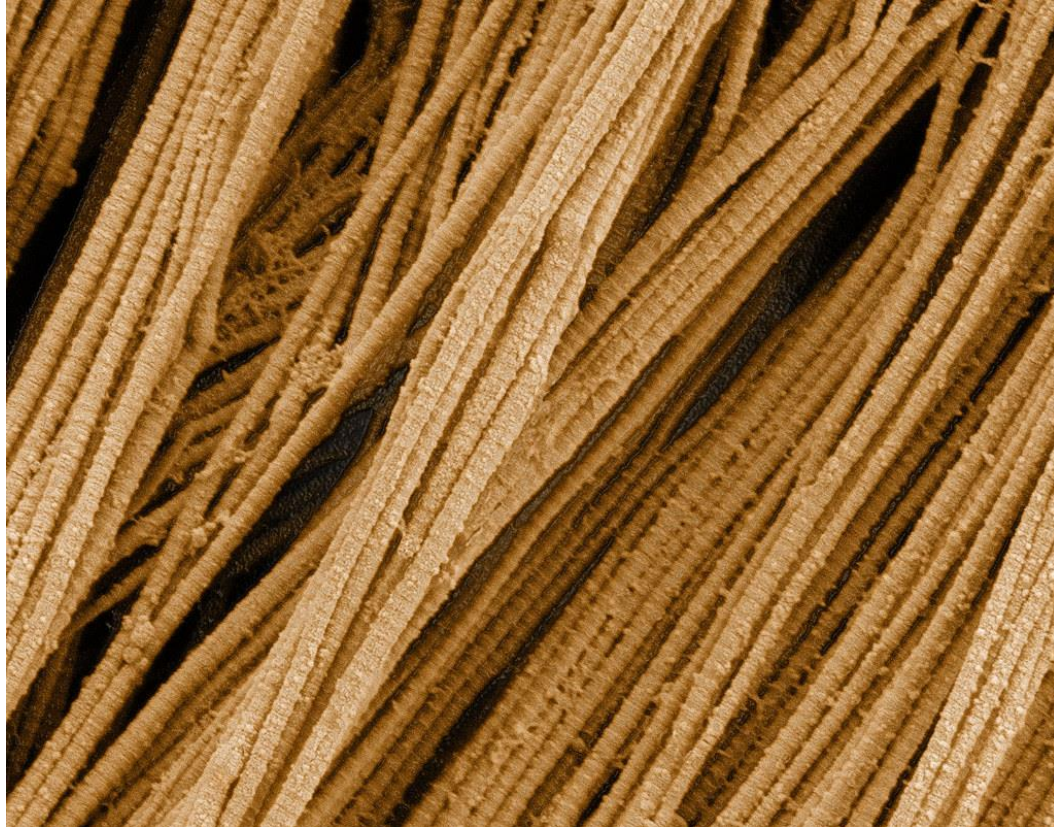
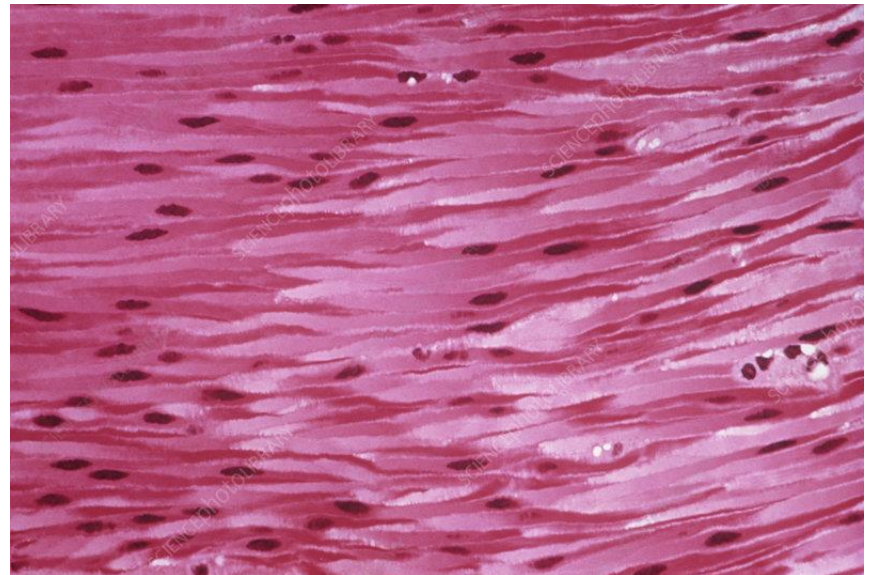
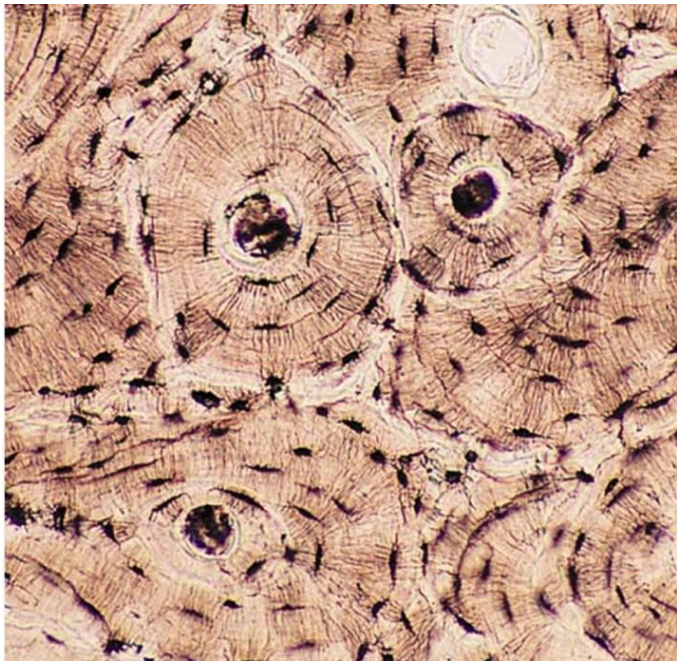
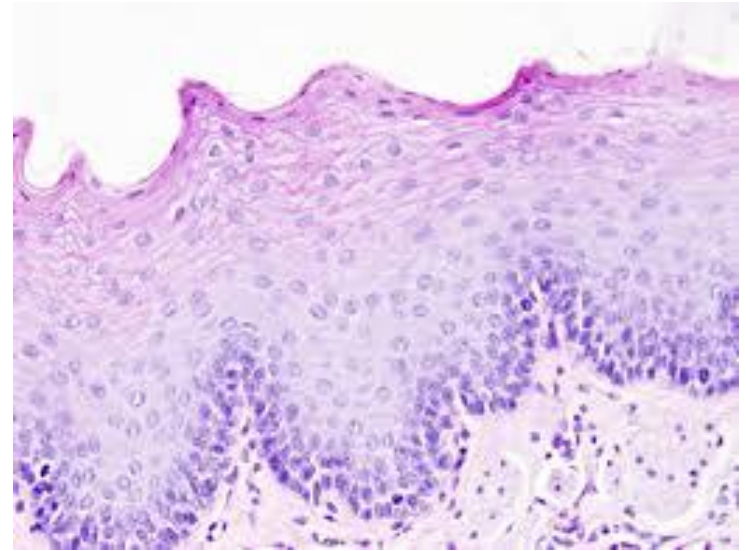
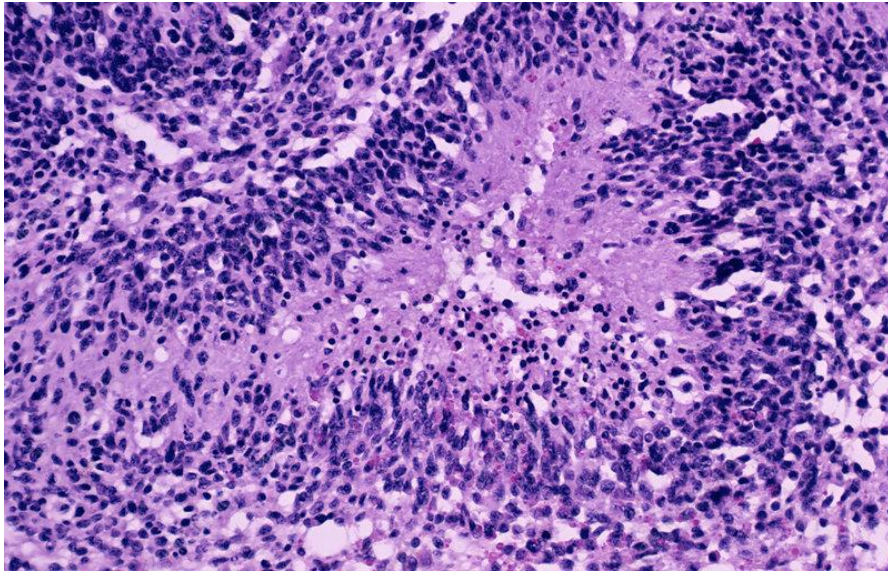
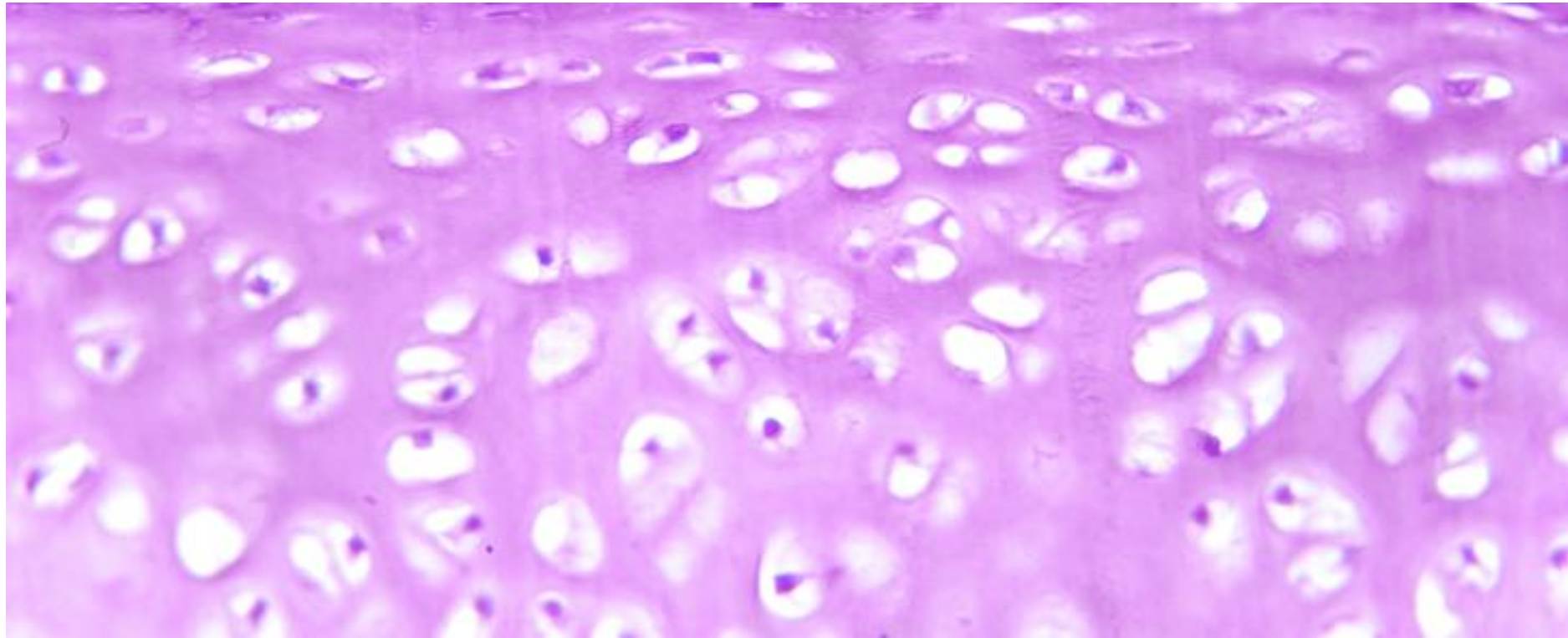


Matriz extracelular

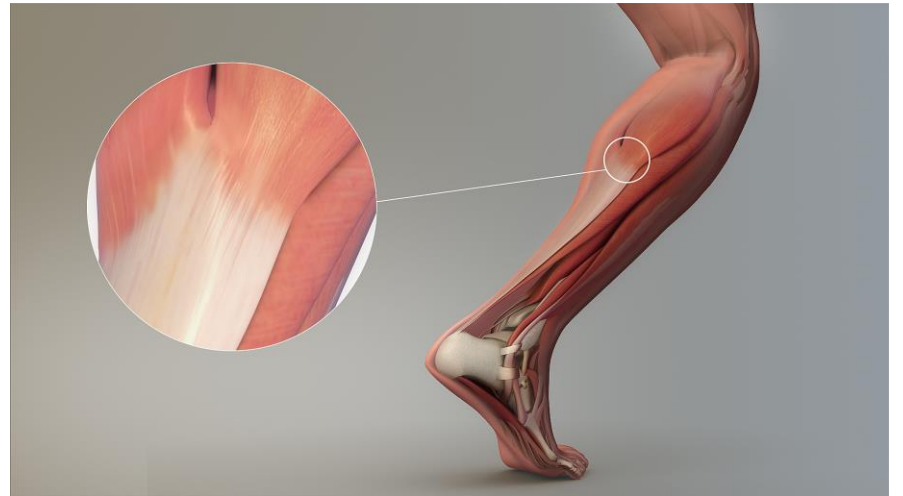


Gonzalo Aparicio
gaparicio@fcien.edu.uy





Tejido conjuntivo: habitualmente la matriz es más abundante que las células



¿Un soporte físico pasivo o activo?

Desarrollo

Migración

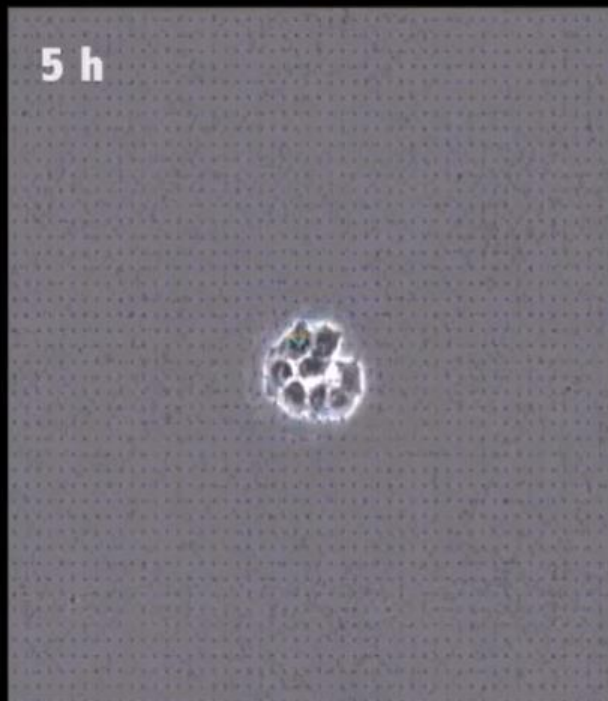


Proliferación

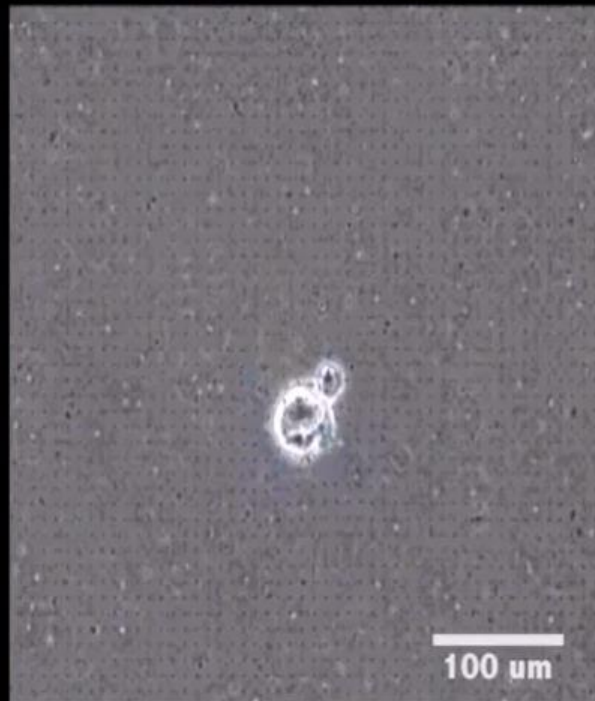
Forma

Fisiología

Thin



Thick



100 μm

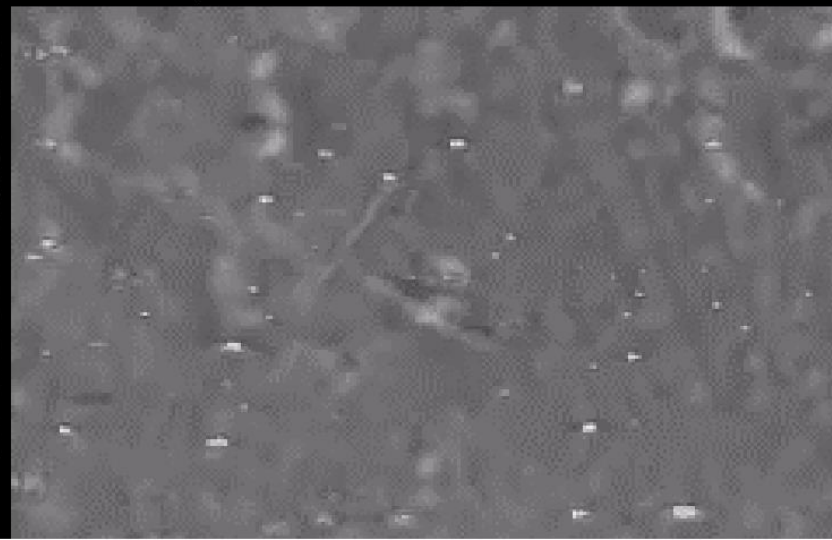
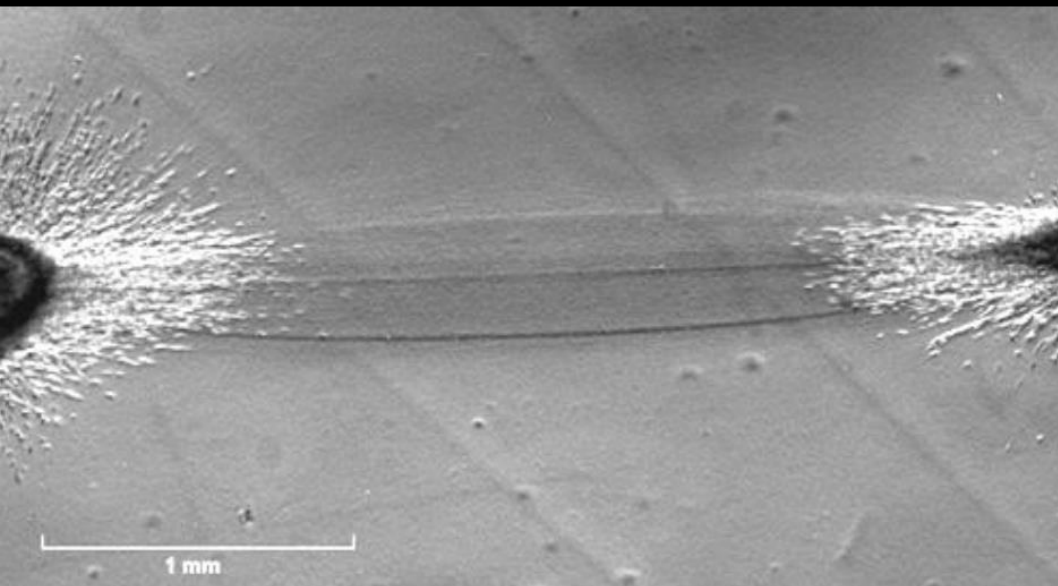
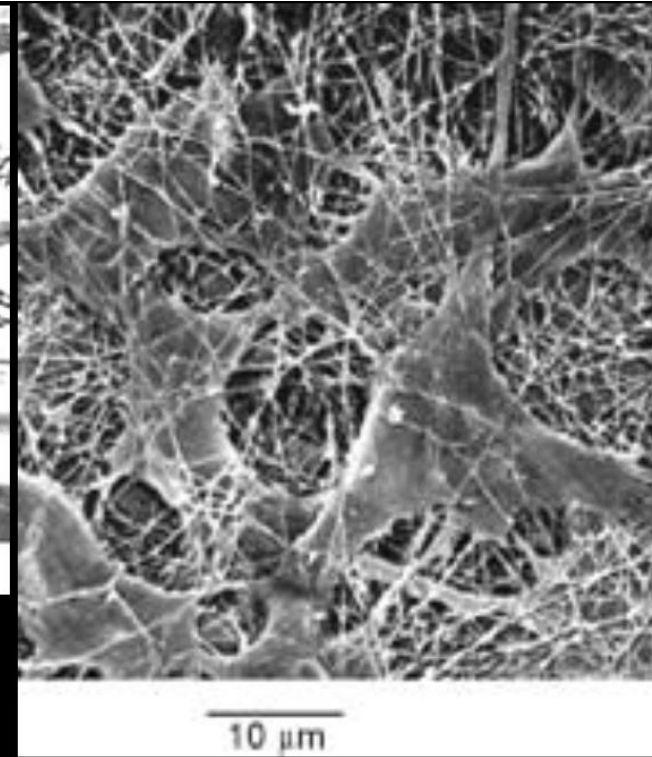
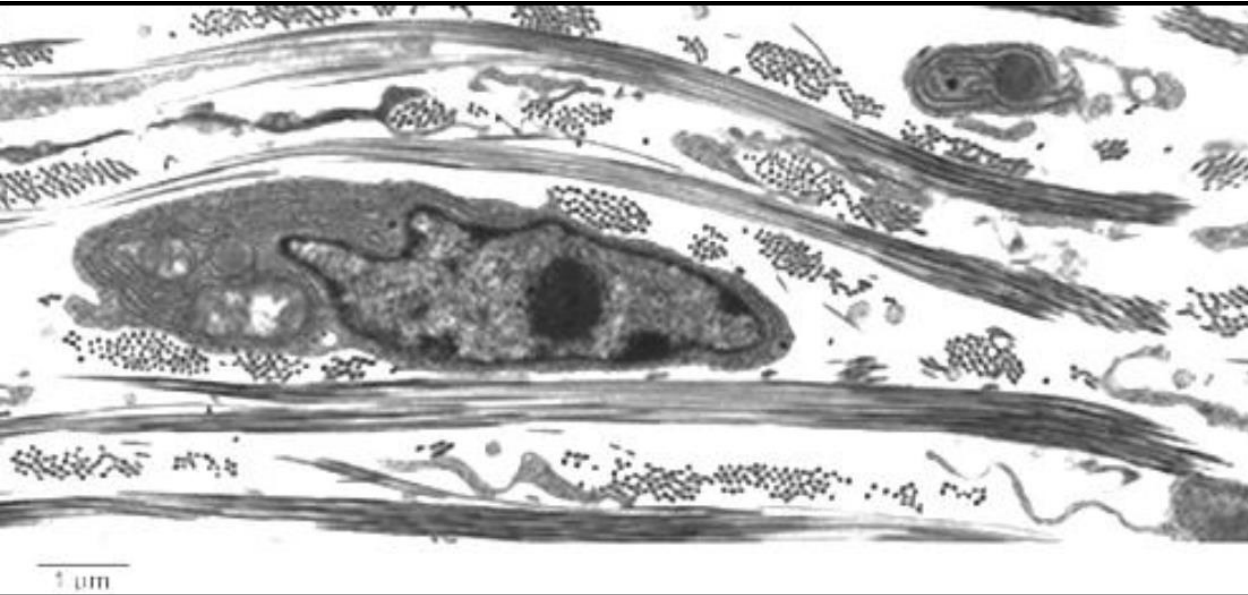
Displacement (μm)



0 4 8 12 15 20

¿Quién produce esta matriz?

El fibroblasto y la matriz extracelular



¿Qué tipos de macromoléculas encontramos en esta matriz?

Glucosaminoglicanos (GAG) $\Rightarrow$ proteoglicanos

Proteínas fibrilares $\Rightarrow$ familia de colágeno

Glucoproteínas (no colágeno)

Alrededor de 300 proteínas en mamíferos

Proteoglicanos 36

Colágeno 40

Glucoproteínas >200

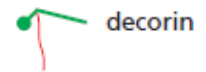
proteoglycans and GAGs



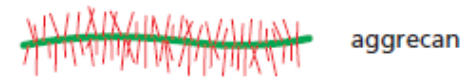
hyaluronan



perlecan



decorin



aggrecan

fibrous proteins



type IV collagen

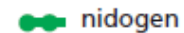


fibrillar collagen

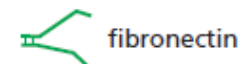
glycoproteins



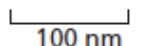
laminin



nidogen



fibronectin



100 nm

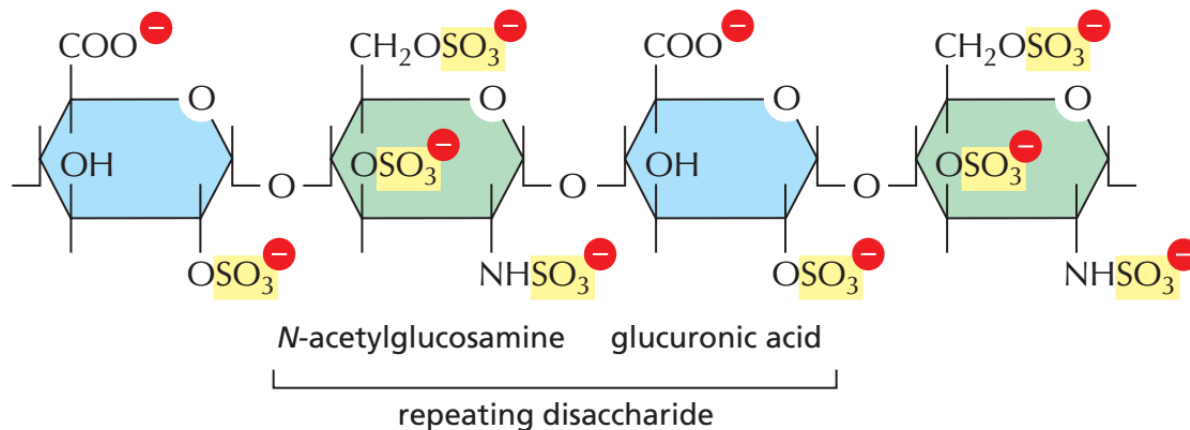
Glucosaminoglucanos (GAGs)

Cadenas de polisacáridos no ramificadas, compuestas por unidades repetidas de disacáridos:

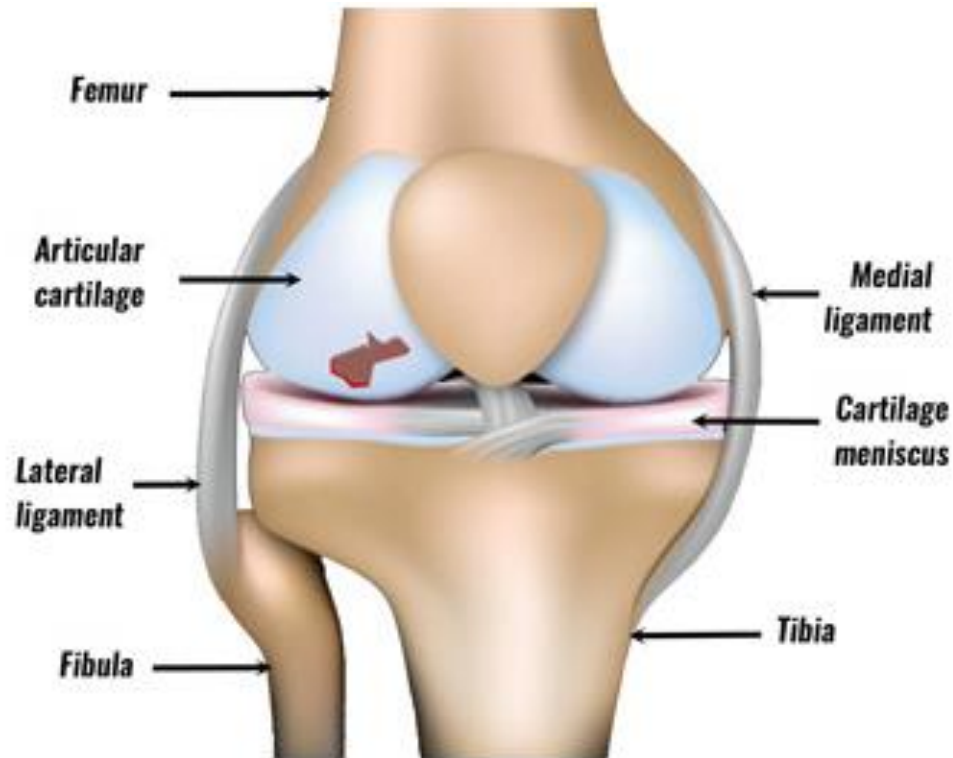
Aminoazúcar (N-acetilglucosamina o N-acetilgalactosamina)

+

ácido urónico (glucurónico o idurónico)



Resiste fuerzas de compresión



● globular protein (MW 50,000)

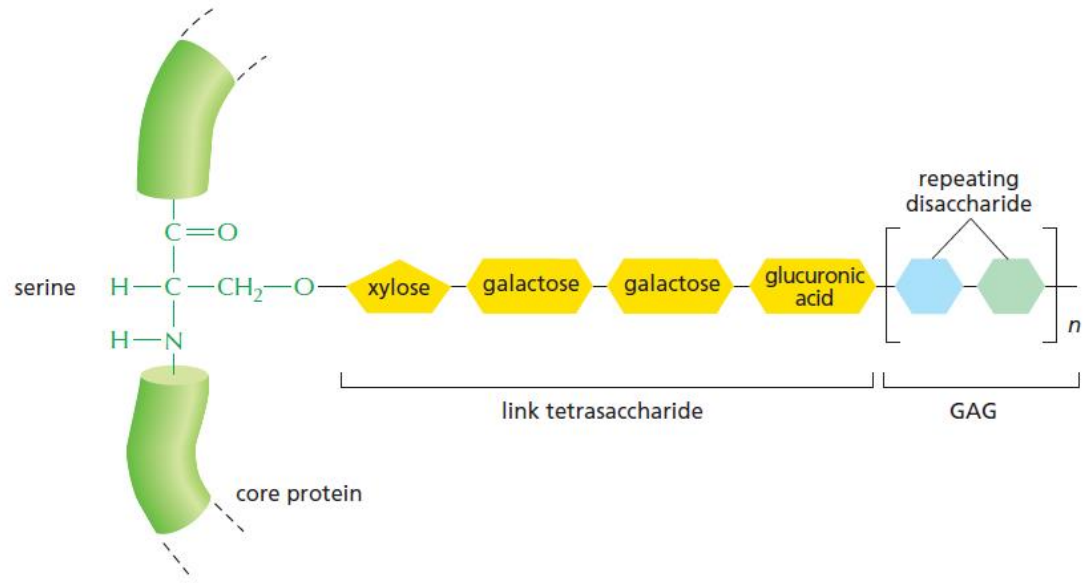
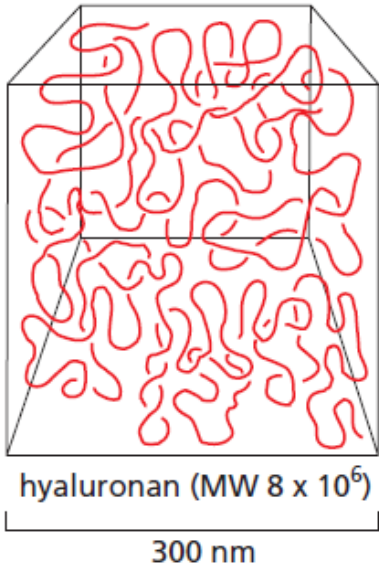


glycogen (MW ~400,000)



spectrin (MW 460,000)

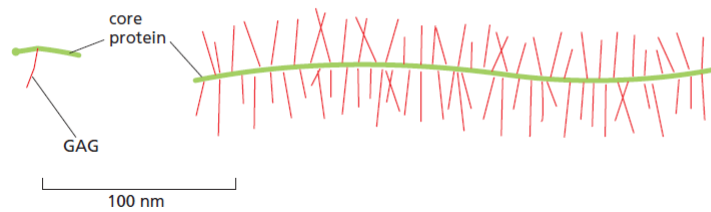
collagen (MW 290,000)



DECORIN
(MW ~40,000)

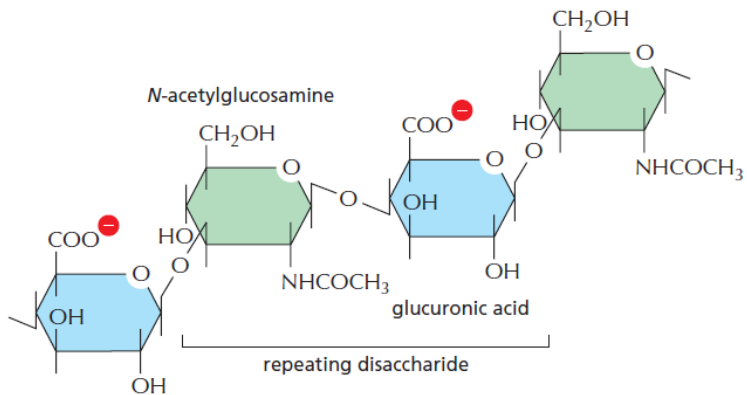
AGGREGAN
(MW $\sim 3 \times 10^6$)

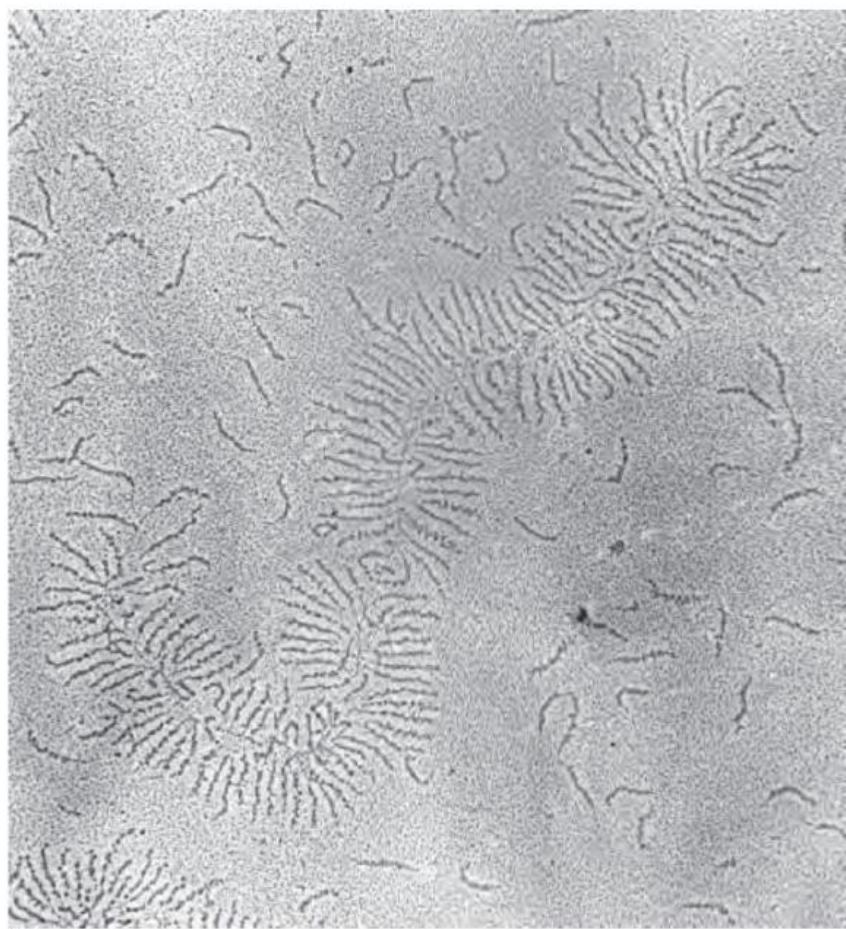
RIBONUCLEASE
(MW ~15,000)



short, branched
oligosaccharide
side chain

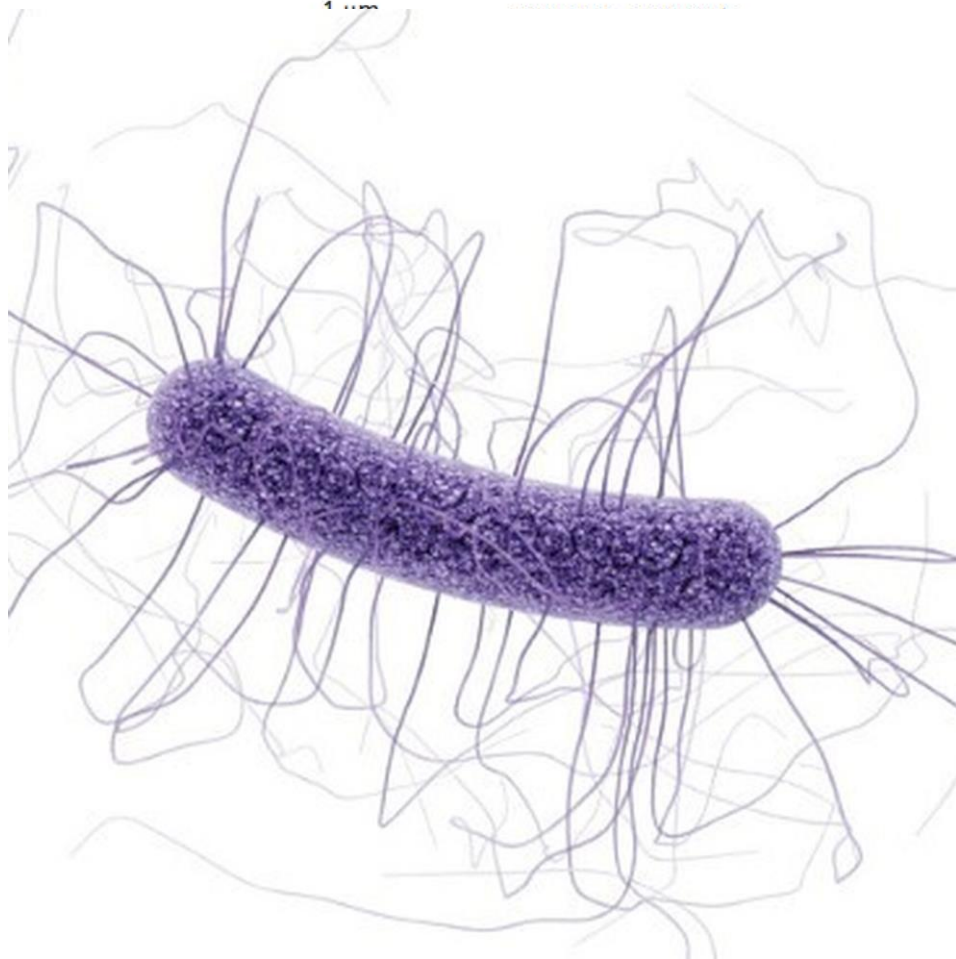
polypeptide chain





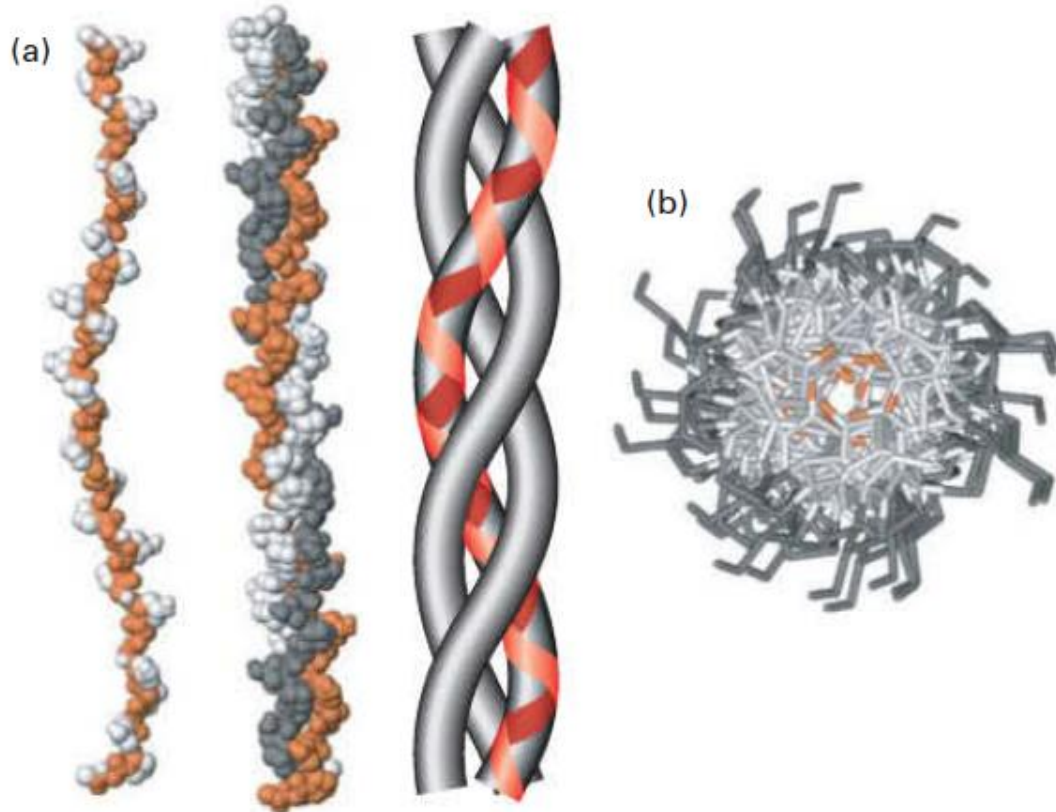
(A)

1 μm



1 μm

Colágeno



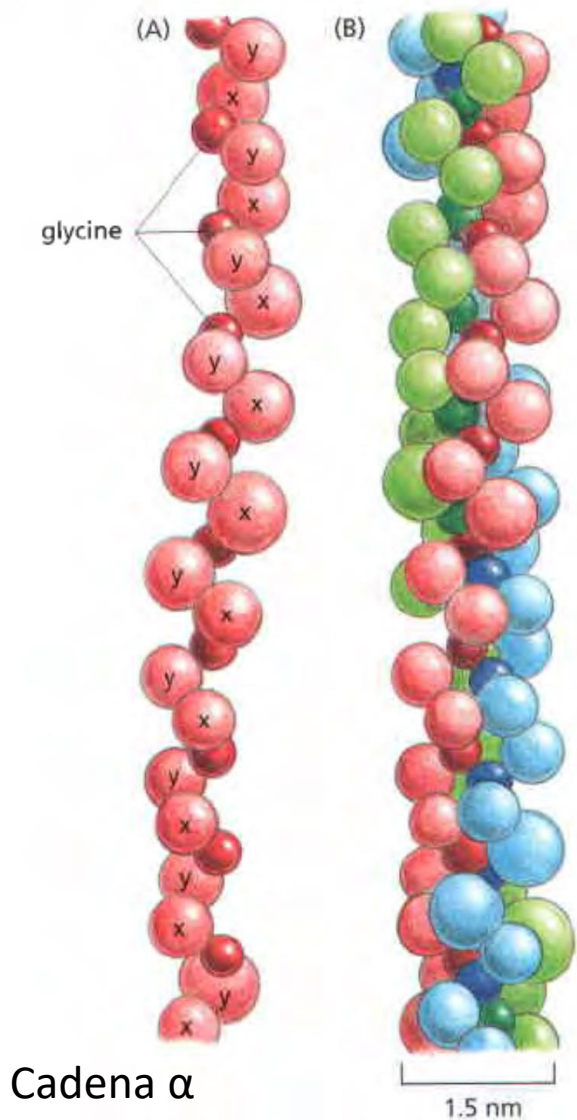
Cadena α

Estructura helicoidal trimérica

25 cadenas α distintas, cada una codificada por un gen diferente, expresándose diversas combinaciones de estos genes en los diferentes tejidos.

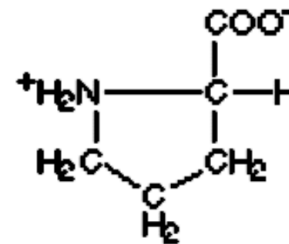
En principio se podrían formar >10000 tipos de moléculas de colágeno triple hélice, solo se han identificado unos 20.

Estructura del colágeno

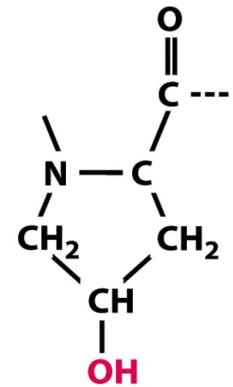


Estructura helicoidal trimérica

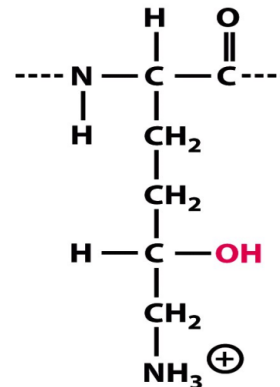
Amino acid sequence – Gly – X – Y – Gly – X – Y – Gly – X – Y –



X frecuentemente es prolina

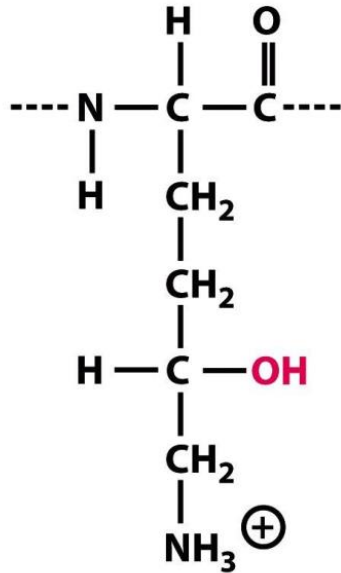


Y frecuentemente es hidroxiprolina

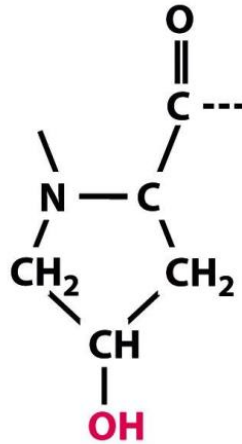


hidroxilisina

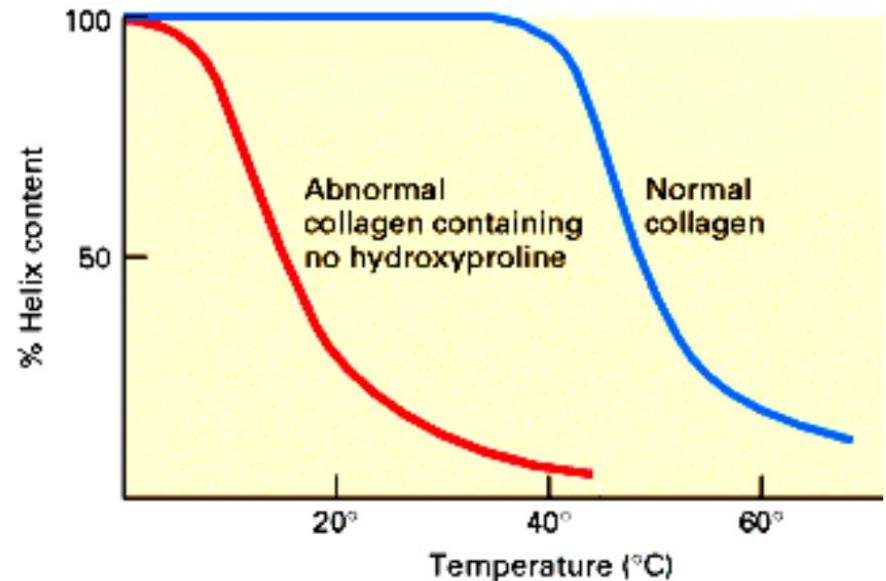
Estructura del colágeno



hydroxylysine
in protein



hydroxyproline
in protein



La hidroxilación de prolina y lisina en colágeno requiere vitamina C (ácido ascórbico)



single collagen
polypeptide chain



triple-stranded
collagen molecule

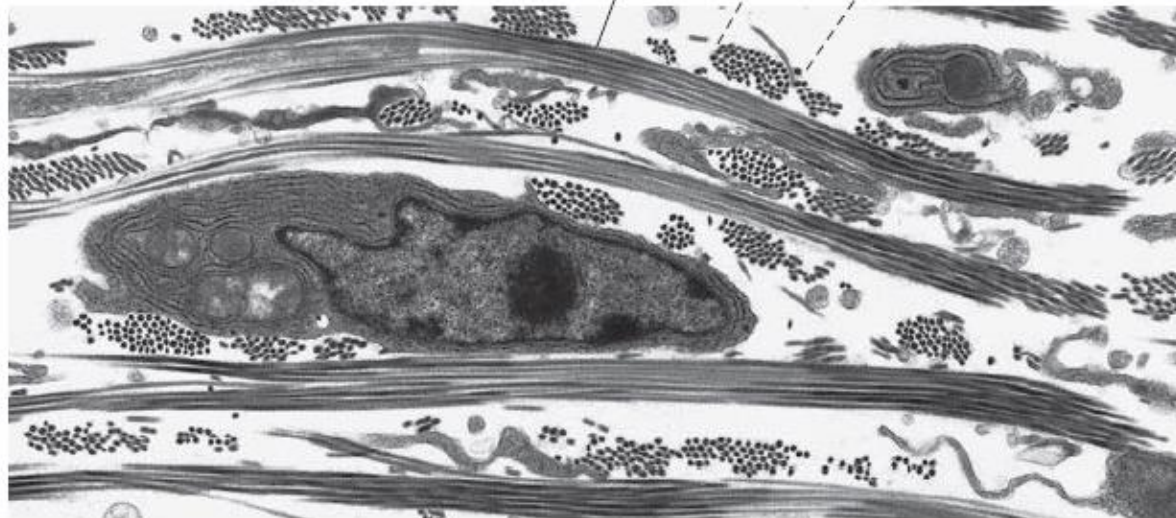
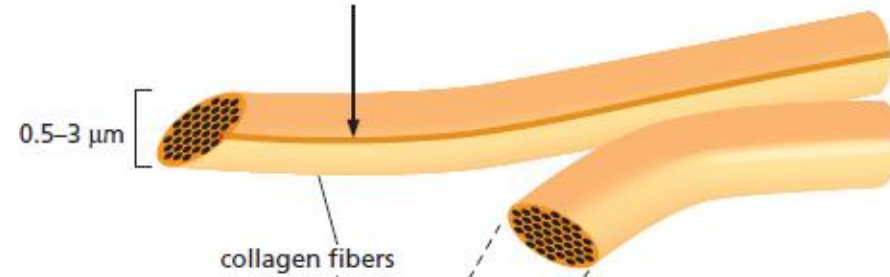


collagen
fibril



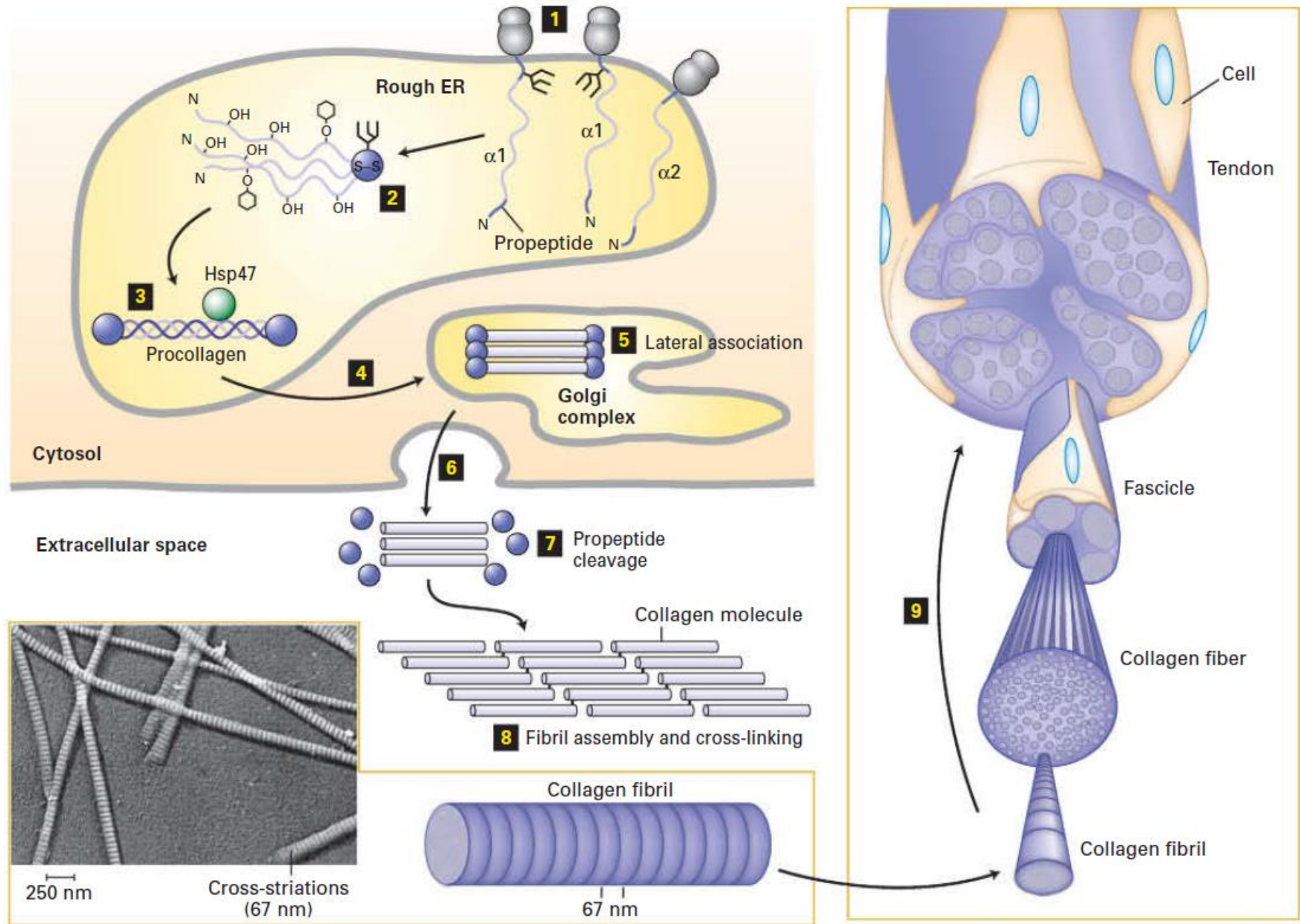
0.5-3 μm

collagen fibers

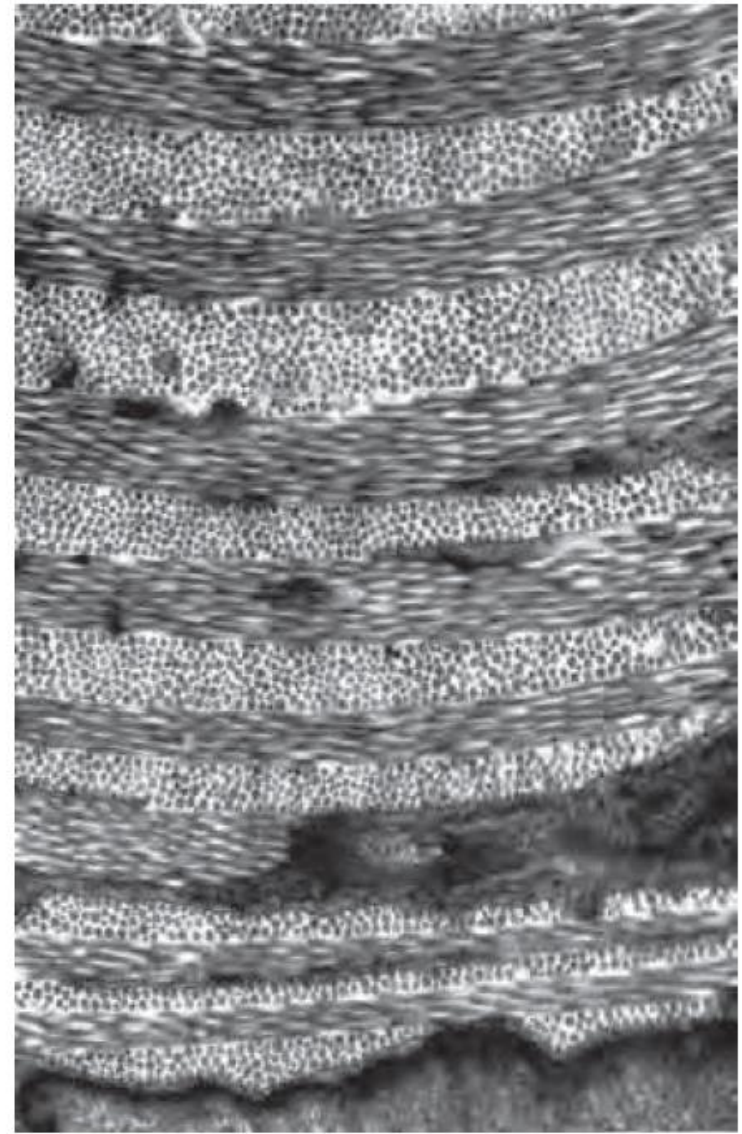


1 μm

Síntesis del colágeno

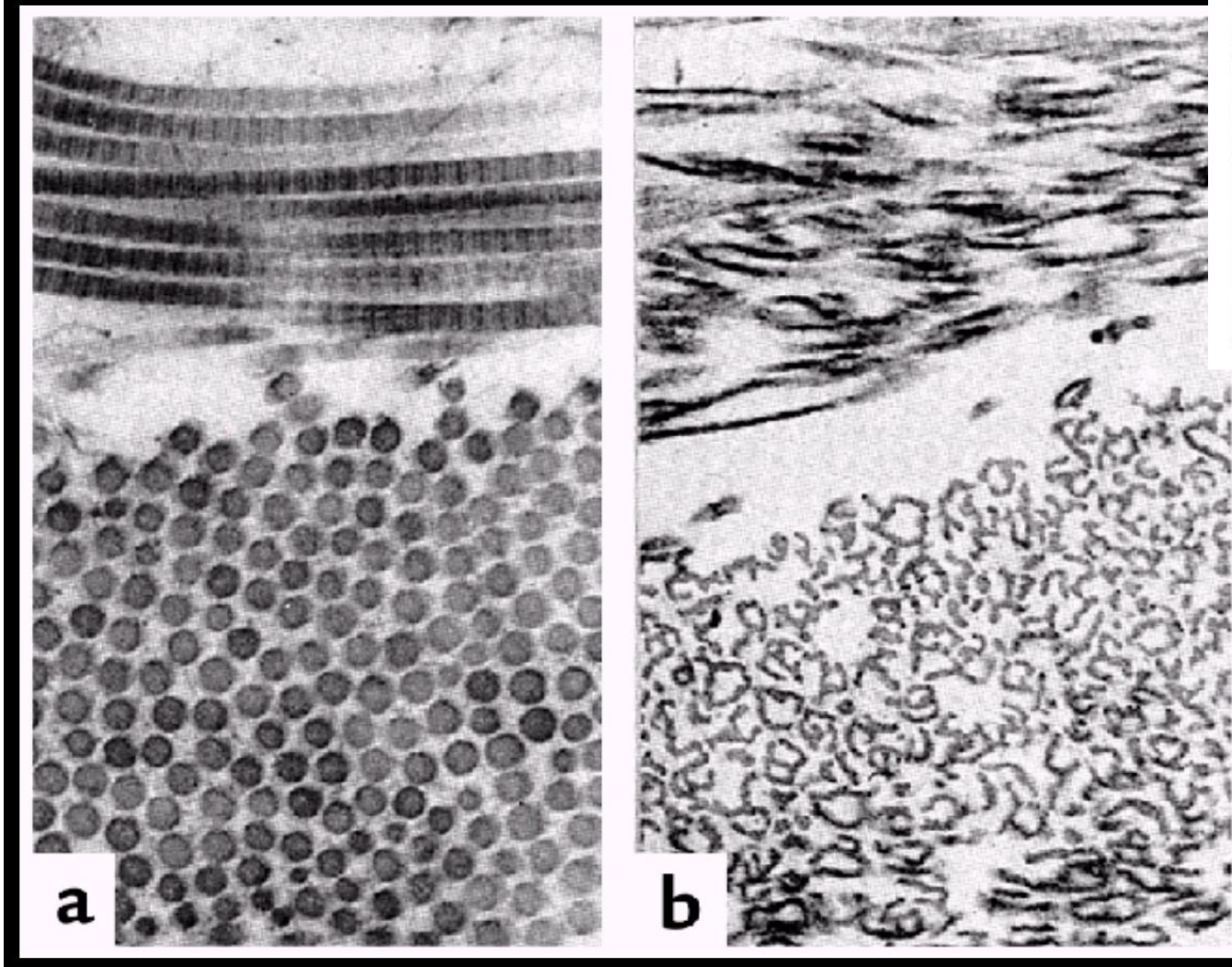


Resiste fuerzas de tensión



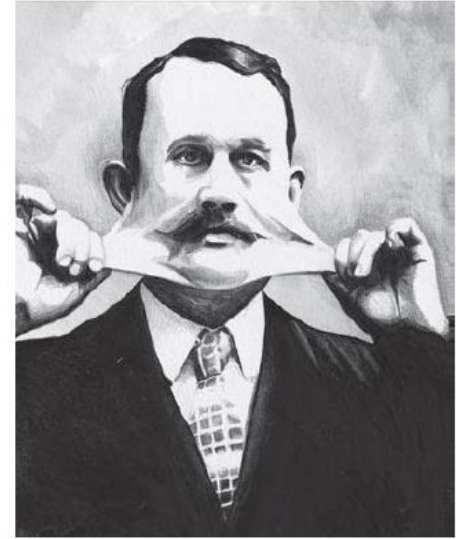
5 μm

Síntesis del colágeno



Piel normal

Dermatosparaxis (falta de procolágeno N-peptidasa)



Variedades de colágeno

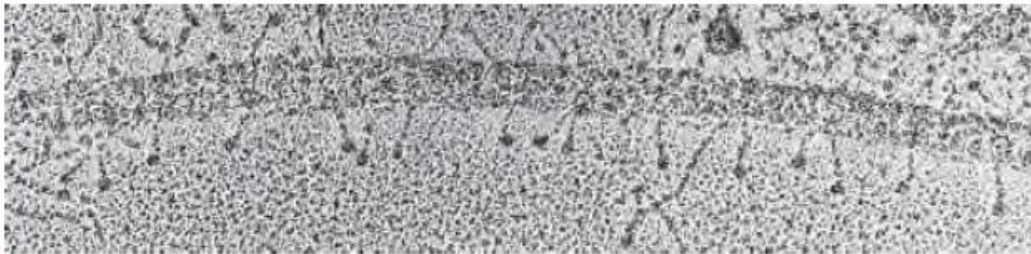
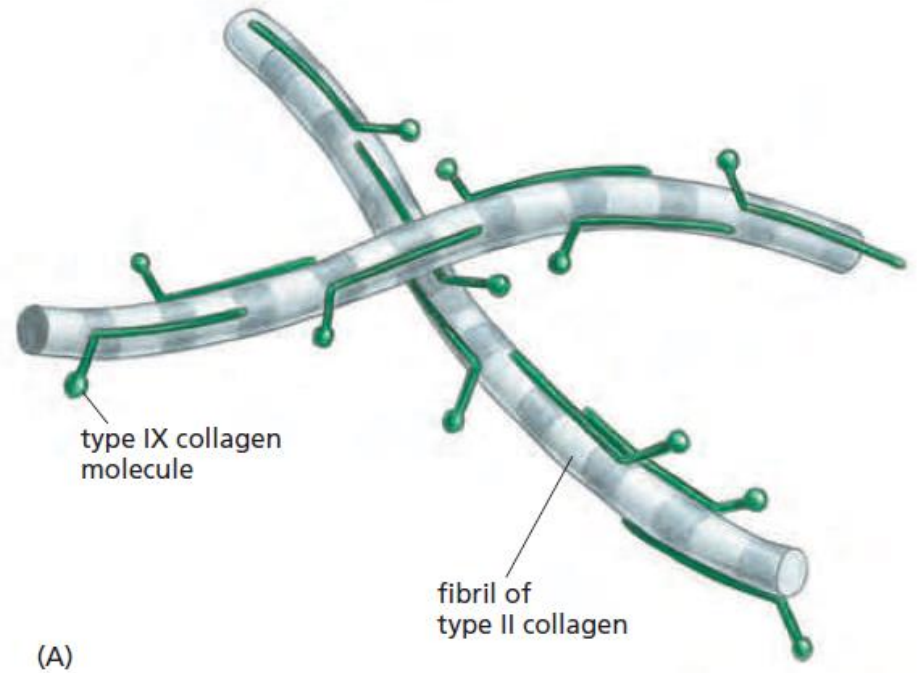
TABLE 19–2 Some Types of Collagen and Their Properties

	Type	Polymerized form	Tissue distribution	Mutant phenotype
Fibril-forming (fibrillar)	I	Fibril	Bone, skin, tendons, ligaments, cornea, internal organs (accounts for 90% of body collagen)	Severe bone defects, fractures (<i>osteogenesis imperfecta</i>)
	II	Fibril	Cartilage, intervertebral disc, notochord, vitreous humor of the eye	Cartilage deficiency, dwarfism (<i>chondrodysplasia</i>)
	III	Fibril	Skin, blood vessels, internal organs	Fragile skin, loose joints, blood vessels prone to rupture (<i>Ehlers–Danlos syndrome</i>)
	V	Fibril (with type I)	As for type I	Fragile skin, loose joints, blood vessels prone to rupture
	XI	Fibril (with type II)	As for type II	Myopia, blindness
Fibril-associated	IX	Lateral association with type II fibrils	Cartilage	Osteoarthritis
Network-forming	IV	Sheetlike network	Basal lamina	Kidney disease (glomerulonephritis), deafness
	VII	Anchoring fibrils	Beneath stratified squamous epithelia	Skin blistering
Transmembrane	XVII	Nonfibrillar	Hemidesmosomes	Skin blistering
Proteoglycan core protein	XVIII	Nonfibrillar	Basal lamina	Myopia, detached retina, hydrocephalus

Note that types I, IV, V, IX, and XI are each composed of two or three types of α chains (distinct, nonoverlapping sets in each case), whereas types II, III, VII, XVII, and XVIII are composed of only one type of α chain each.

Los principales tipos localizados en tejido conjuntivos son I, II, III, V y XI, siendo el tipo I el principal de la piel y de los huesos y el más abundante.

Variedades de colágeno



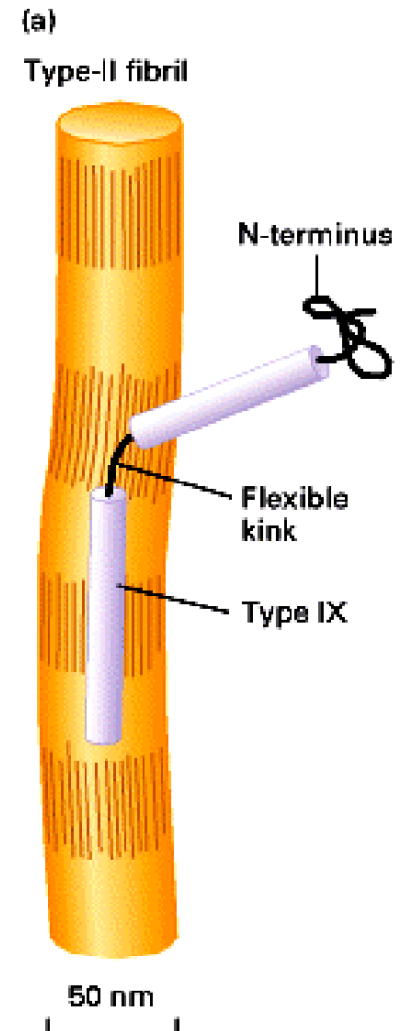
100 nm

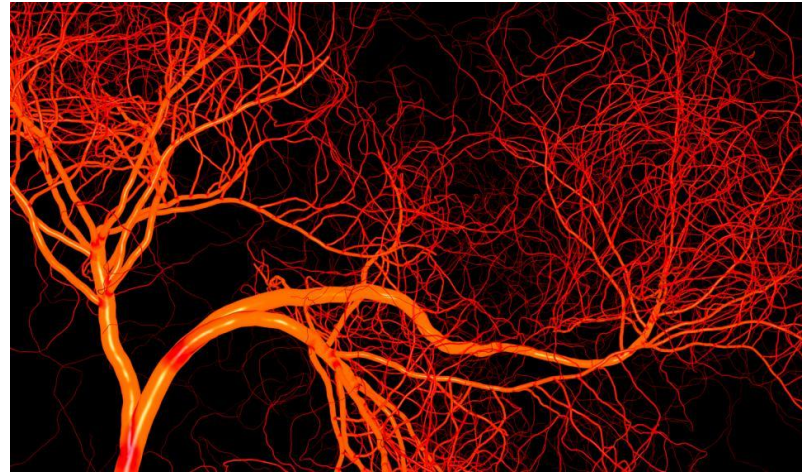


Colágeno tipo IX

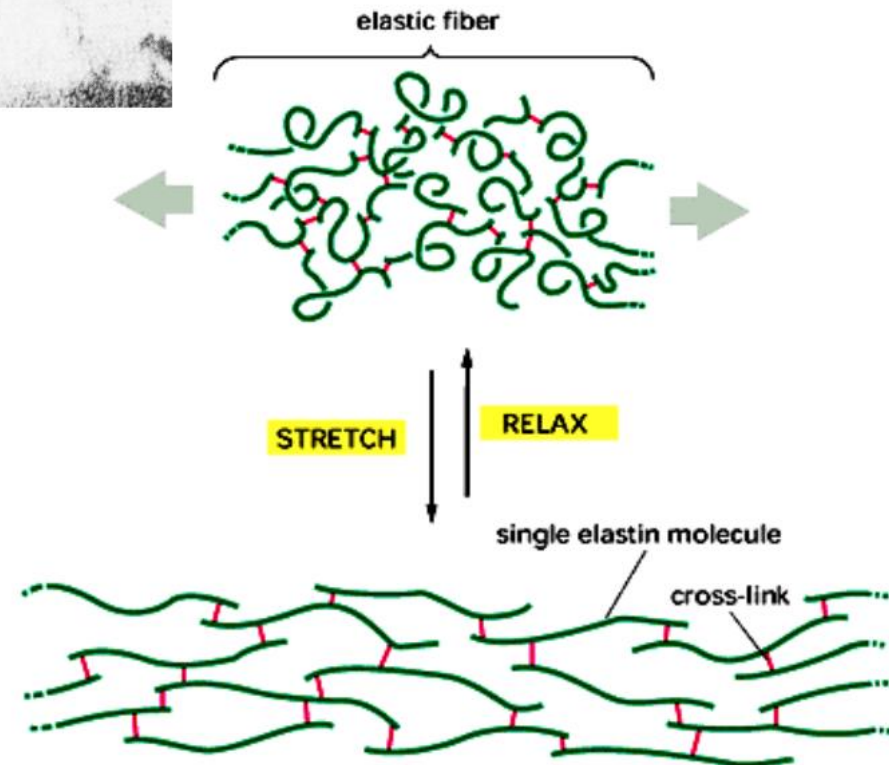
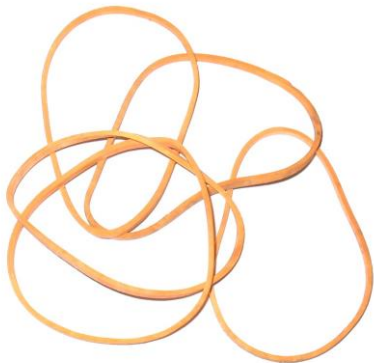
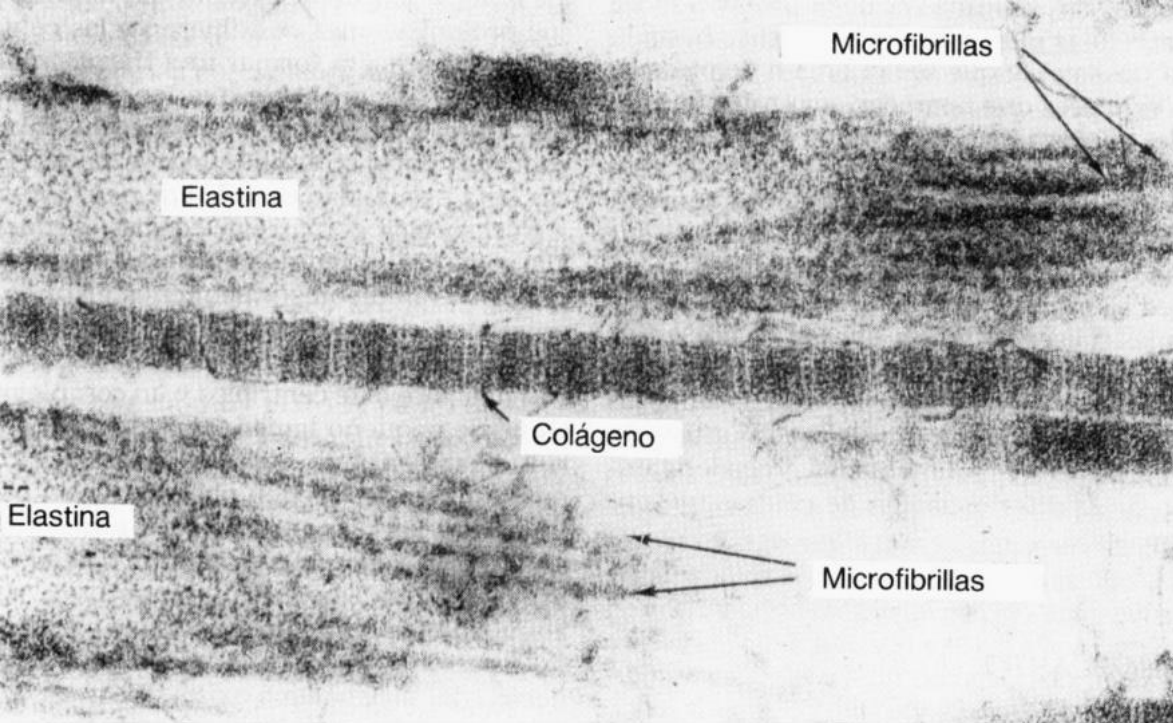
Colageno tipo IX es colágeno asociado a fibrillas, difiere en varios aspectos:

- 1- Estructura helicoidal interrumpida por 1 o 2 dominios no helicoidales
- 2- No se procesa proteolíticamente, retienen propéptidos
- 3- Se unen a fibrillas de colágeno tipo II, por ejemplo en cartílago, córnea.

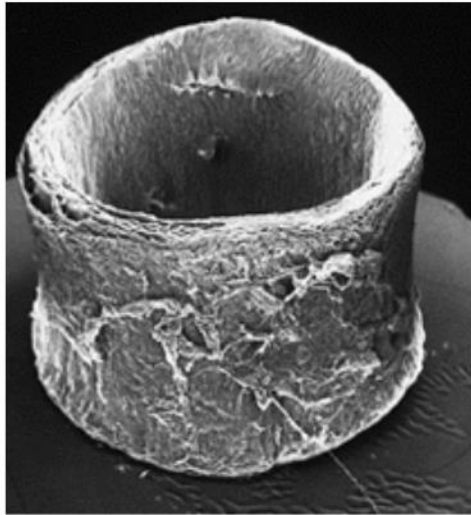




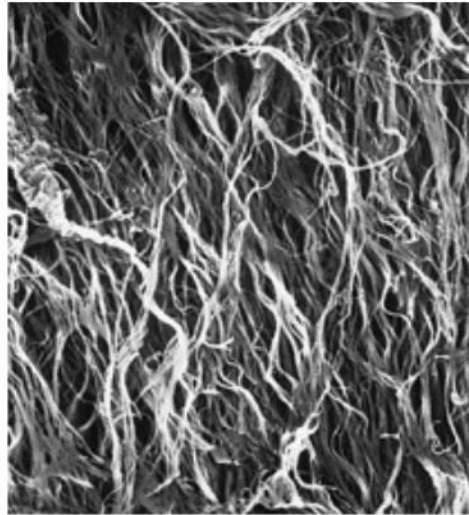
Fibras elásticas



Láminas elásticas en las arterias

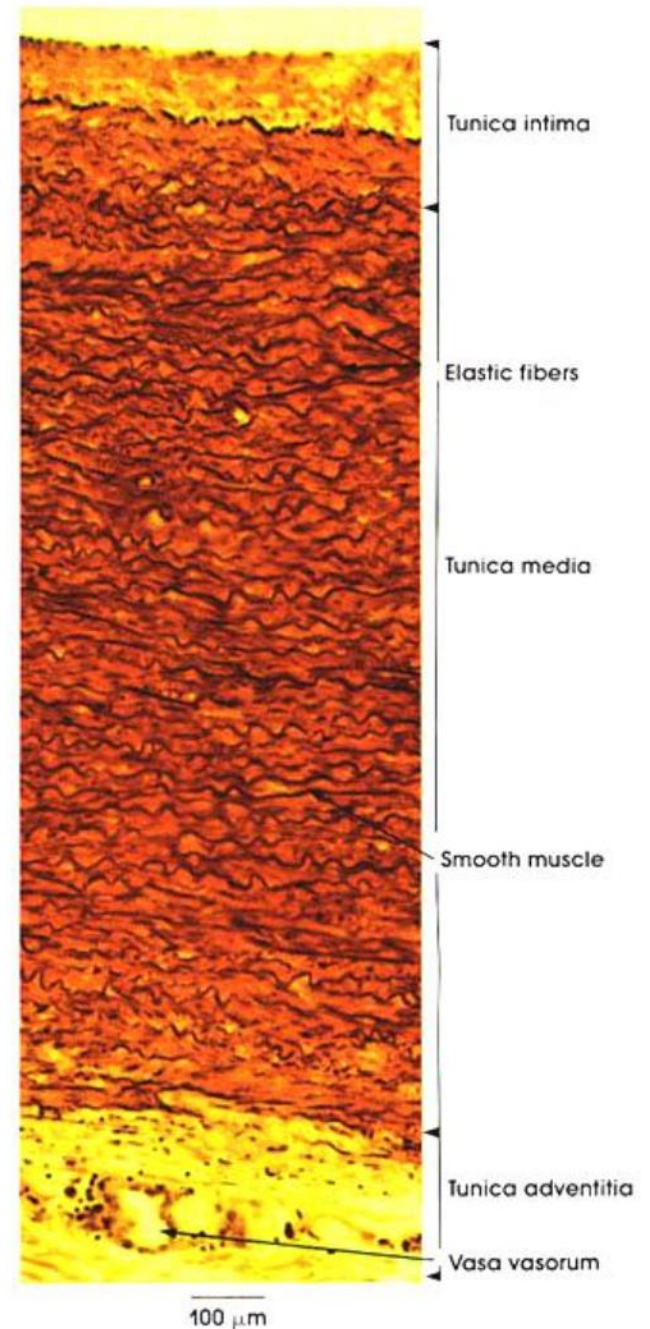


1 mm



(B)

100 μm



Tunica intima

Elastic fibers

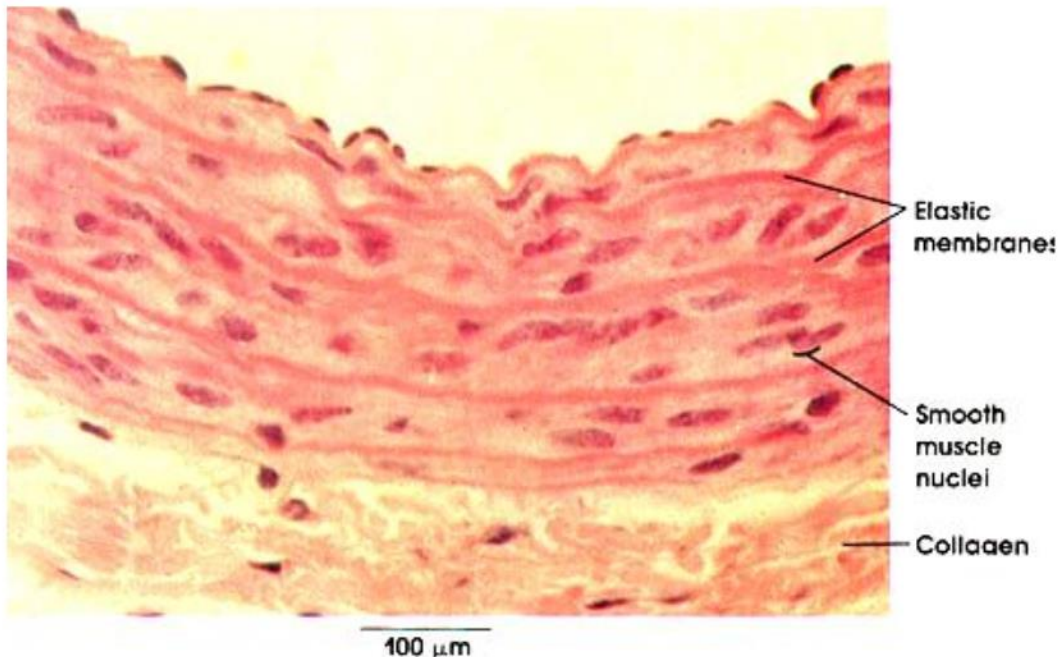
Tunica media

Smooth muscle

Tunica adventitia

Vasa vasorum

100 μm



Elastic membranes

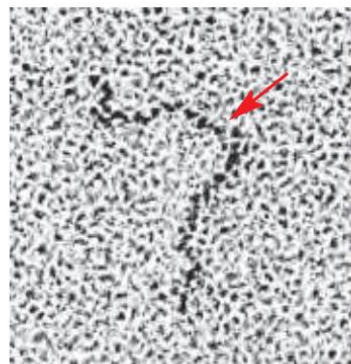
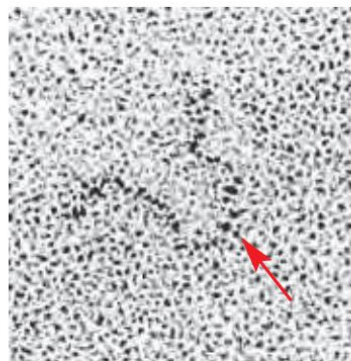
Smooth muscle nuclei

Collagen

100 μm

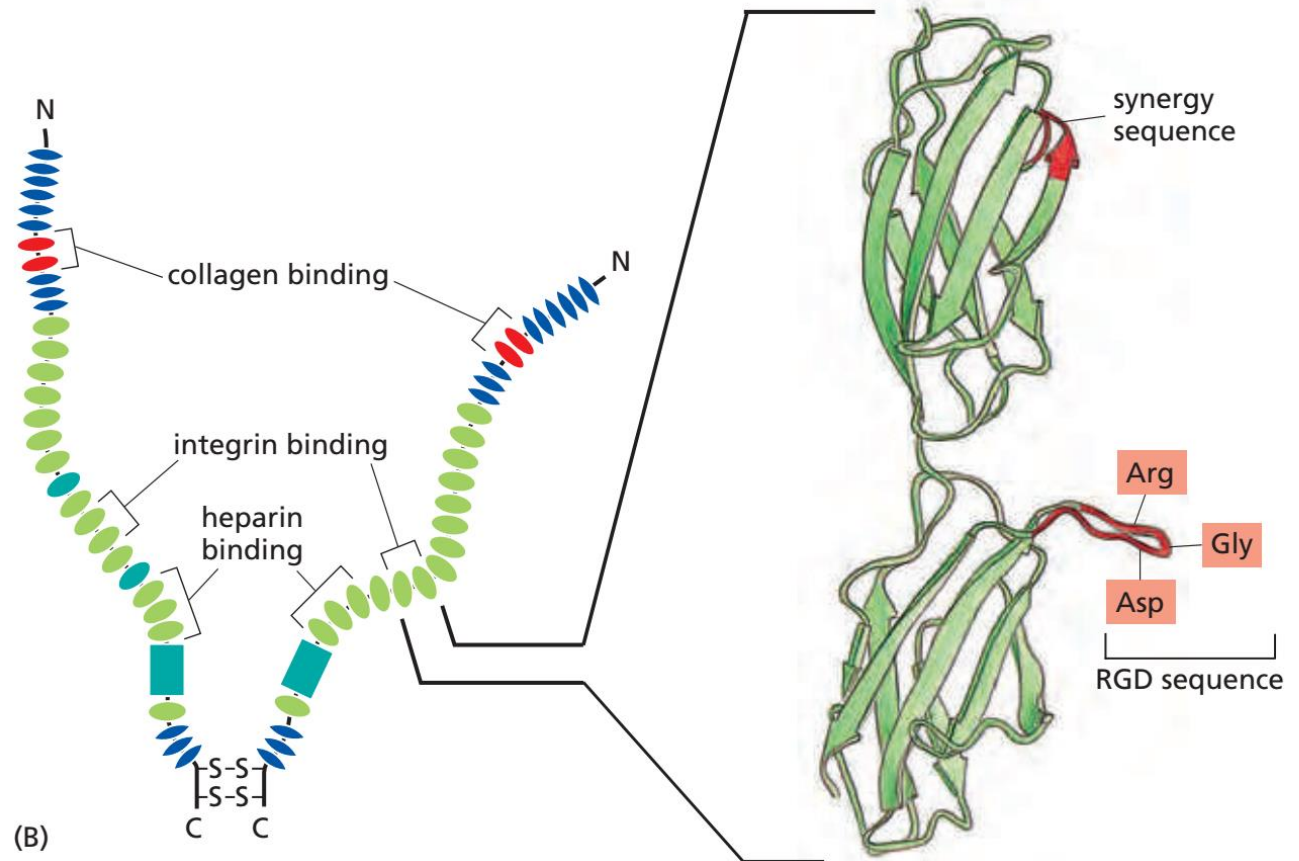
La elastina puede representar hasta 50% del peso seco de las arterias

Glucoproteínas adhesivas: fibronectina



100 nm

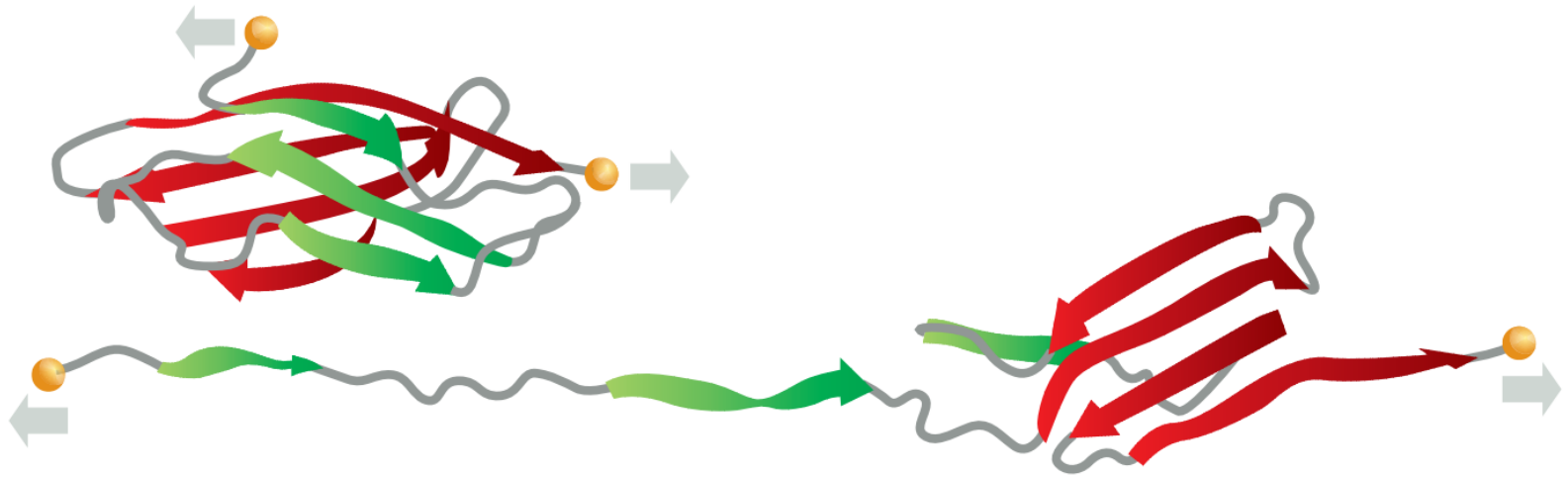
(A)



(B)

(C)

Dominio de fibronectina tipo III



Diferencia con colágeno en
la formación de fibrillas

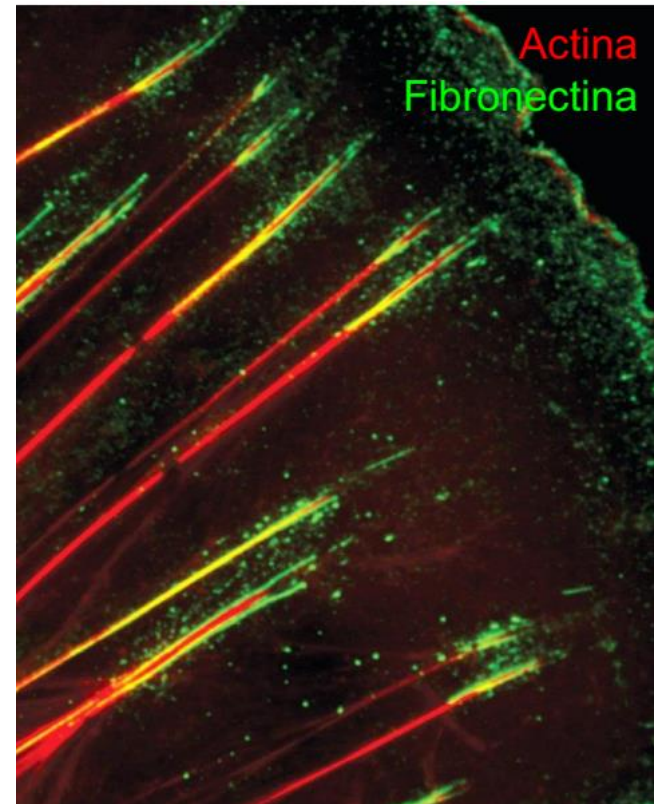
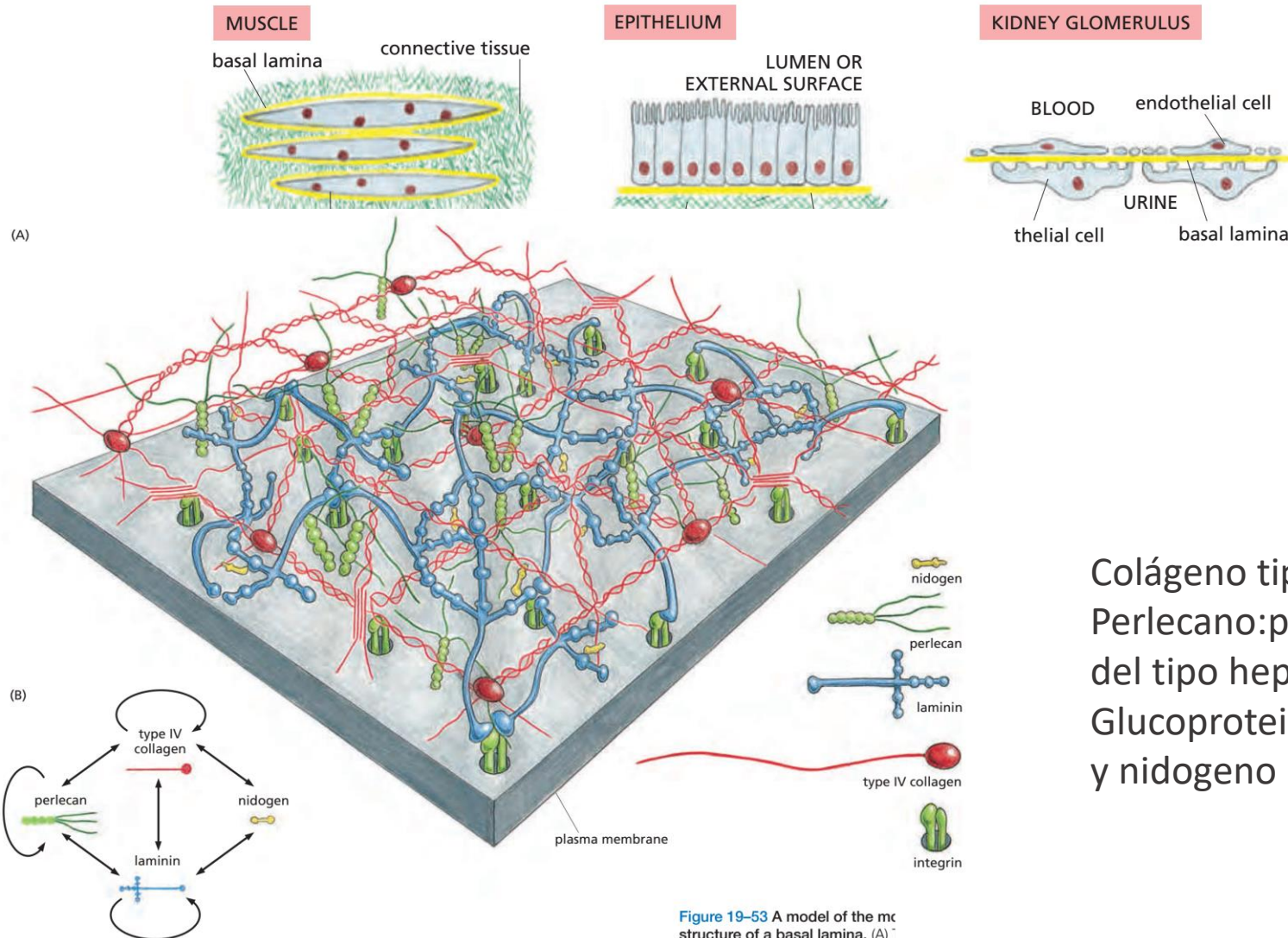


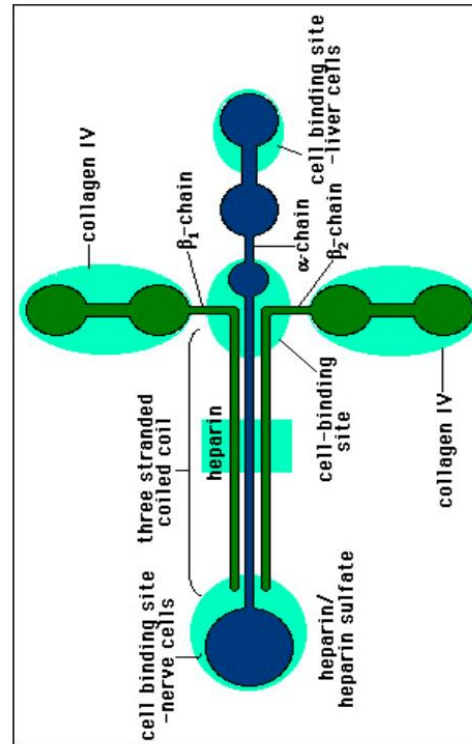
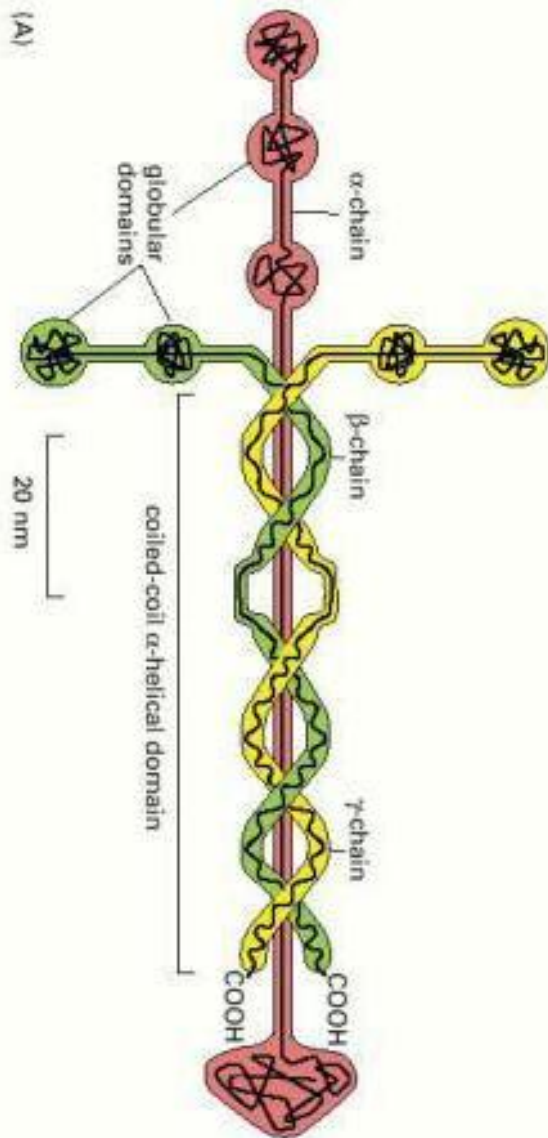
Lámina basal → es una fina capa de matriz extracelular que separa el tejido epitelial y muchos tipos de células, como las fibras musculares o las células adiposas, del tejido conjuntivo.



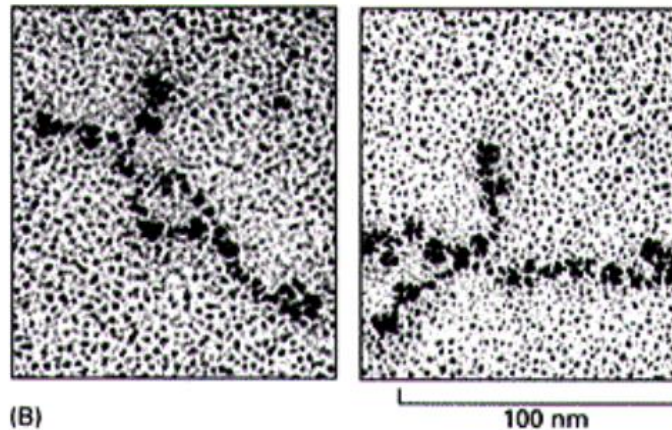
Colágeno tipo IV
Perlecano: proteoglicano del tipo heparán sulfato
Glucoproteínas: laminina y nidogeno

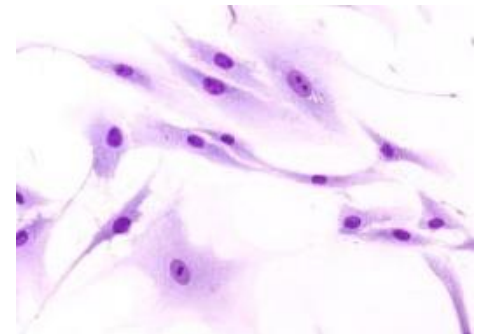
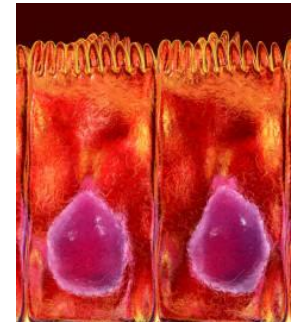
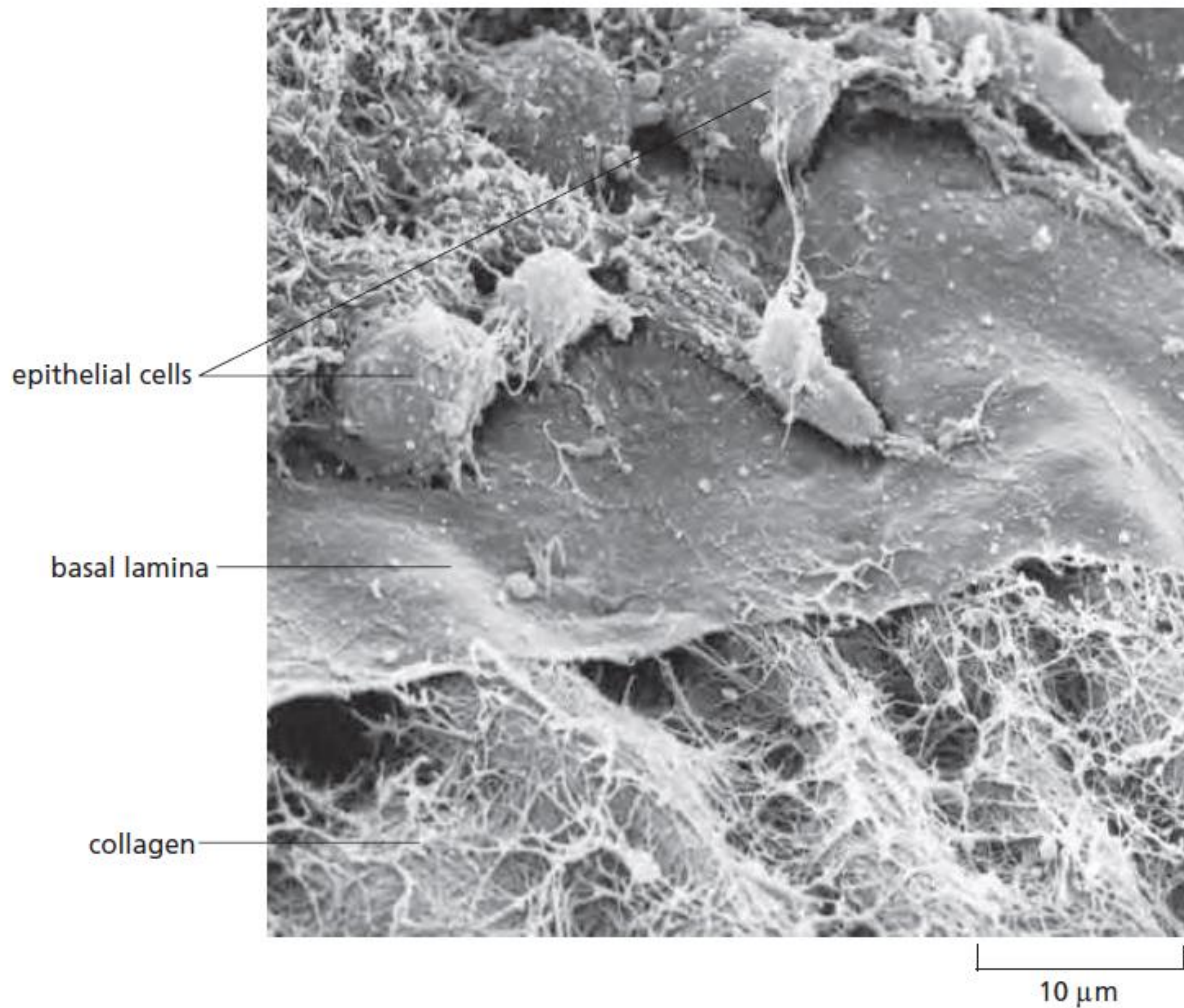
Figure 19-53 A model of the molecular structure of a basal lamina. (A) The basal lamina is formed by specific

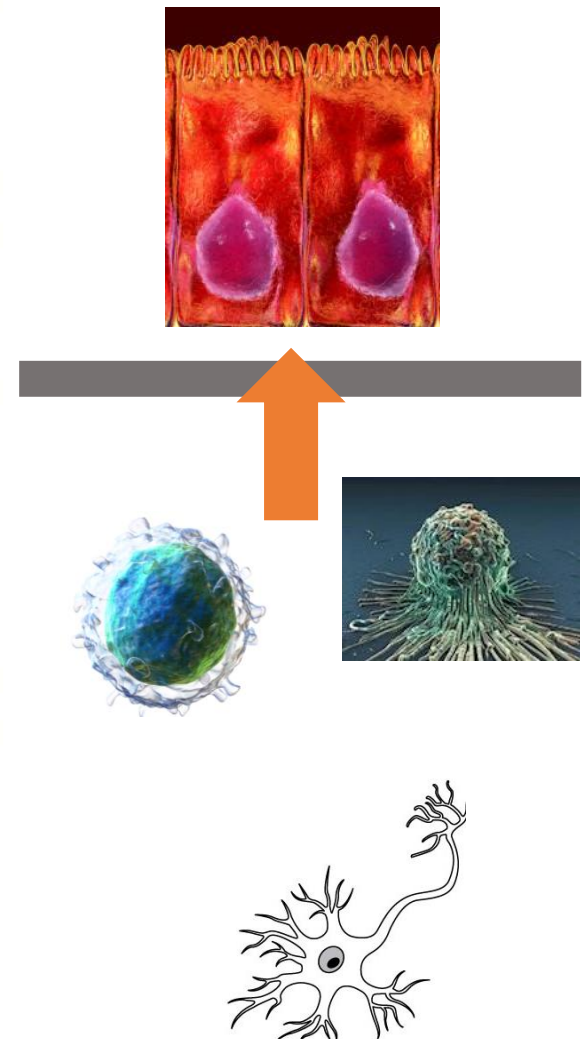
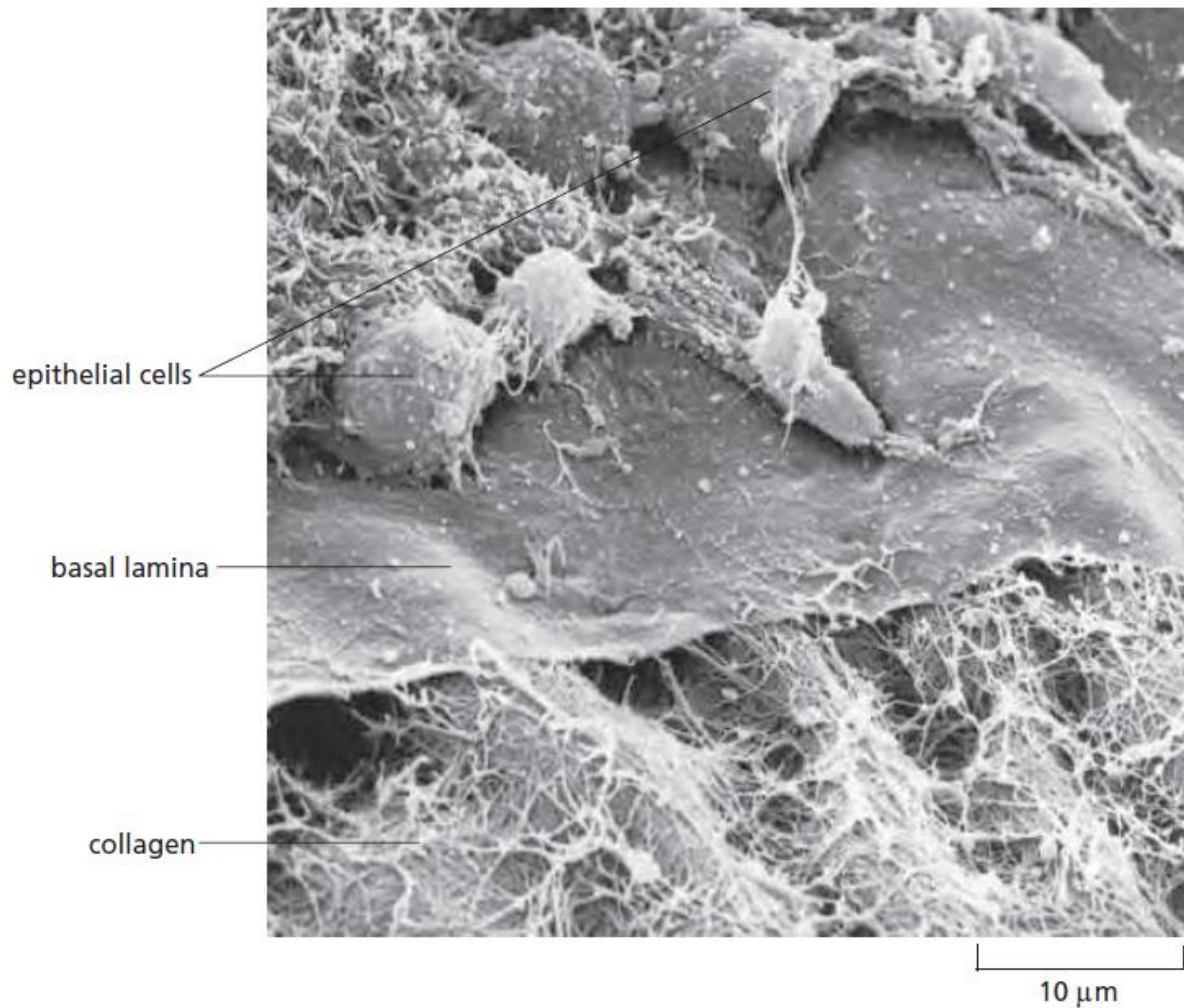
Glucoproteínas adhesivas: laminina



5 tipos de cadenas α
4 tipos de cadenas β
3 tipos de cadenas γ







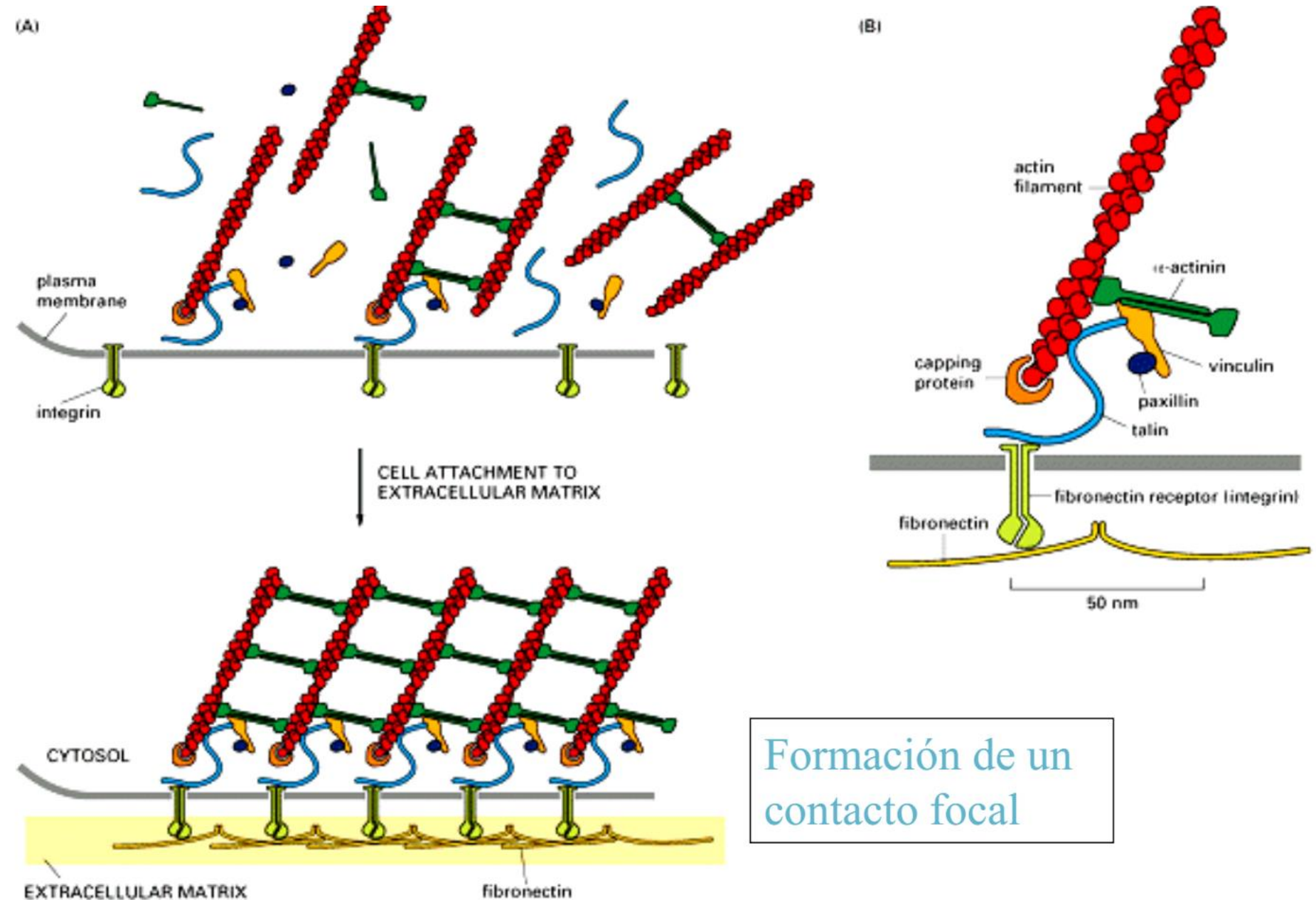
Remodelación y degradación de la matriz: Metaloproteinasas (MMPs)

-En humanos 23 MMPs
-Inhibición de MMPs en terapia
contra el cáncer

Table 1. Classification of the main members of MMP family with their biological effect, chromosomal location and the group of substrates^{6,11,12}.

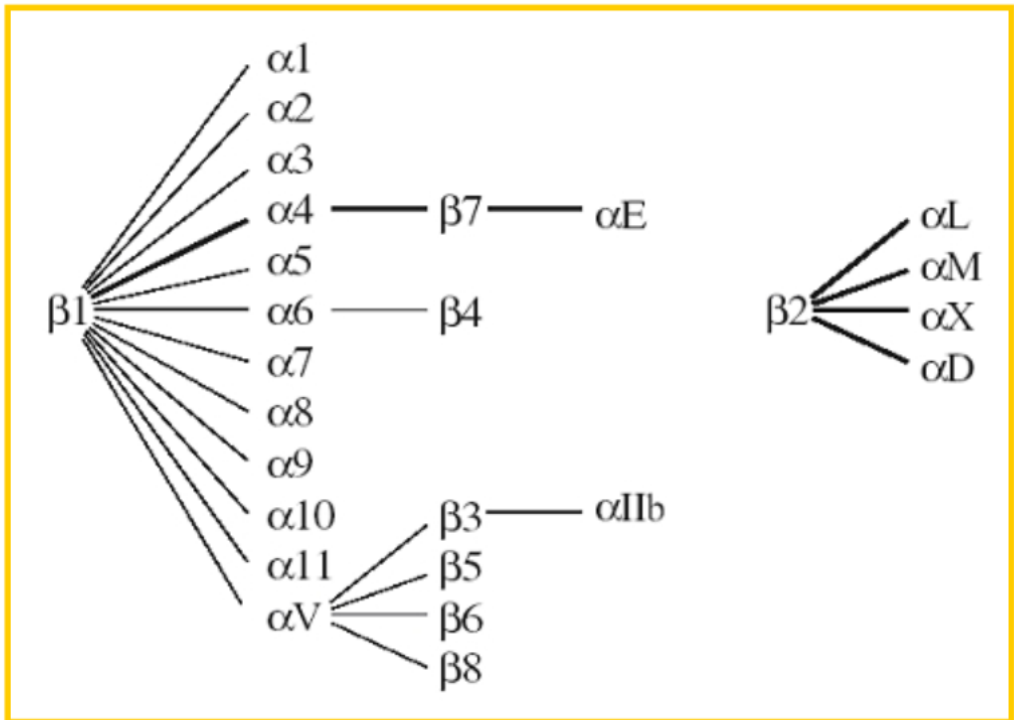
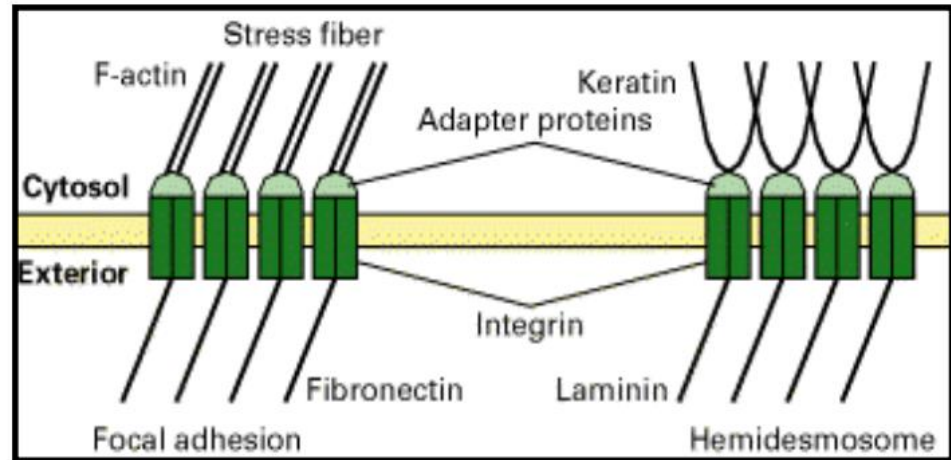
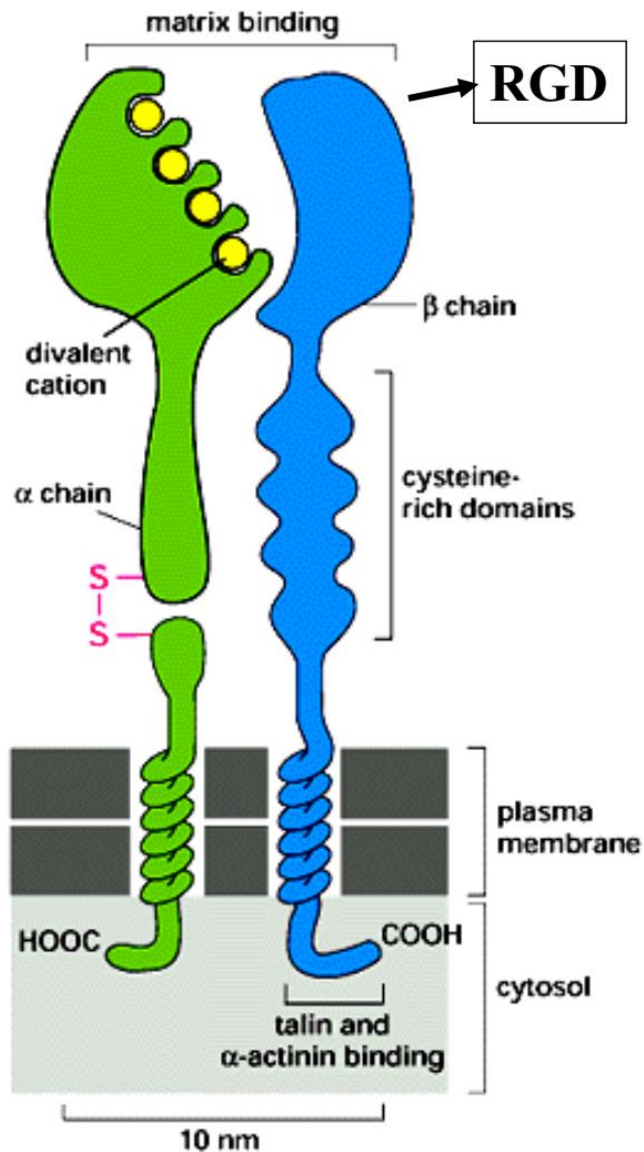
Traditional classification (common name)	Numerical classification	Biological effect	Chromosomal location	Group of substrates for enzymes
MMP classification				
<i>Collagenases</i>				
Collagenase-1	MMP-1	The migration of keratinocytes, reepithelialization, cell migration, platelet aggregation, increase in the bioavailability of IGF-1, cell proliferation, pro-inflammatory effect, and PARP1 activation; in cancer progression – proteolytic activity, degrade physical barriers	11q22-q23	Collagen (I, II, III, VII, VIII, X), casein, entactin, laminin, pro-MMP-1, -2, -9, and serpins
Collagenase-2	MMP-8	The activation of osteoclasts, the enhancement of collagen affinity, β -FGF release, anti-inflammatory activity; in cancer progression – cleavage of α - and β -chemokines and regulation of their mobilization	11q21-q22	Collagen (I–III, V, VII, VIII, X), gelatin, aggrecan, fibronectin
Collagenase-3	MMP-13	In cancer progression- induction of EMT; cell migration	11q22.3	
<i>Gelatinases</i>				
Gelatinase A	MMP-2	The growth of axons, cell migration, the differentiation of mesenchymal cell with inflammation phenotype, enhancement of collagen affinity, cell proliferation, migration of epithelial cells, anti-inflammatory, an increase in the bioavailability of TGF- β , neuronal apoptosis leading to neurodegeneration; in cancer progression – cleavage of IGF-1 binding proteins, proliferation	16q13	Gelatin, collagen (IV–VI, X), elastin, fibronectin
Gelatinase B	MMP-9	Collagen affinity enhancing, pro-inflammatory and anti-inflammatory activity, tumor cell resistance, IL-2 response reduction, hypertrophic chondrocyte apoptosis and the subsequent incorporation of new units of functional osteoblasts; in cancer progression–activation of TGF- β	20q11.2-q13.1	Gelatin, collagens (IV, V, VII, X, XIV), elastin, fibrillin, osteonectin
<i>Stromelysins</i>				
Stromelysin-1	MMP-3	Migration of cells, epithelial cells apoptosis, the formation of epithelial bubbles, epithelial–mesenchymal conversion, angiostatin-like elements generation, the collagen affinity enhancement, release of bFGF, increase in the bioavailability of IGF-1, cell proliferation, pro-inflammatory and anti-inflammatory activity, increase the bioavailability of TGF- β , disorder in cells aggregation, increase in cell invasiveness; in cancer progression–degradation of COL-IV, perlecan; release of VEGF and bFGF, upregulation of angiogenesis	11q23	Laminin, aggrecan, gelatin, fibronectin
Stromelysin-2	MMP-10	In cancer progression–degradation of COL-IV, COL-XVIII, perlecan; generation of tumstatin, endostatin, angiostatin, and endorepellin	11q22.3-q23	Collagens (III–V), gelatin, casein, aggrecan, elastin, MMP-1,8
Stromelysin-3	MMP-11	In cancer progression – release of α 1-proteinase inhibitor, decrease cancer cell sensitivity to NK cells	22q11.2	Fibronectin, laminin, aggrecan, gelatin
Matrilysin	MMP-7	Adipocyte differentiation, collagen affinity enhancement, an increase in the bioavailability of IGF 1 and TGF- β , cell differentiation, abnormal cell aggregation and increase in cells invasiveness, apoptosis induced by Fas receptor activation, the effect of pro-inflammatory activation of osteoclasts, vasoconstriction and cell growth	11q21-q22	Collagen (IV–X), fibronectin, laminin, gelatin, aggrecan, pro-MMP-9
Metalloelastase	MMP-12		11q22.2-q22.3	Elastin, gelatin, collagen I, IV, fibronectin, laminin, vitronectin, proteoglycan
Matrilysin-2	MMP-26		11p15	Gelatin, collagen IV, pro-MMP-9
<i>Membrane-type MMPs (MT-MMP)</i>				
MT-MMP-1	MMP-14	Anti-inflammatory, cell migration, the formation of renal tubules, epithelial cell migration, adhesion reduction, flattening of the cells reduction, trailers embryo to the uterine epithelium	14q11-q12	Collagen (I, II, III), gelatin, fibronectin, laminin aggrecan, tenascin
MT-MMP-2	MMP-15	Adhesion and cell flatterling reduction	15q13-q21	Fibronectin, laminin, aggrecan, perlecan
MT-MMP-3	MMP-16	Adhesion and cell flatterling reduction	8q21	Collagen III, gelatin, casein
MT-MMP-4	MMP-17		12q24.3	Fibrinogen, TNF precursor
MT-MMP-5	MMP-24		20q11.2	Proteoglycans

Uniones célula-matriz a través de las integrinas



Integrinas

Ca²⁺ and Mg²⁺



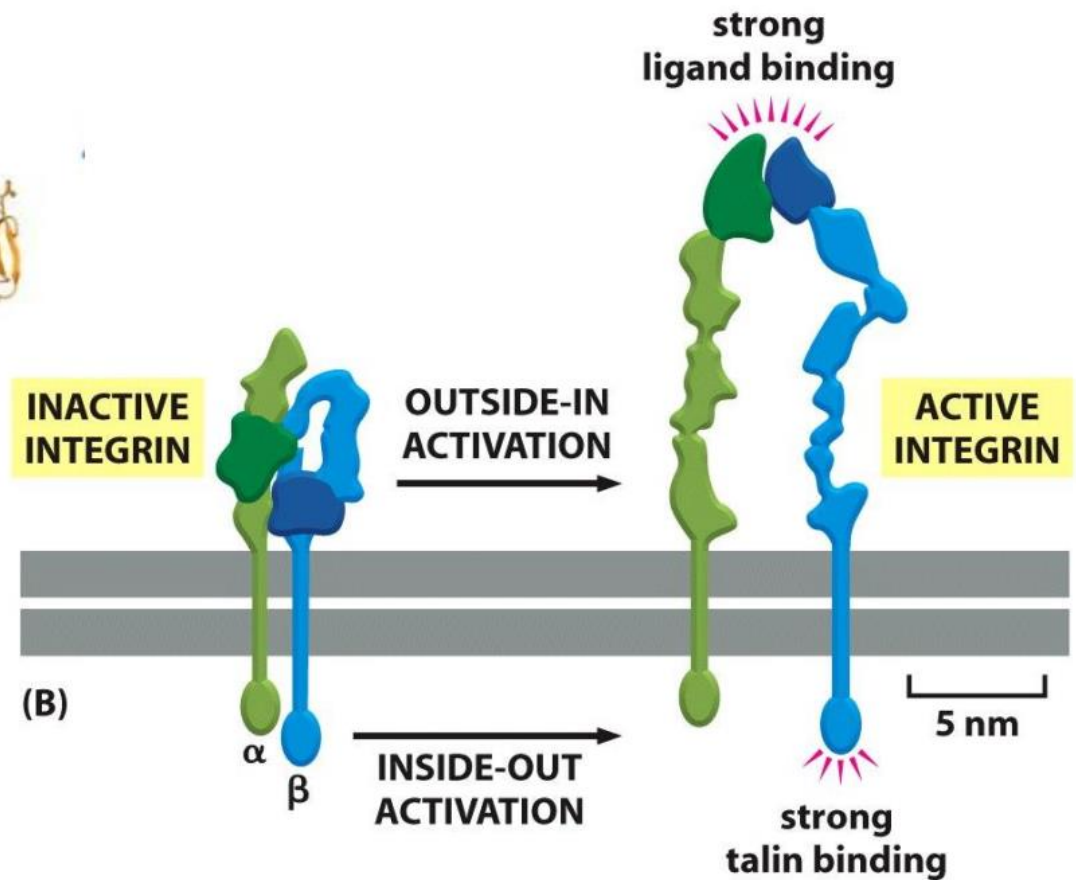
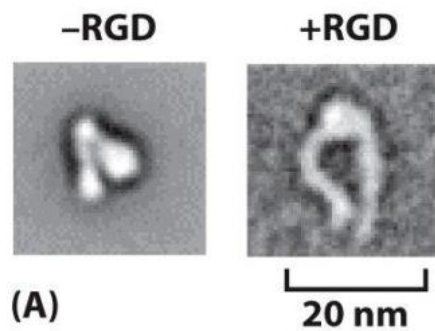
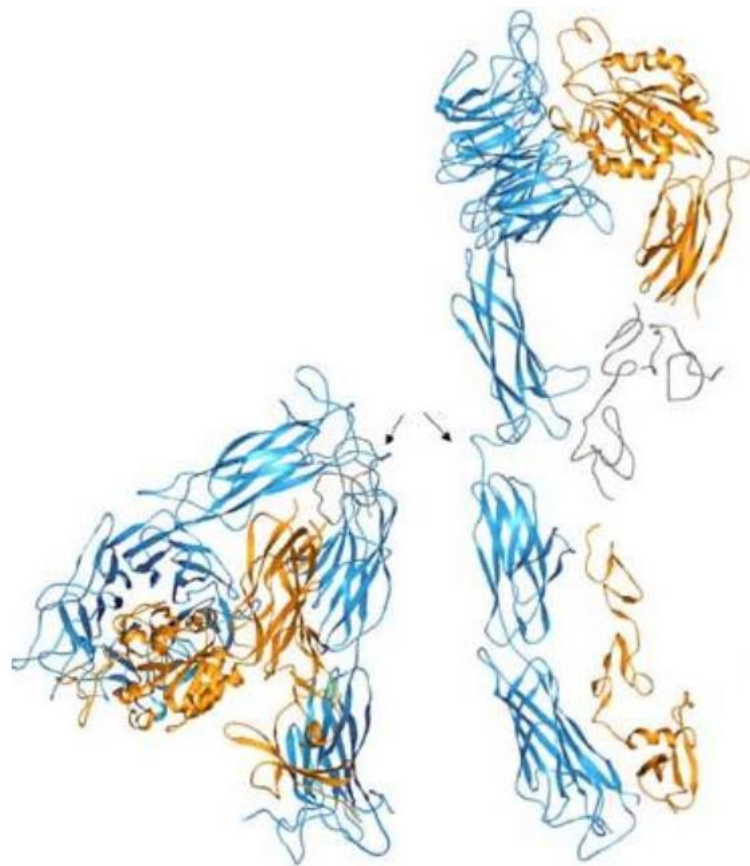
24 tipos de integrinas, formadas por combinaciones de 8 β y 18 α.

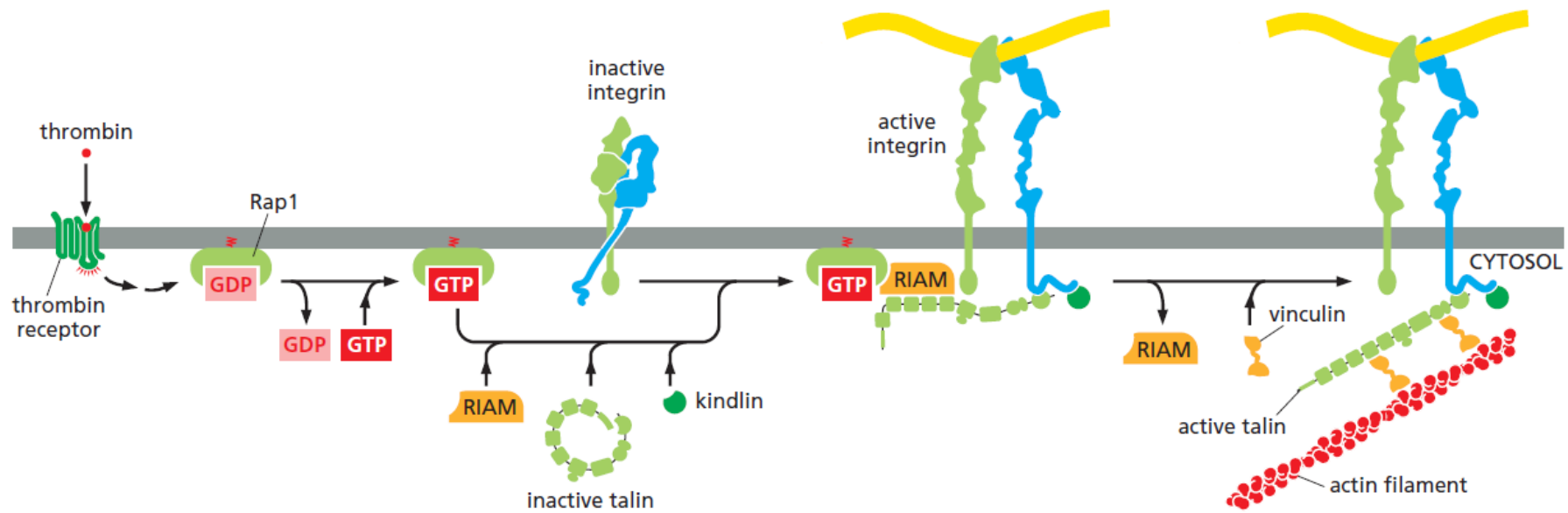
TABLE 19–3 Some Types of Integrins

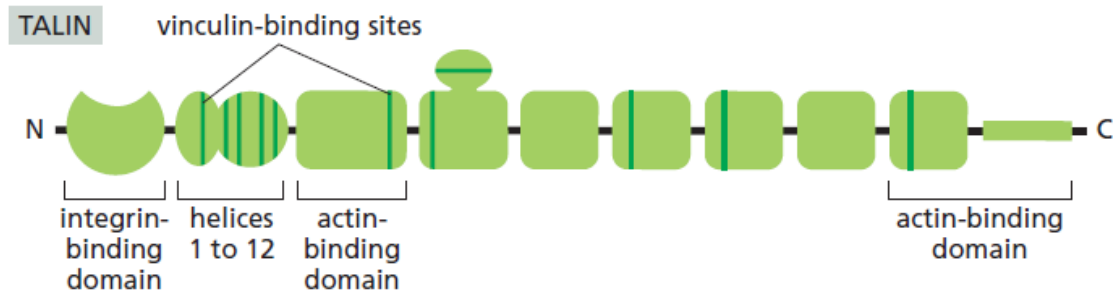
Integrin	Ligand*	Distribution	Phenotype when α subunit is mutated	Phenotype when β subunit is mutated
$\alpha_5\beta_1$	Fibronectin	Ubiquitous	Death of embryo; defects in blood vessels, somites, neural crest	Early death of embryo (at implantation)
$\alpha_6\beta_1$	Laminin	Ubiquitous	Severe skin blistering; defects in other epithelia also	Early death of embryo (at implantation)
$\alpha_7\beta_1$	Laminin	Muscle	Muscular dystrophy; defective myotendinous junctions	Early death of embryo (at implantation)
$\alpha_L\beta_2$ (LFA1)	Ig superfamily counterreceptors (ICAM1)	White blood cells	Impaired recruitment of leucocytes	Leukocyte adhesion deficiency (LAD); impaired inflammatory responses; recurrent life-threatening infections
$\alpha_{IIb}\beta_3$	Fibrinogen	Platelets	Bleeding; no platelet aggregation (Glanzmann's disease)	Bleeding; no platelet aggregation (Glanzmann's disease); mild osteopetrosis
$\alpha_6\beta_4$	Laminin	Hemidesmosomes in epithelia	Severe skin blistering; defects in other epithelia also	Severe skin blistering; defects in other epithelia also

*Not all ligands are listed.

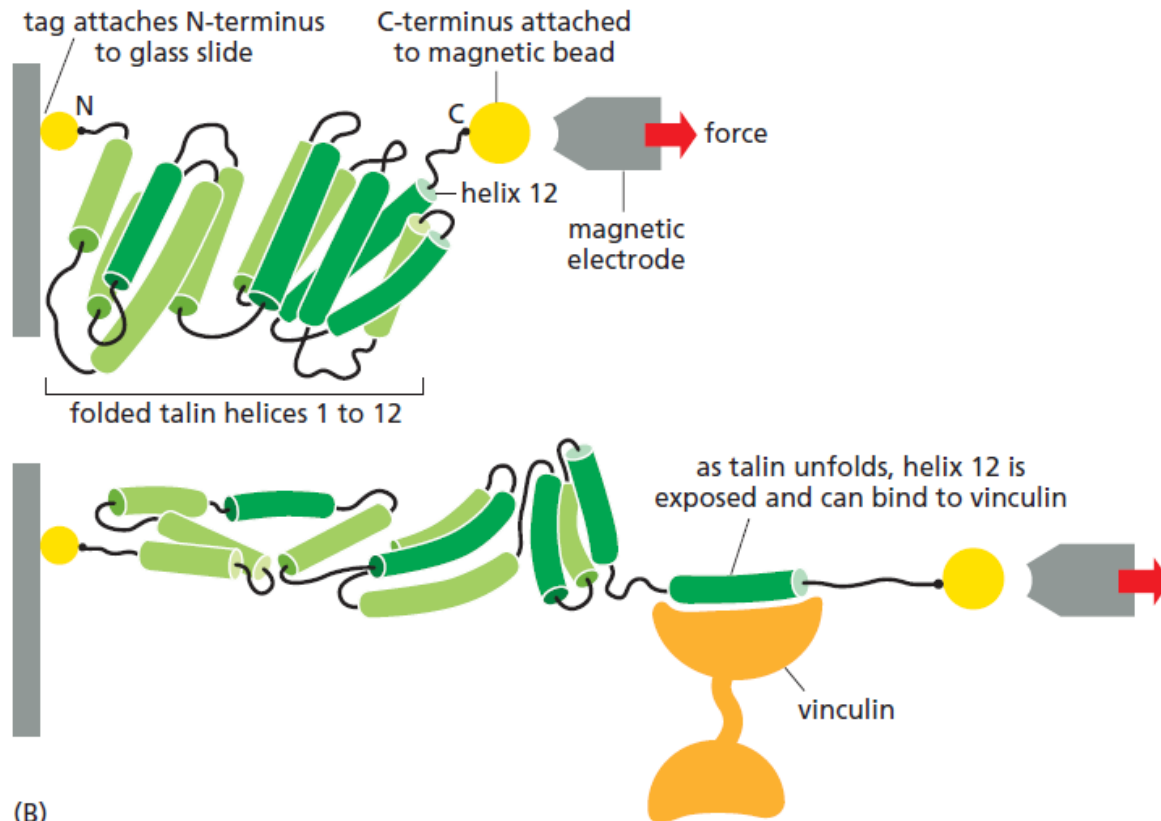
Integrinas





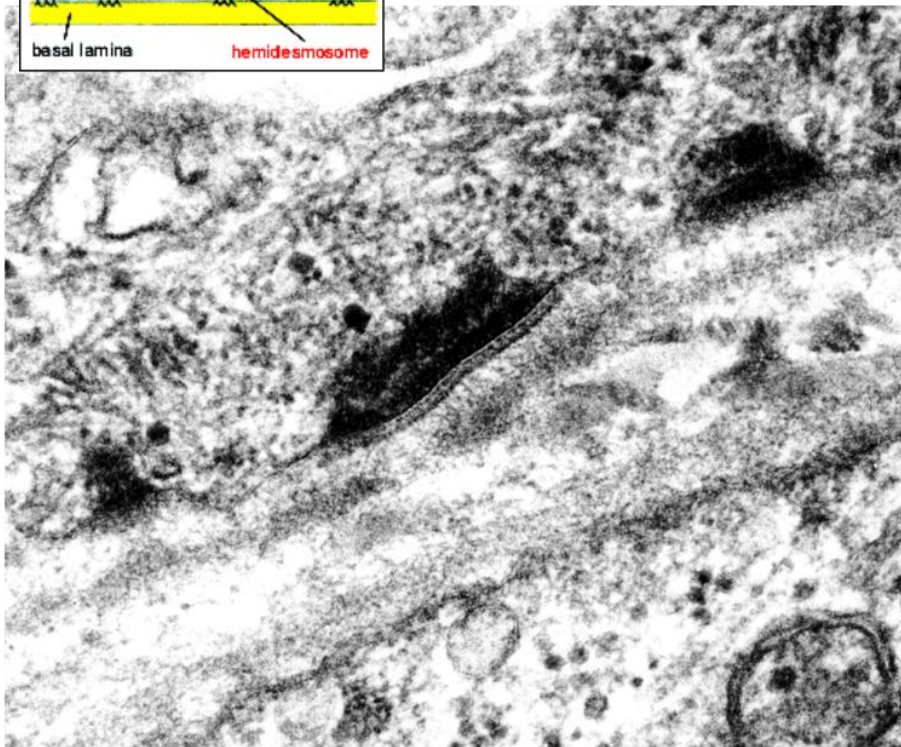
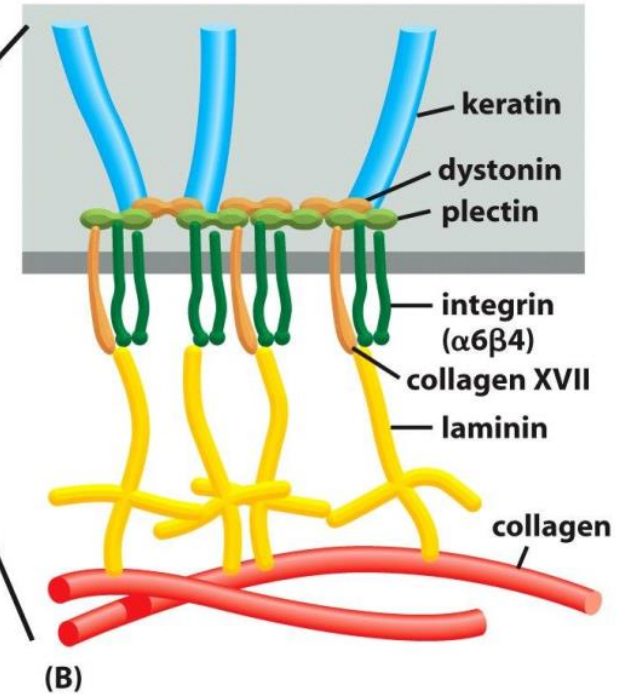
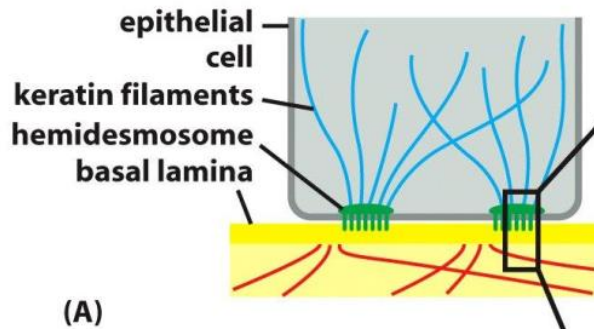
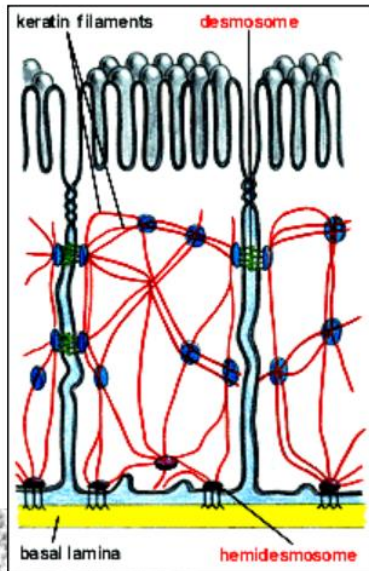


(A)



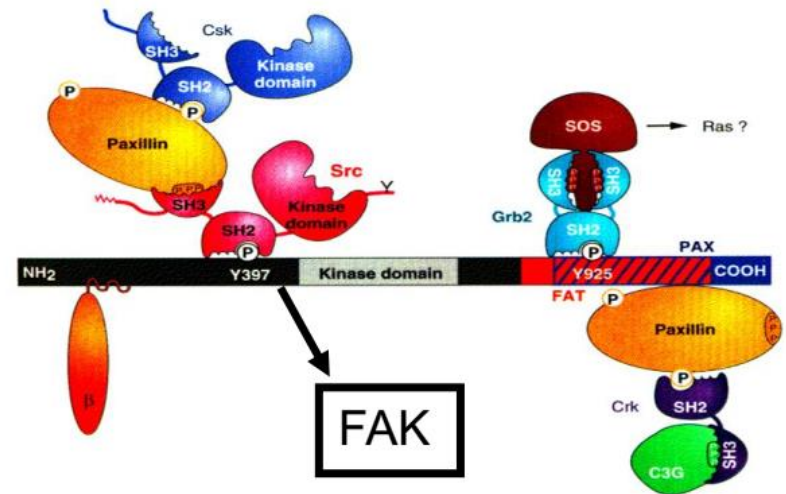
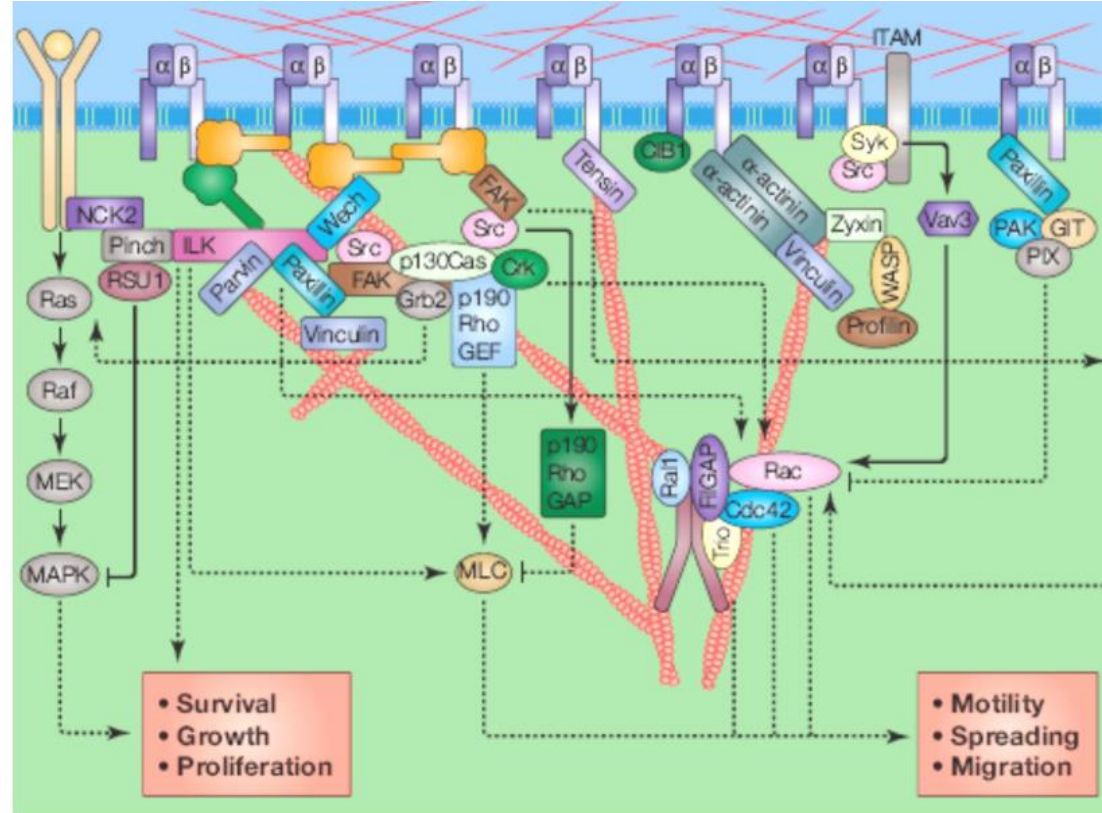
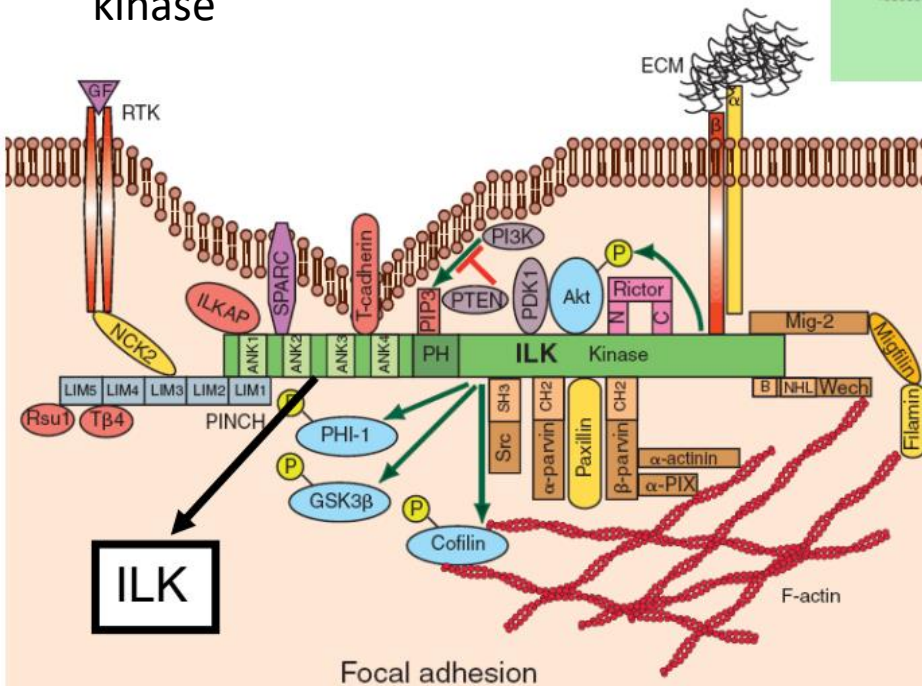
(B)

Hemidesmosoma



Integrinas y señalización intracelular

ILK: Integrin-linked kinase



proteína quinasa de las adhesiones focales

Muchas gracias por su atención