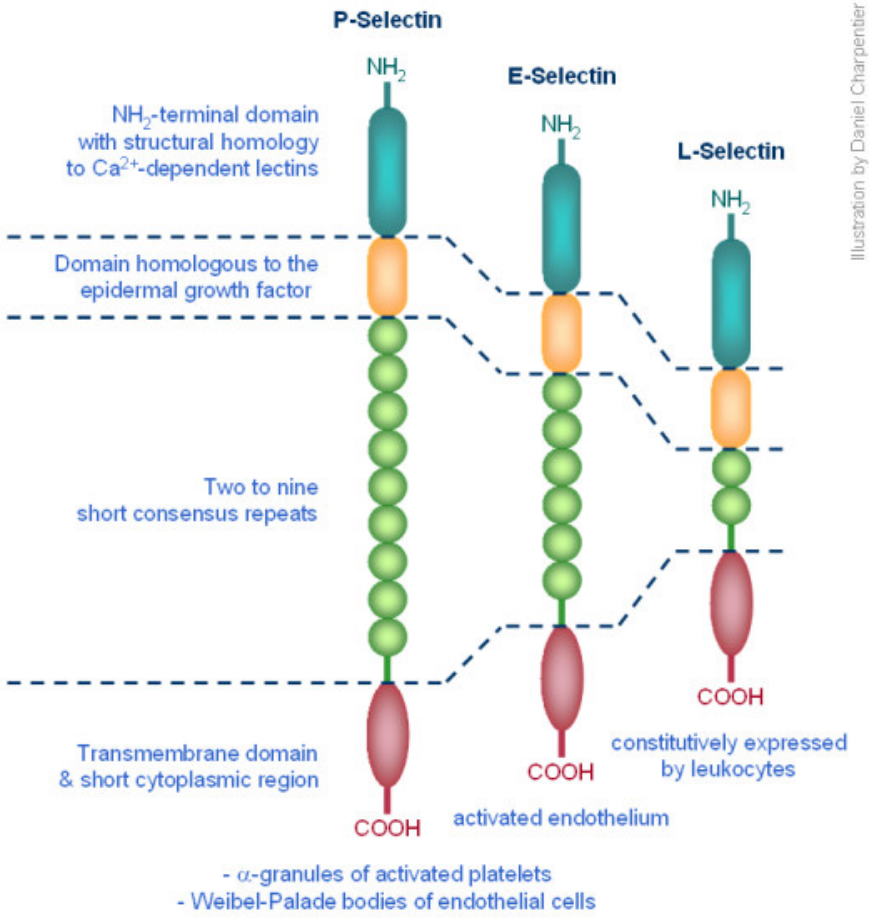
Integrins

- 2-subunit receptor:
  - α-subunit: Ca binding sites
  - β -subunit: ligand binding sites –recognizing RGD sequence

- Types: 14 different α-subunits, 8 different β-subunits
- β_1 – many cell types, commonly bound to ECM components
- β_2 – only white blood cells (WBC)
  - EXCEPTION because cell-cell adhesion;
    WBC-endothel: chemotaxis, extravasation
  - β_3 – thrombocytes, eg. in fibrinogen receptor
- β_4 – binds laminin
  - Formation of HEMIDESMOSOMES
    (epithel-BasementMembrane connection)

Selectins

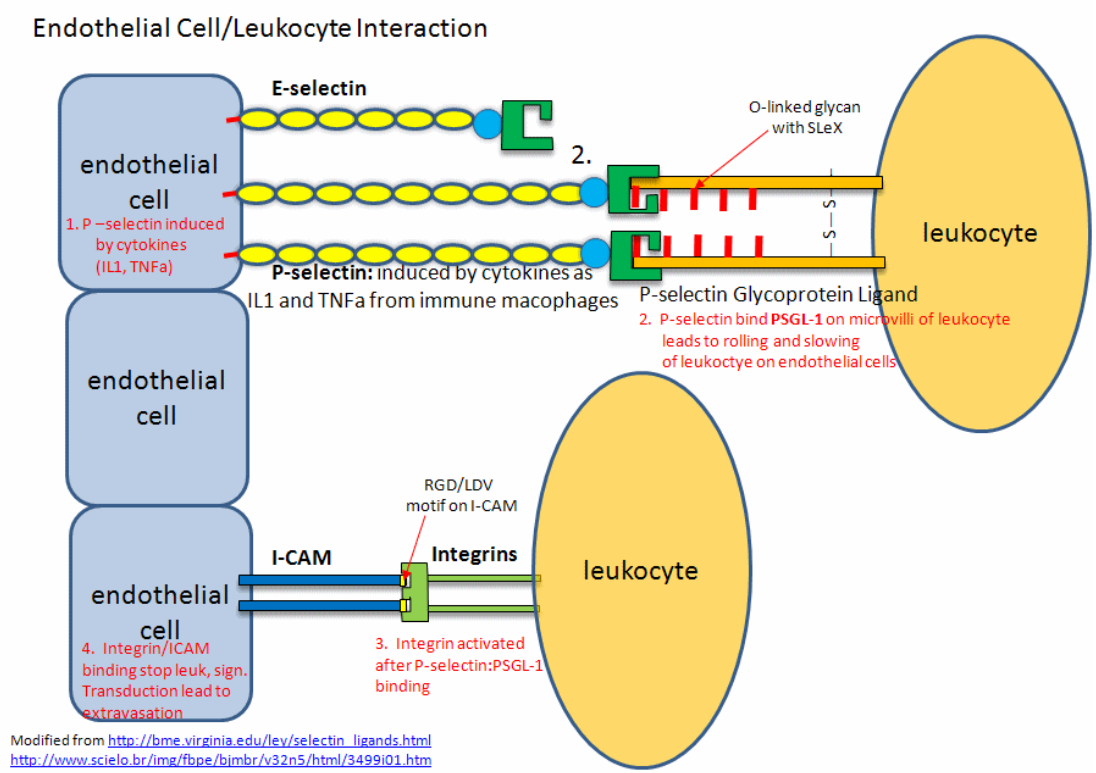
- Heterophil:
  different rec. and diff. ligand
- Ca-dependent
- Lectin domain:
  sugar/oligosaccharide recognition



- Types:
  - L : leukocytes (constitutive)
  - P : endothel cells, thrombocytes (not constitutive, only if endothel activated)
  - E : endothel cells (constitutive)

Ig - CAM

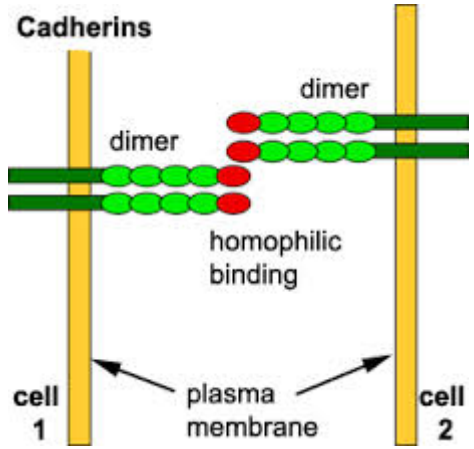
- Homo- és heterophil, Ca-independent
- Types:
  - ICAM-1, 2 (intercell. adh. molec.): heterophil bonds, binds to β_2 integrins
  - NCAM (neural cell adh. molec.): homophil bonds
- Function: tissue remodelling (embryonic development, regeneration)



Cadherins

- homophil, Ca-dependent
- 3-4 Ca binding domain
  - If there's no Ca – conformation change – degradation
- Key role in embryogenesis
- adults: development of normal cell-cell interactions

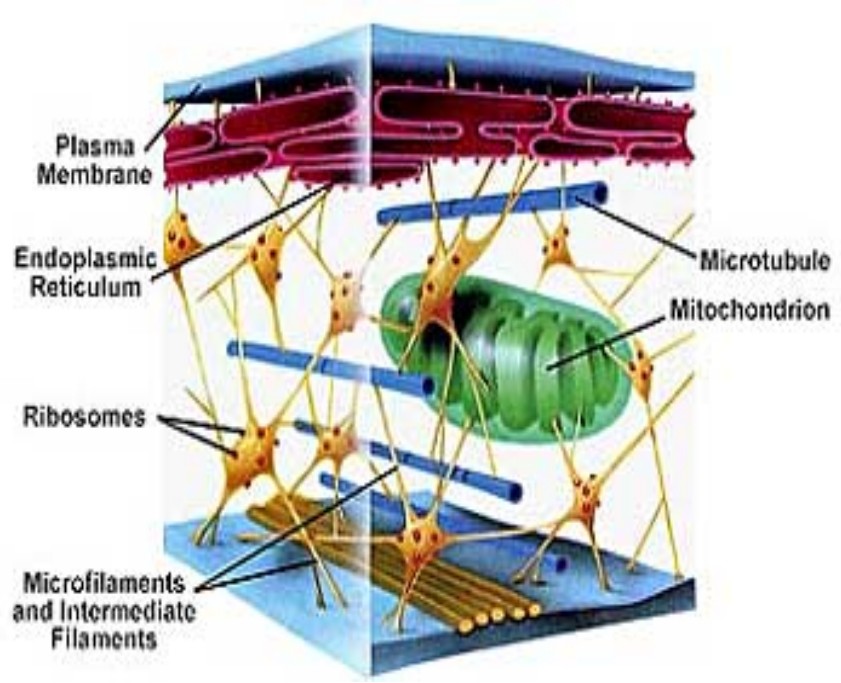
- Spec. desmosomal cadherins
  - DESMOSOME:
    stable composition of epithel
  - cadherins eg. desmoglein, desmocollin
  - IC binding to intermediate filaments



Cytosceleton

Intracellular filamentum system

- Cell shape
- Tract for motion
- <u>3 types :</u>
  1. Microfilaments
  2. Intermediate filaments
  3. Microtubules

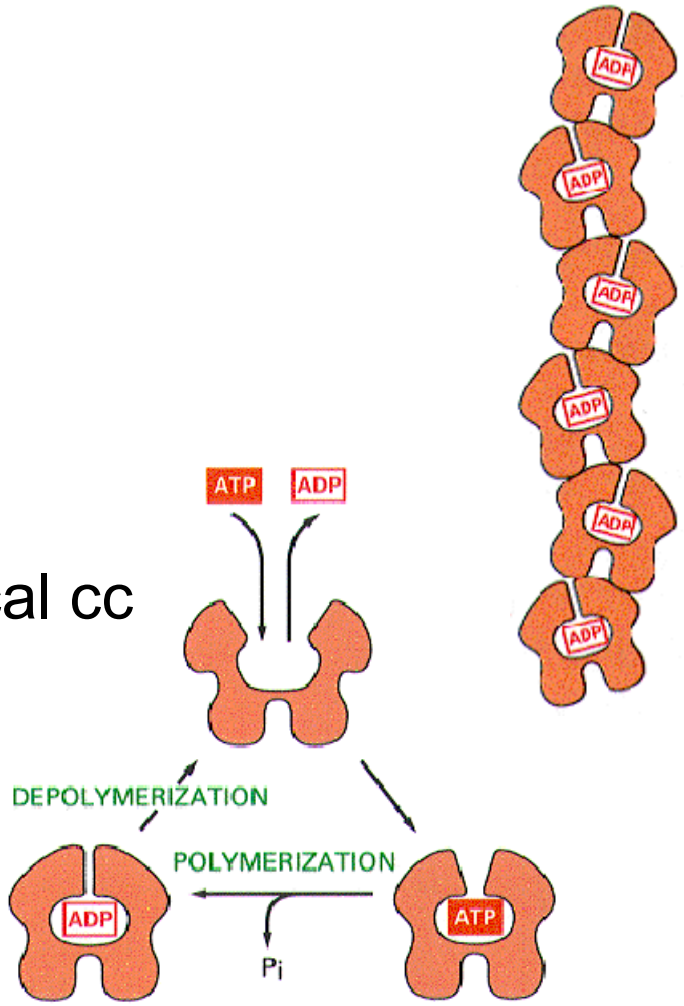


Microfilaments

- Basic in each cell
- Width: 7nm
- Monomer: globular actin
- Polimerization into F-actin

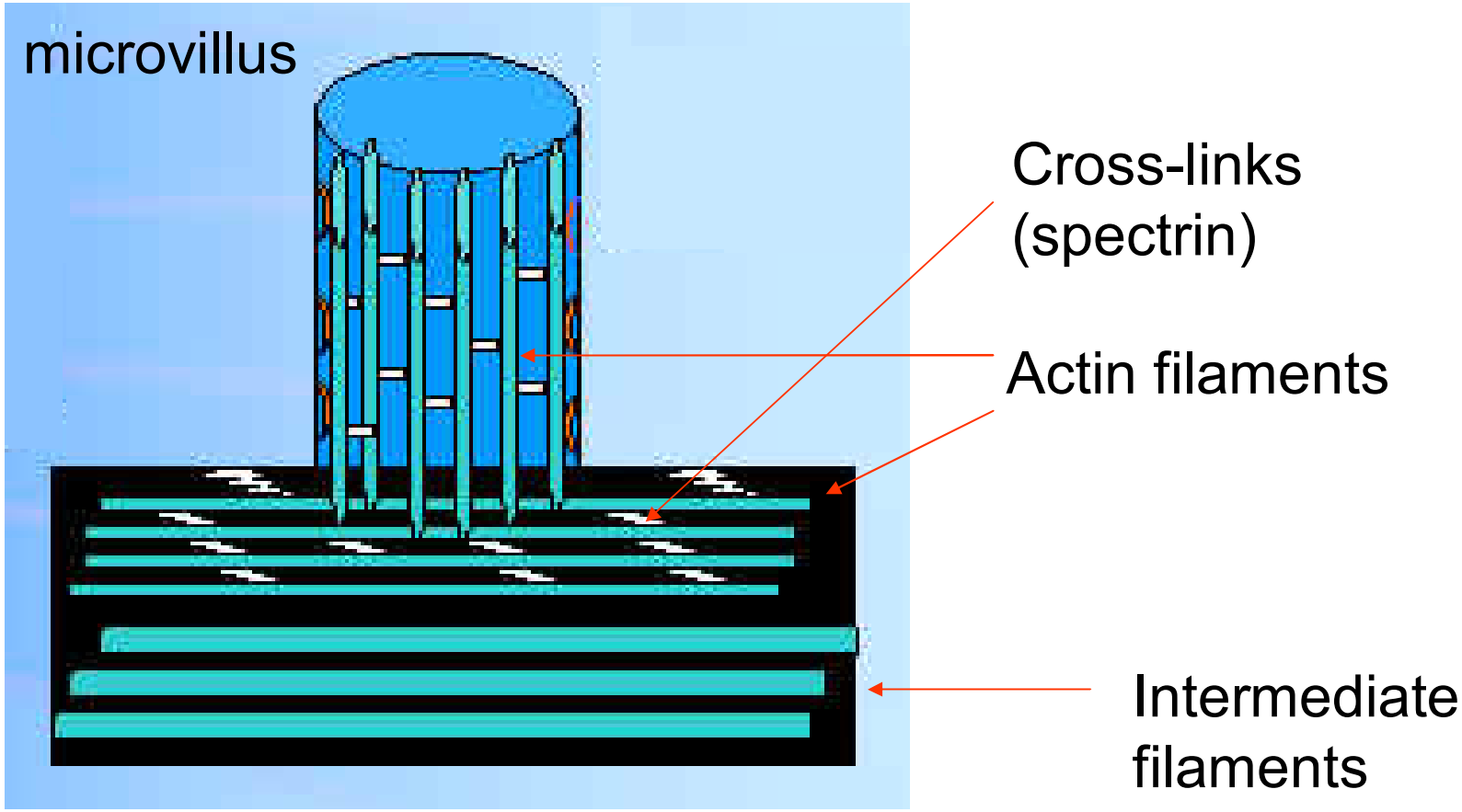
  ATP dependent, polarized
- Fast remodelling
- Polimerization starts at critical cc

but actin binding proteins can withhold it



Task of actin I

- **framework**



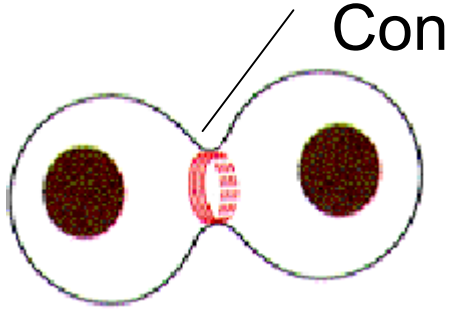
Task of actin II.

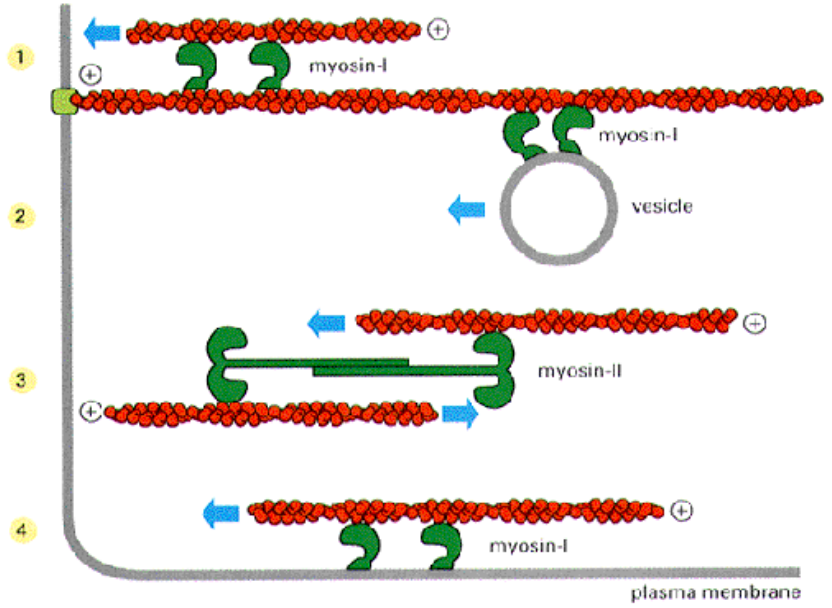
- **Tract for motion**

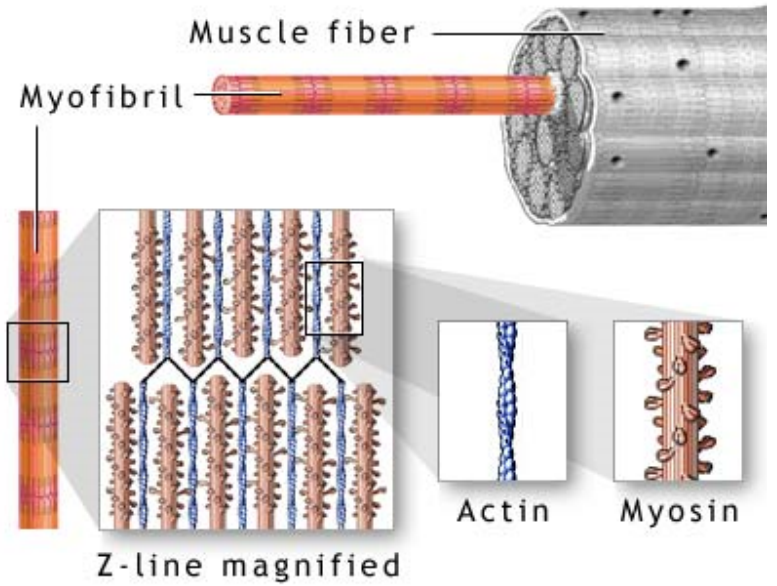
The mechanoenzyme myosin

myosin I – membrane-cytosceleton interaktion (vesicle transport)

myosin II – muscle, cytokinesis

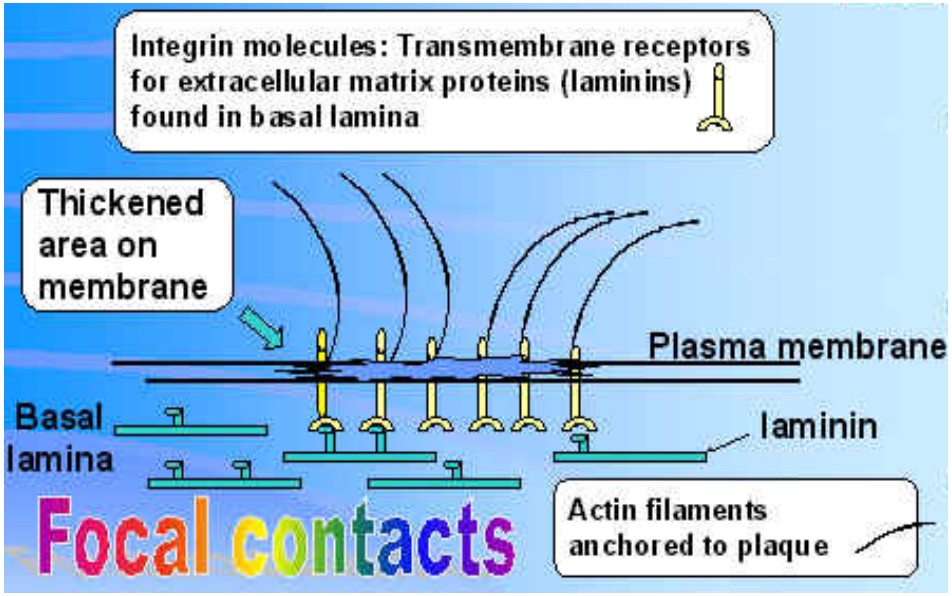


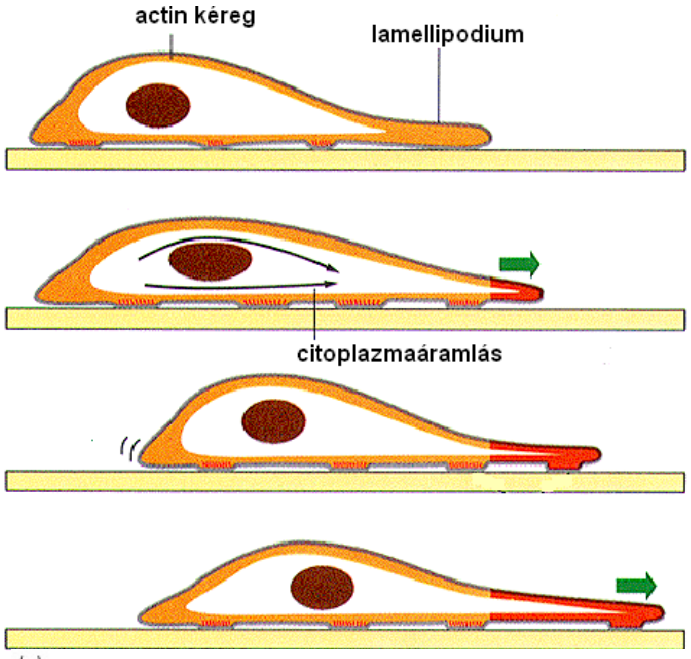


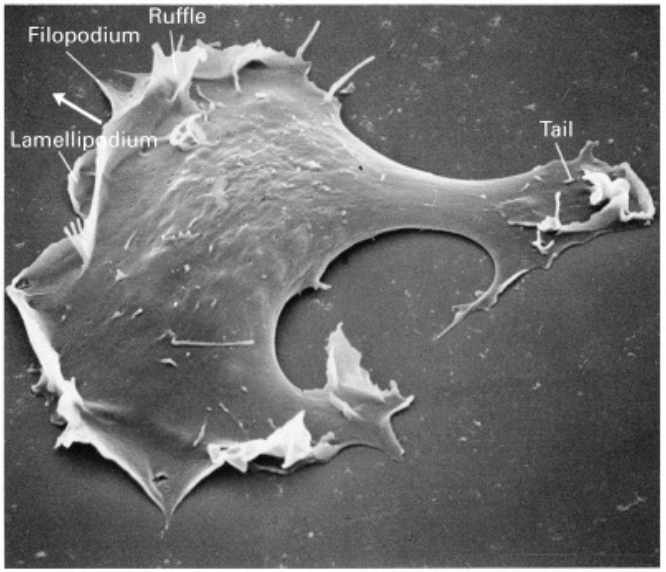


Task of actin III

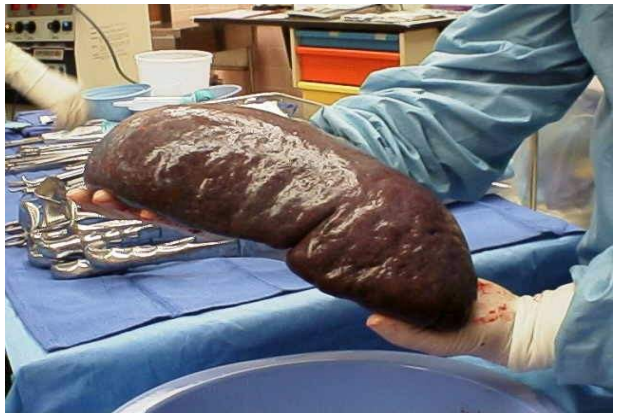
- Polimerization in response to extracellular effects – focal adhesive plaques: binding to extracellular elements
- Plasma membrane cambers in the direction of polimerisation– phagocytosis, chemotaxis







Pathobiochemistry of microfilaments



- **hereditary spherocytosis**

  Spectrin defect ⟶ unstable cytosceleton, spherical RBCs, degraded by the spleen
- **Duchenne's disease**

  (dystrophia musculorum progressiva)

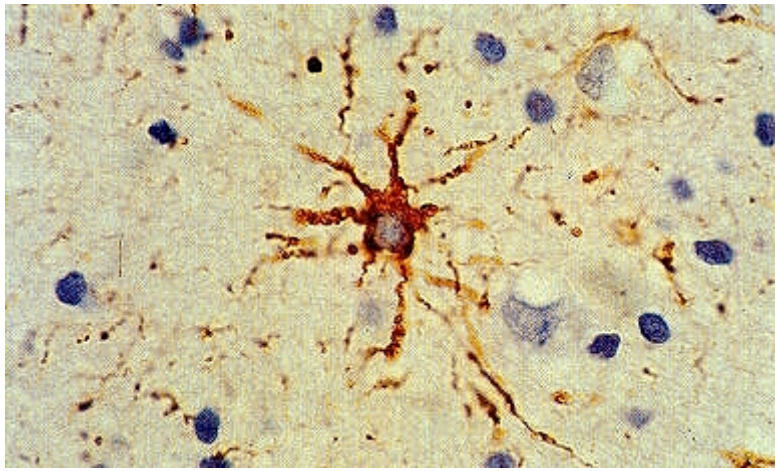
  dystrophin defect – vulnerable to mechanic effects
  cytosceleton ⟶ fibre damage
- Role of F-actin in certain bacterial infections

  (Listeria – actin)

Intermediate filaments

- Width 10 nm
- Hardening of cells
- Stabilizing
- No polarization
- Much in those cells which undergo strong mechanic effects
- Diagnostic importance:

  determination of origin of anaplastic tumors



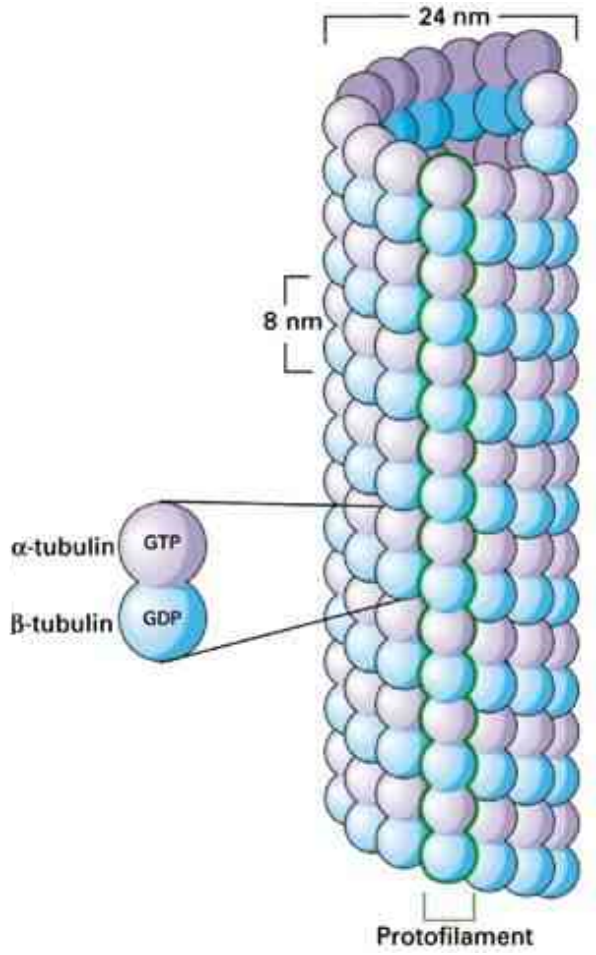
GFAP staining

Types of intermediate filaments

Nuclear	Lamin	inner sruface of nuclear membrane
Epithelial	Keratin I and II (acidic and basic)	Epithel and adnexa (hair, nail, etc)
Vimentin-like	Vimentin	certain mesenchymal cells
	Desmin	muscle
	GFAP	Glial cells
	Periferin	certain neurons
Axonal	Neurofila-ments	Neurons

Microtubules I

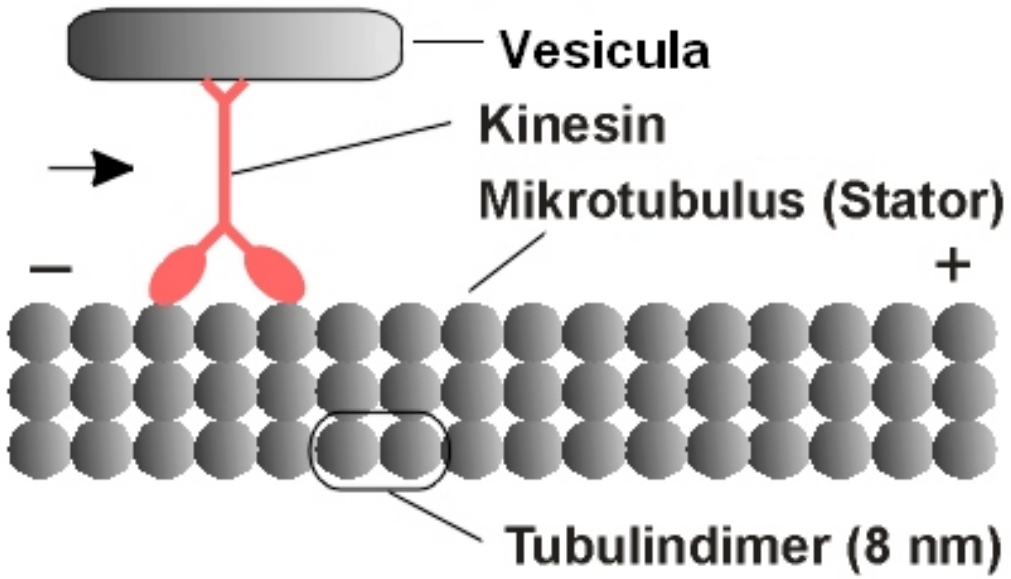
- Width: 24 nm
- Tract for motion
- Polimerized from tubulin dimers
- Fast remodelling
- Polarizedt (+ and – end)
- Building up in positive direction
- Degrading in negative direction



Microtubules II

- Polimerization: starts from centriolum, basal body(MTOC)

  negative end here



- Mechanoenzymes:

  Kinesin - → +

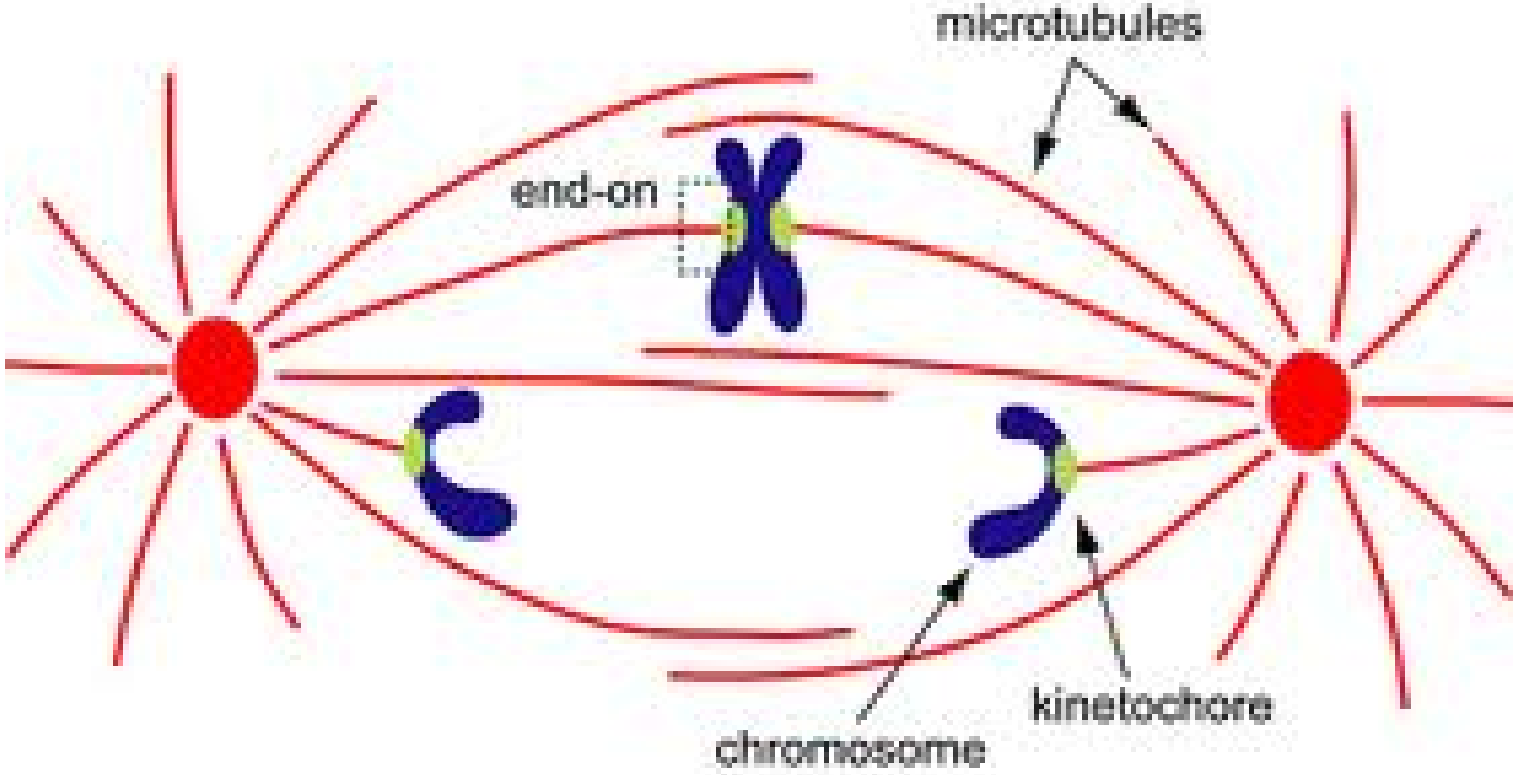
  Dinein + → -

- Tasks:

  1. proliferation – chromosome wandering
  2. neurons – fast axonal transport
  3. kinocilia, flagella
  4. other cells – transport of IC organelles, vesicles

Functions of microtubules

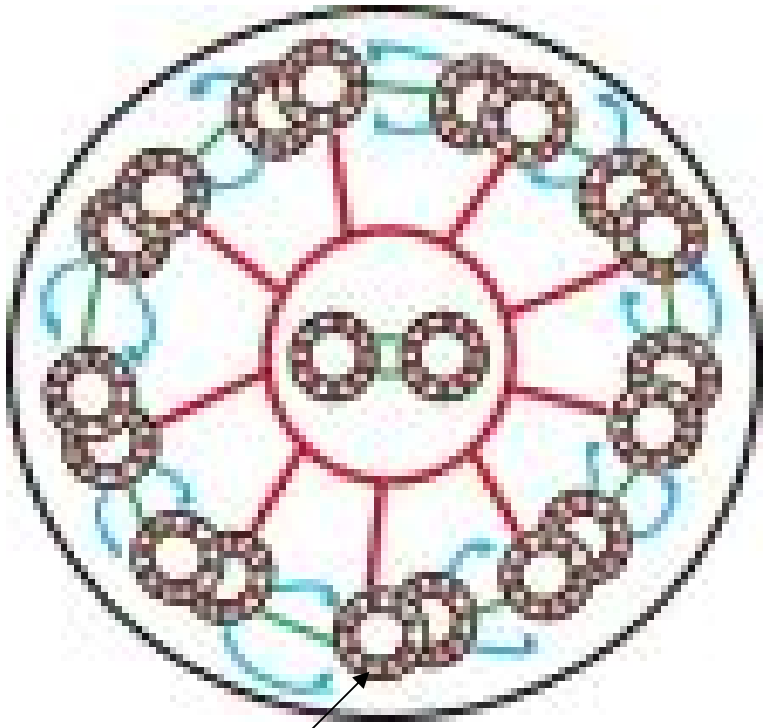
Cell proliferation



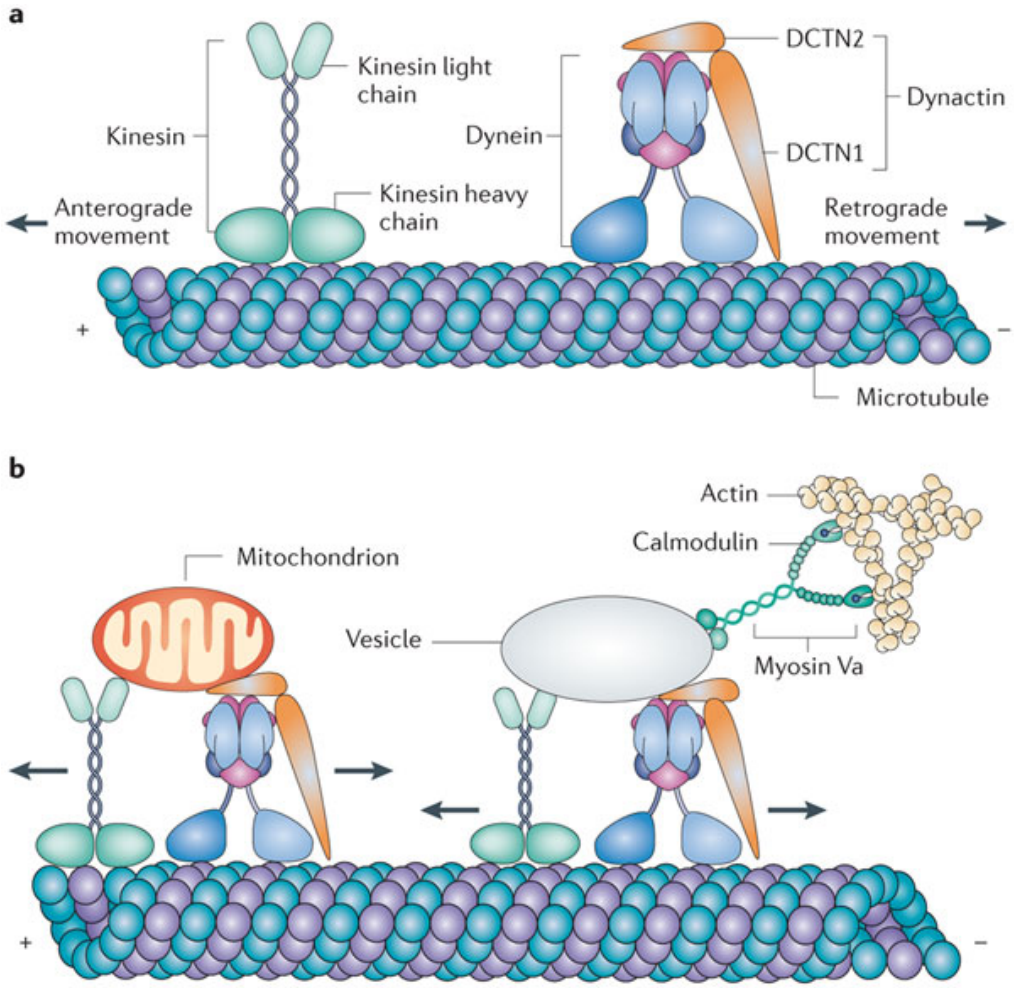
No cell proliferation without proper microtubule function
MT toxins – cytostatic drugs
pl. colchicin, taxol, Vinca alcaloids

Functions of microtubules

Cross section of cilium



Dinein arms



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