(Sejt-sejt kölcsönhatások, extracelluláris mátrix és integrinek az embrióban)

Epitheliális morfogenezis: a lamina basalis szerepe a sejtmigrációban és a hám-lefűződésben

Semmelweis Egyetem, ÁOK, Anatómiai, Szövet- és Fejlődéstani Intézet
Dr. Kocsis Katalin
2019.10.30.

Hámok
Sejt-sejt kapcsoló struktúrák

During embryogenezis, simple epithelial sheets are converted into functional three-dimensional tissues and organs.

Epithelial architecture:

Epithelia form the covering of all body surfaces with specialized function.

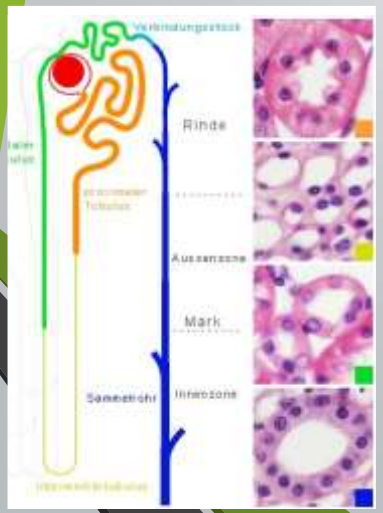
- filtration – kidney tubules absorption – intestine - secretion – exocrine glands

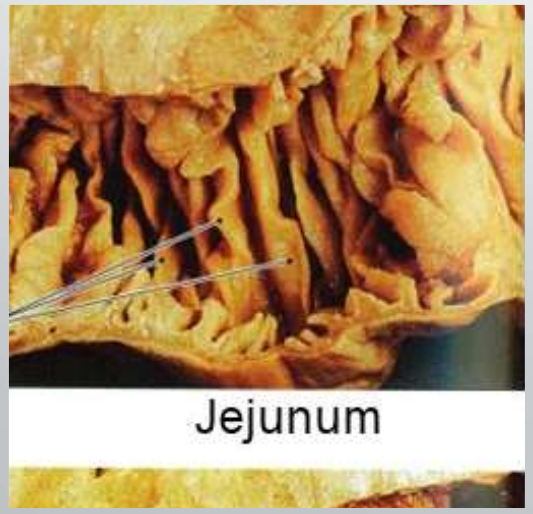
Az egy rétegű hámból, hogyan alakul ki a 3 dimenziós, funkcióval rendelkező szövet?

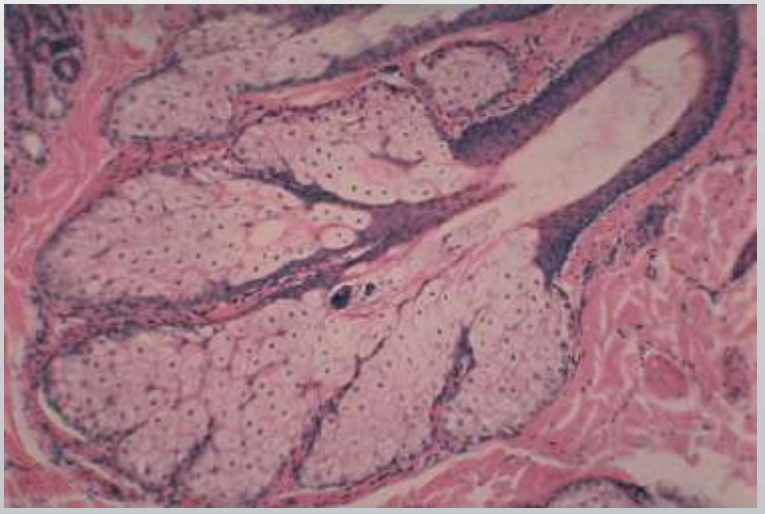
Hámszövet:

szorosan egymás mellett elhelyezkedő sejtekből áll, amelyeket sejtkapcsoló struktúrák kapcsolnak össze.

A test külső és belső felszínén mindenhol, specializálódott funkcióval ellátott szövettípus: - filtráció – vese - abszorpció – bélhám - szekréció – exokrin mirigyek

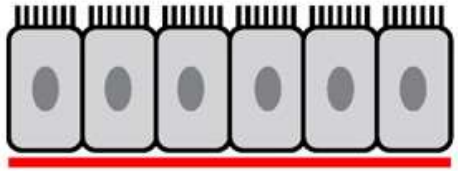




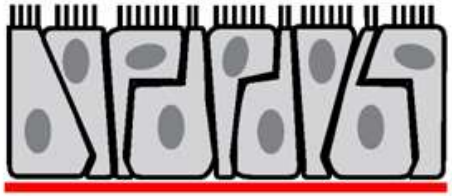


B

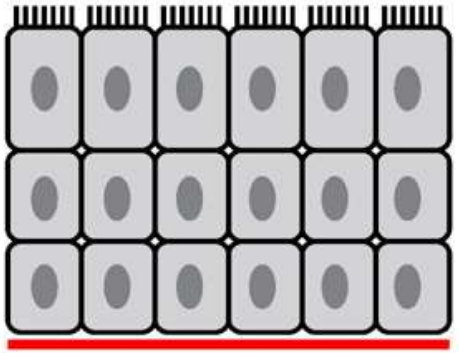
Simple Epithelium
(e.g. large intestine)



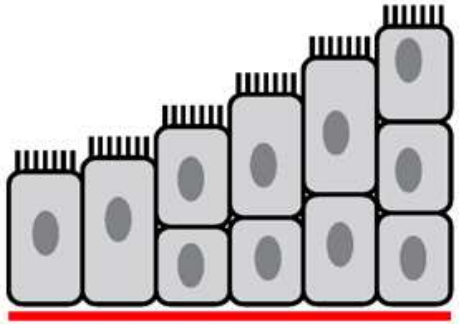
Pseudo-stratified Epithelium
(e.g. epididymis)



Stratified Epithelium
(e.g. conjunctiva)

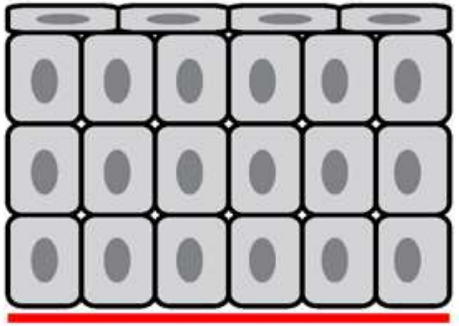


Transitional Epithelium
(e.g. urethra)



Squamous Epithelium
(e.g. lung alveolus)

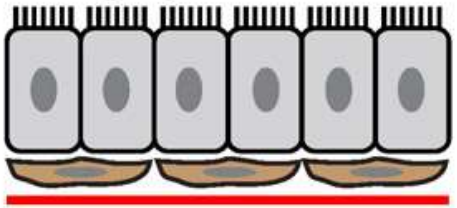
Squamous Stratified Epithelium
(e.g. skin)



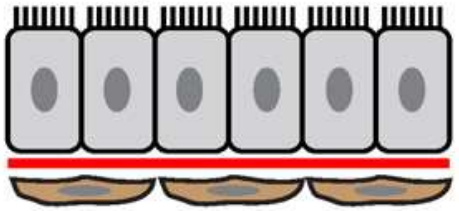
C

Basally located cell, positive
for some muscle genes,
e.g. alpha smooth muscle actin

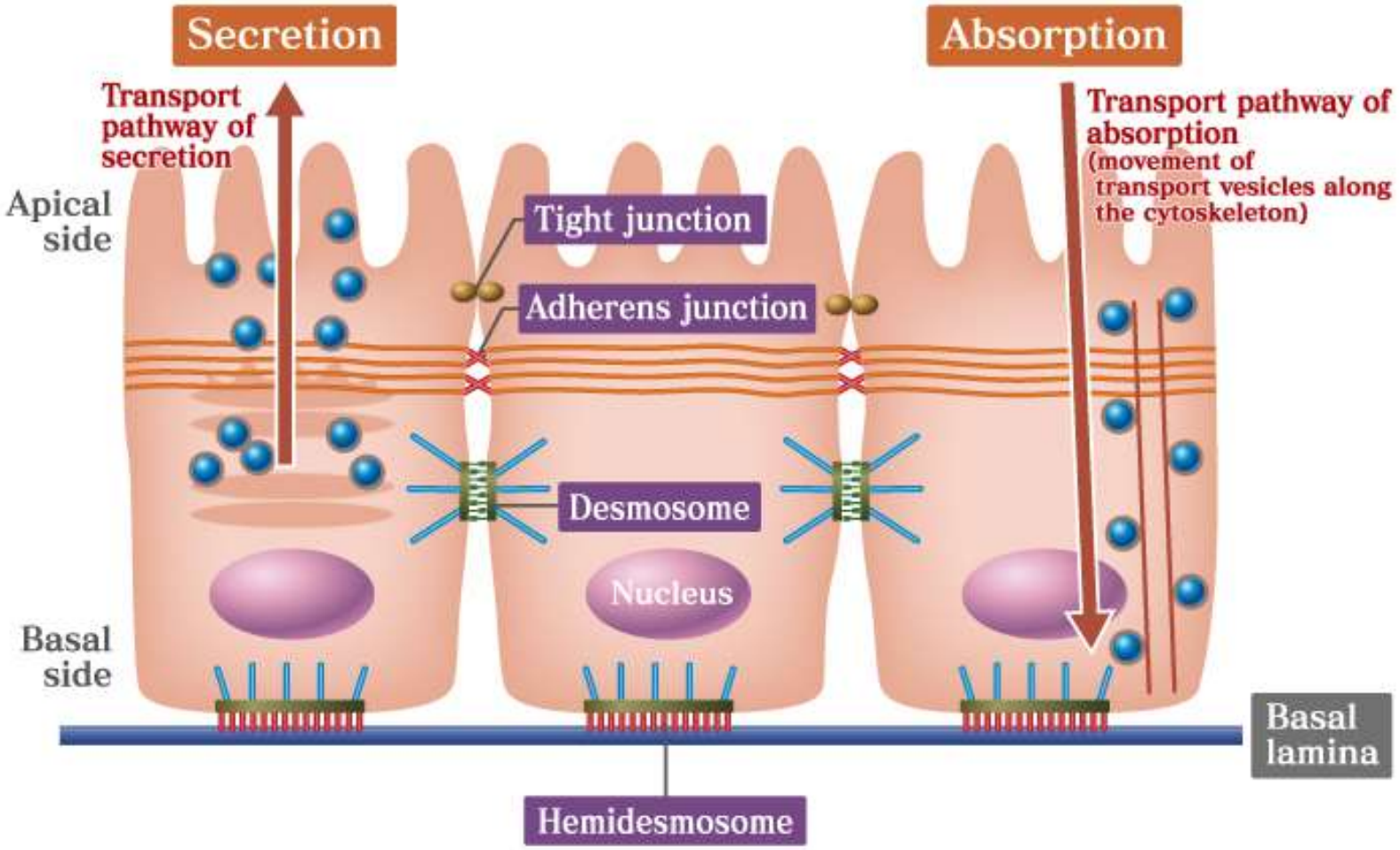
Myoepithelial Cells



Myofibroblasts

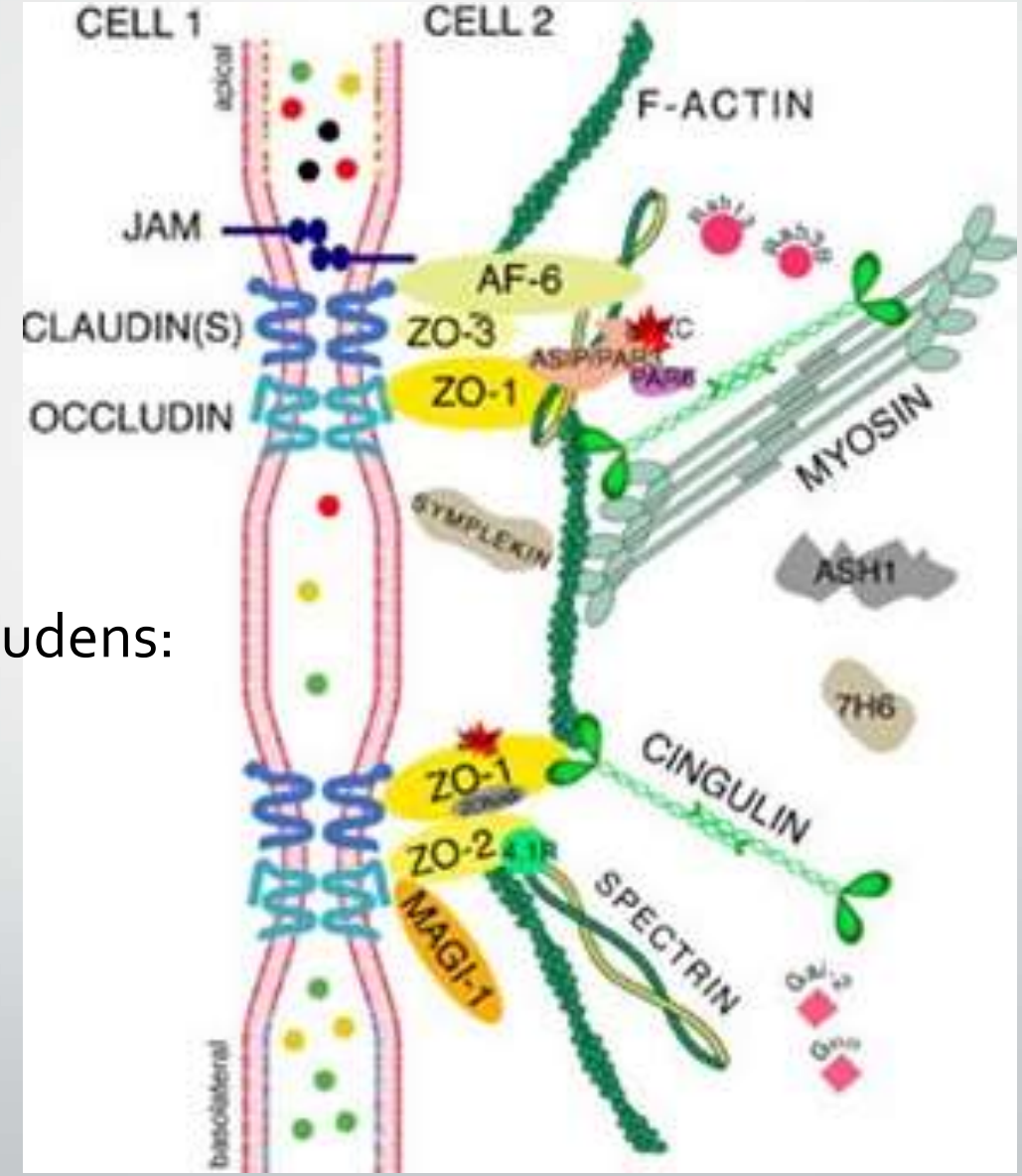


Polarity of the cell and cell-cell contacts
Sejtek polaritása, sejtkapcsoló struktúrák

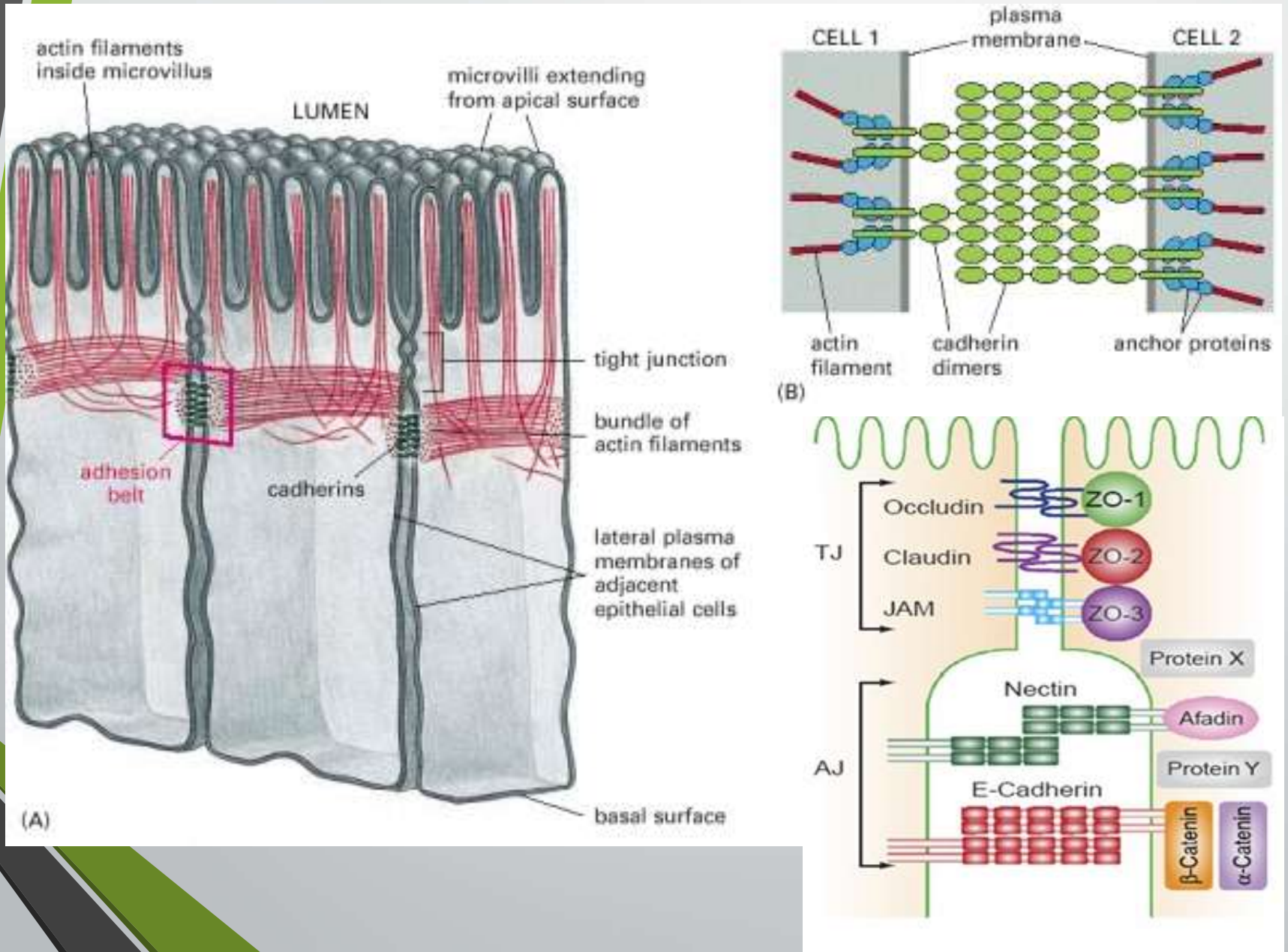


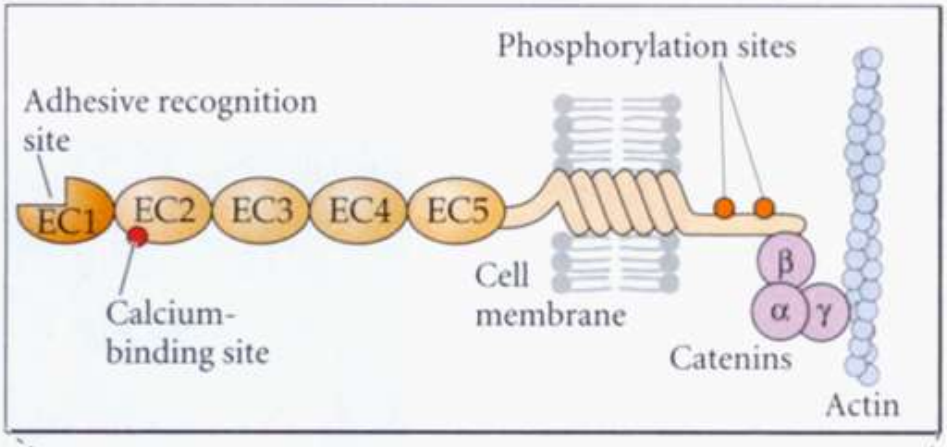
©CSLS / The University of Tokyo

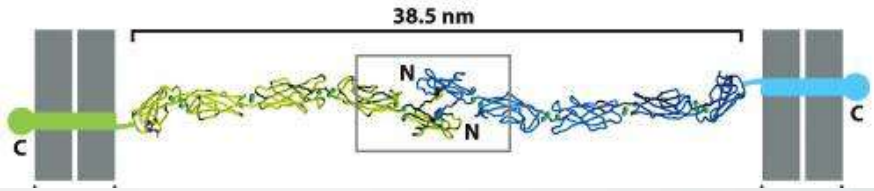
Tight junction/Zonula occludens:

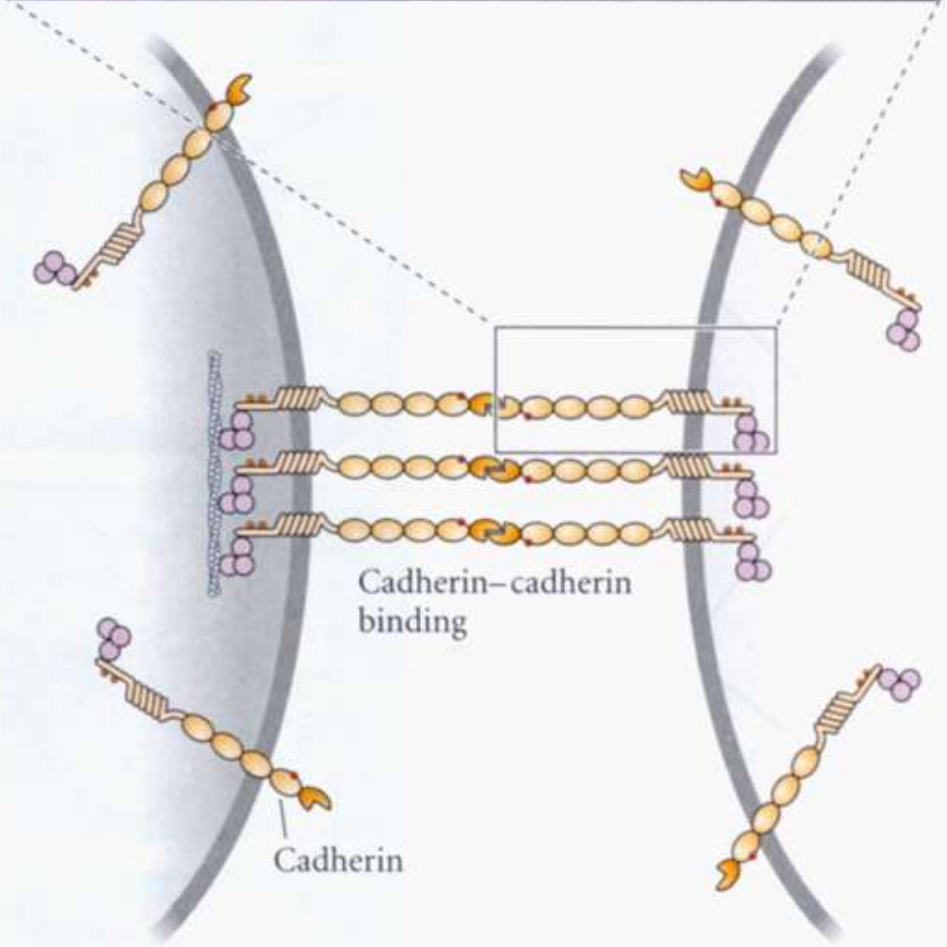


Zonula adherens: MECHANIKAI KAPCSOLAT







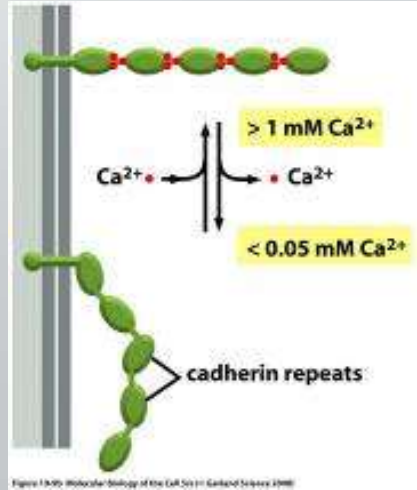


Cadherinek közvetítette sejtadhézió:

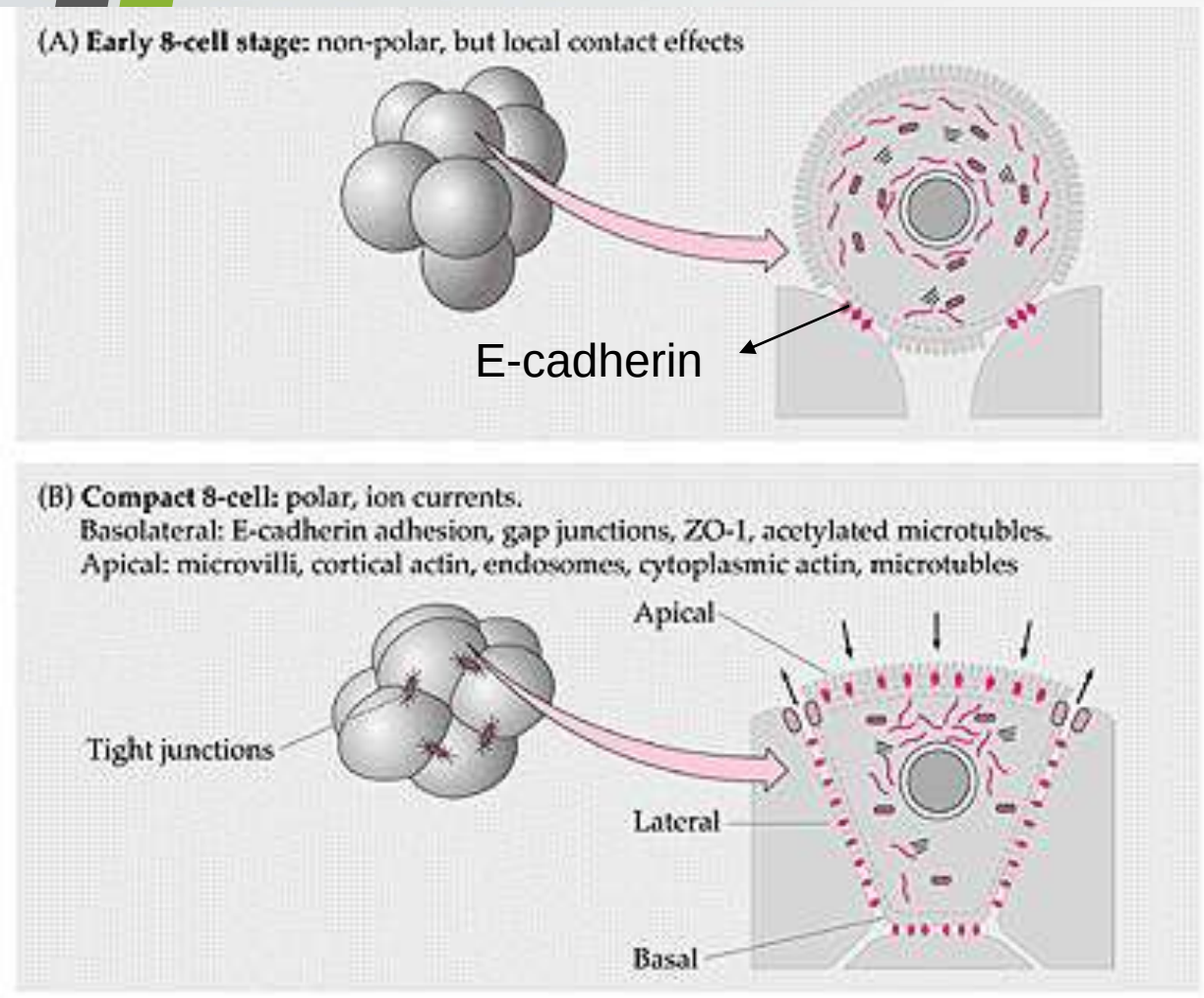
CADHERIN

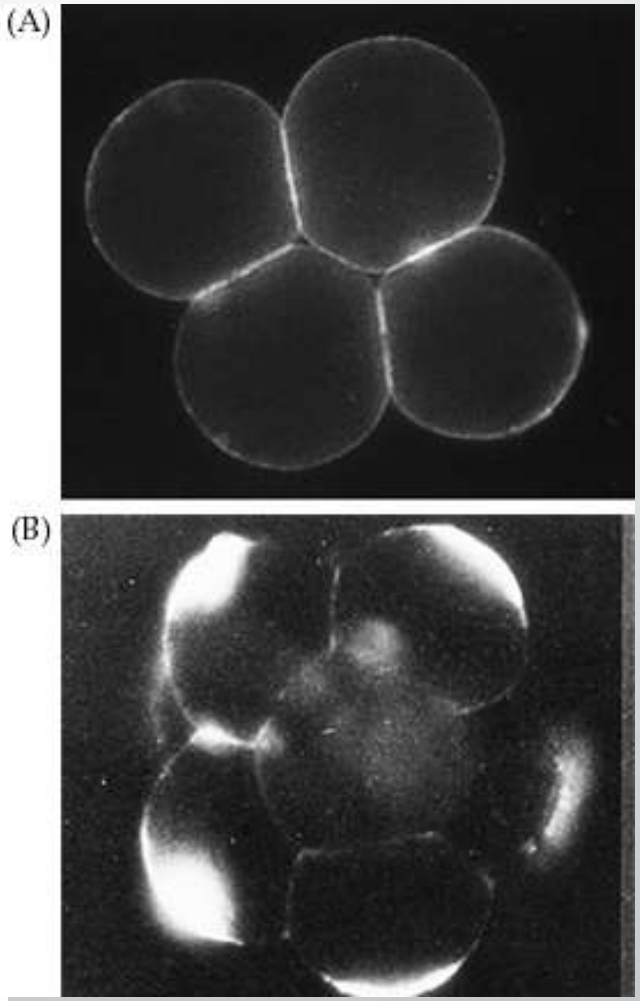
Ca - dependens

sejtadhézió

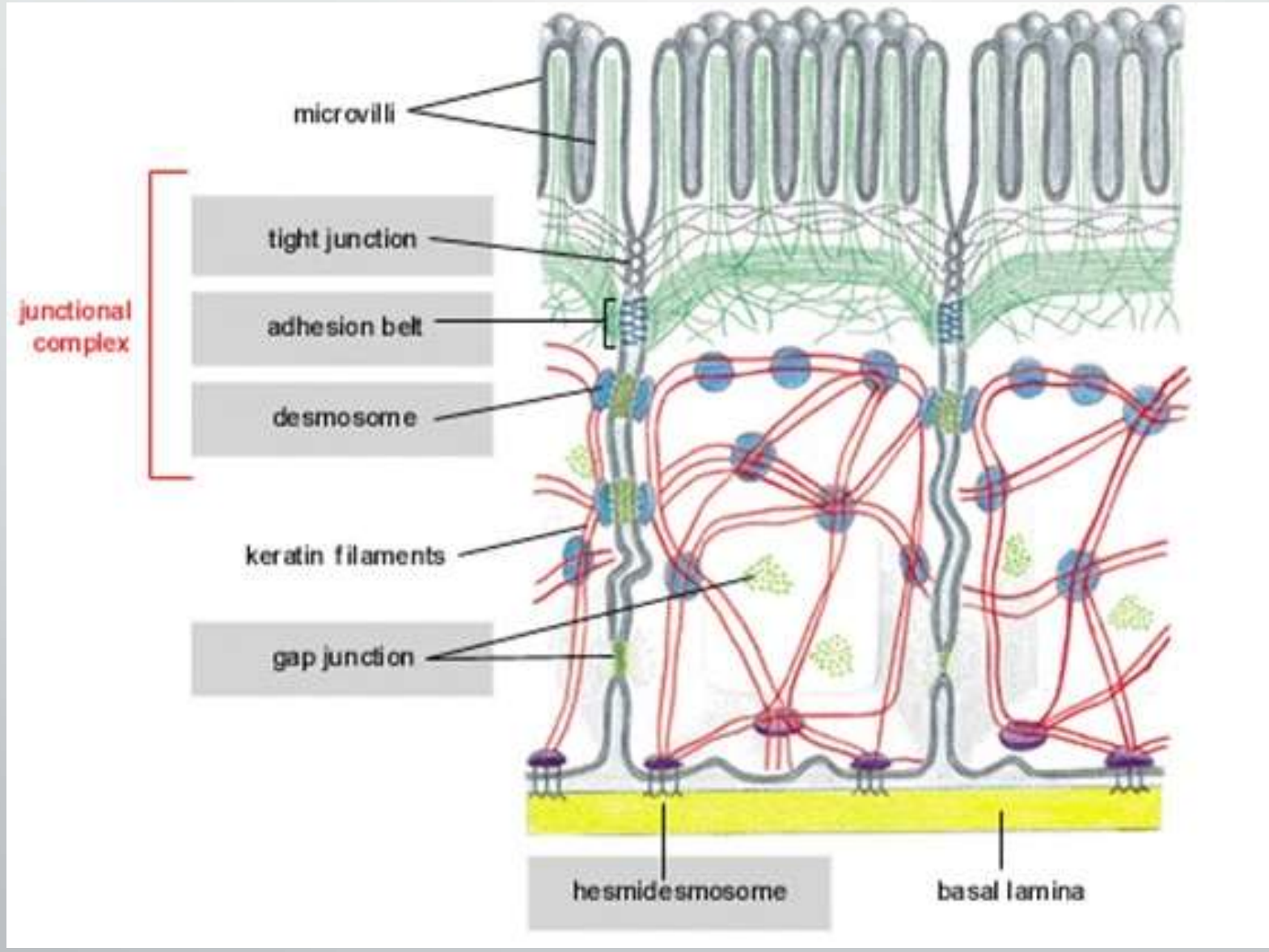


A kompaktizáció - E-cadherin expressio fontossága

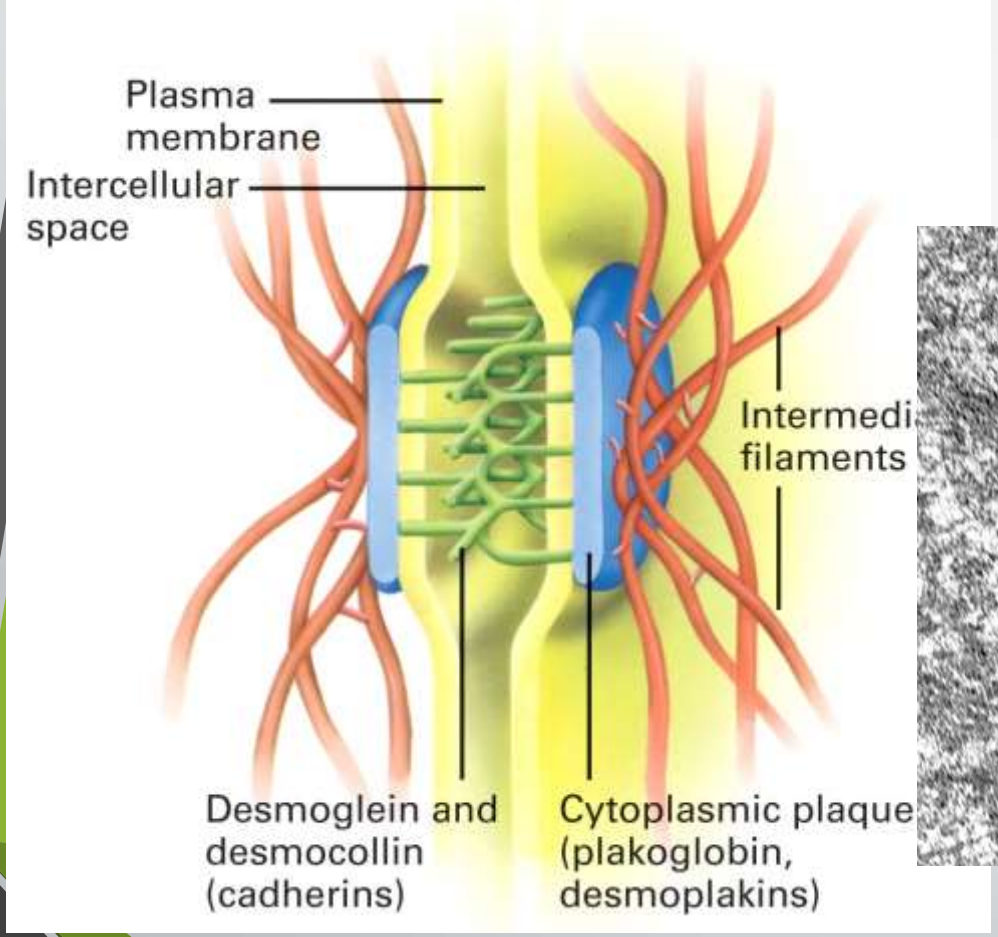


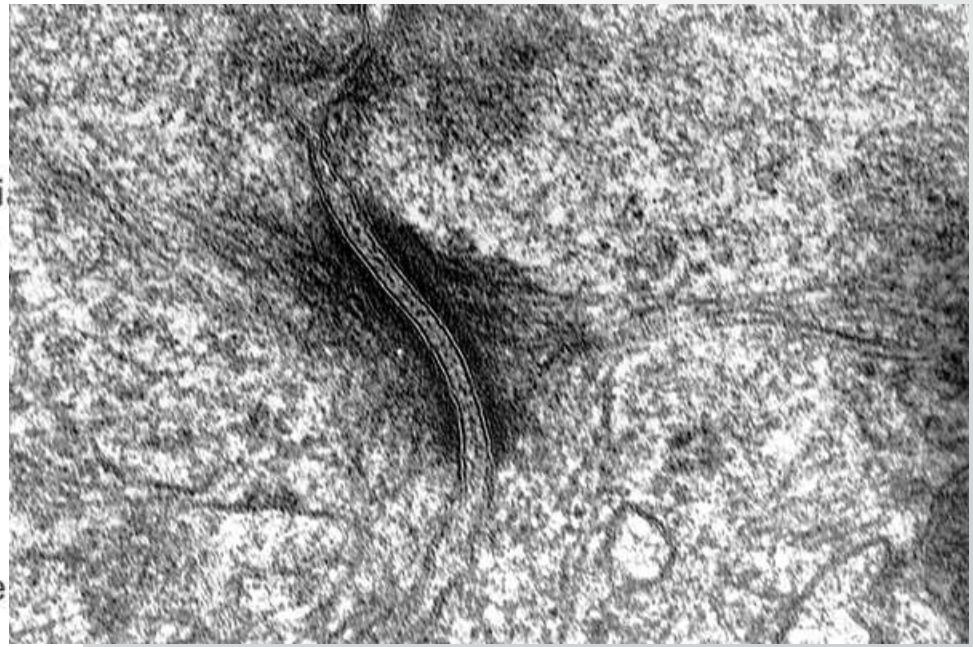


E-kadherin=uvomorulin: 54,000 D sejtadhéziós molekula


microvilli
junctional complex
tight junction
adhesion belt
desmosome
keratin filaments
gap junction
hesmidesmosome
basal lamina

Desmosoma: erős mechanikai kapcsolat



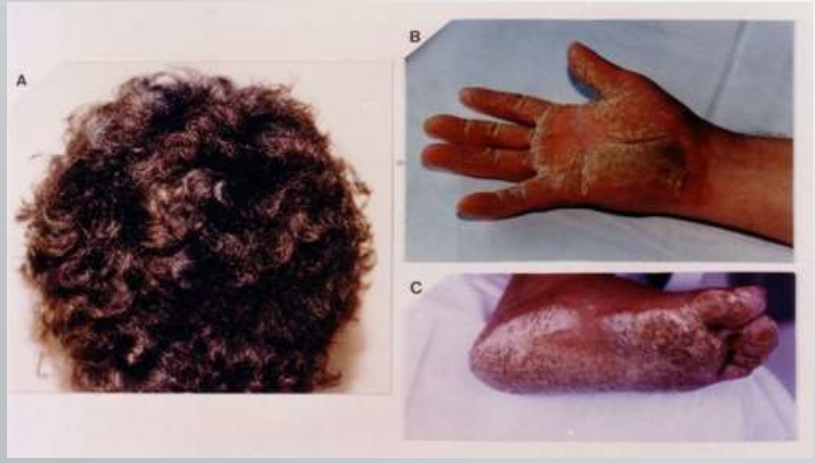


Desmosomális rendellenességek

Naxos-szindróma

-gyapjas haj
-palmoplantar keratoma
-kardiomyopathia

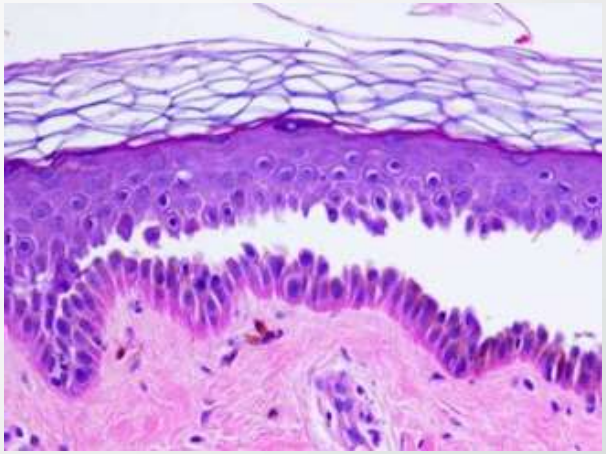
(desmoglobin, plakoglobin mutáció)

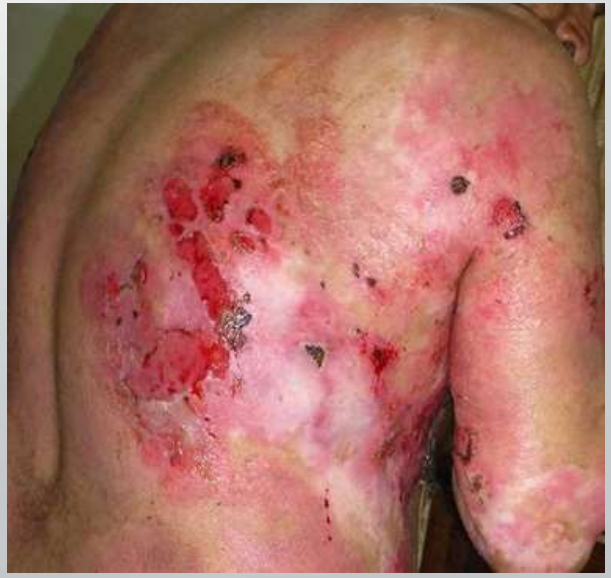


http://commons.wikimedia.org/wiki/Image:Naxos_disease.jpg

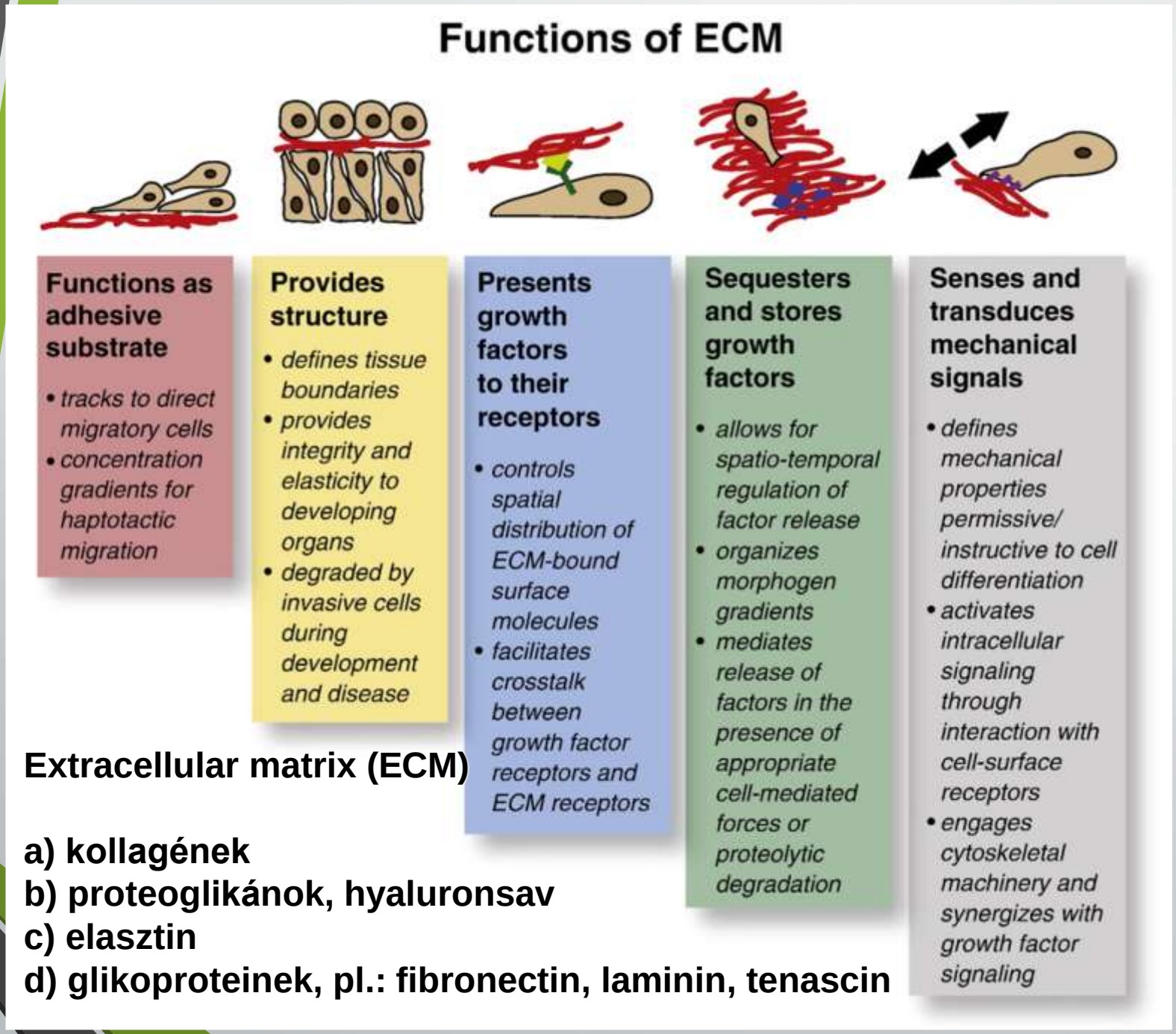
Pemphigus vulgaris

Desmoglein1
Desmoglein3





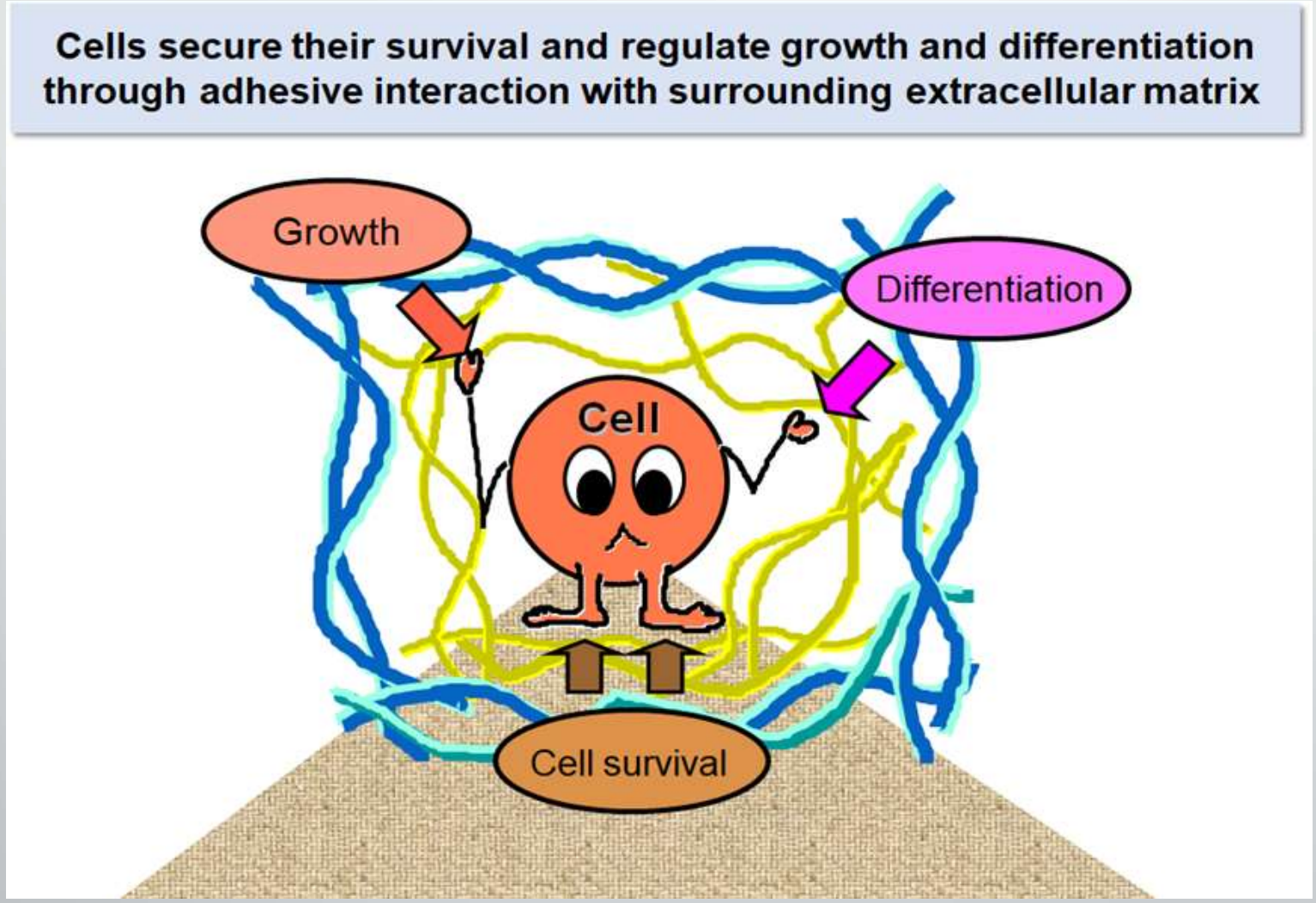
ECM



Extracellular matrix (ECM)

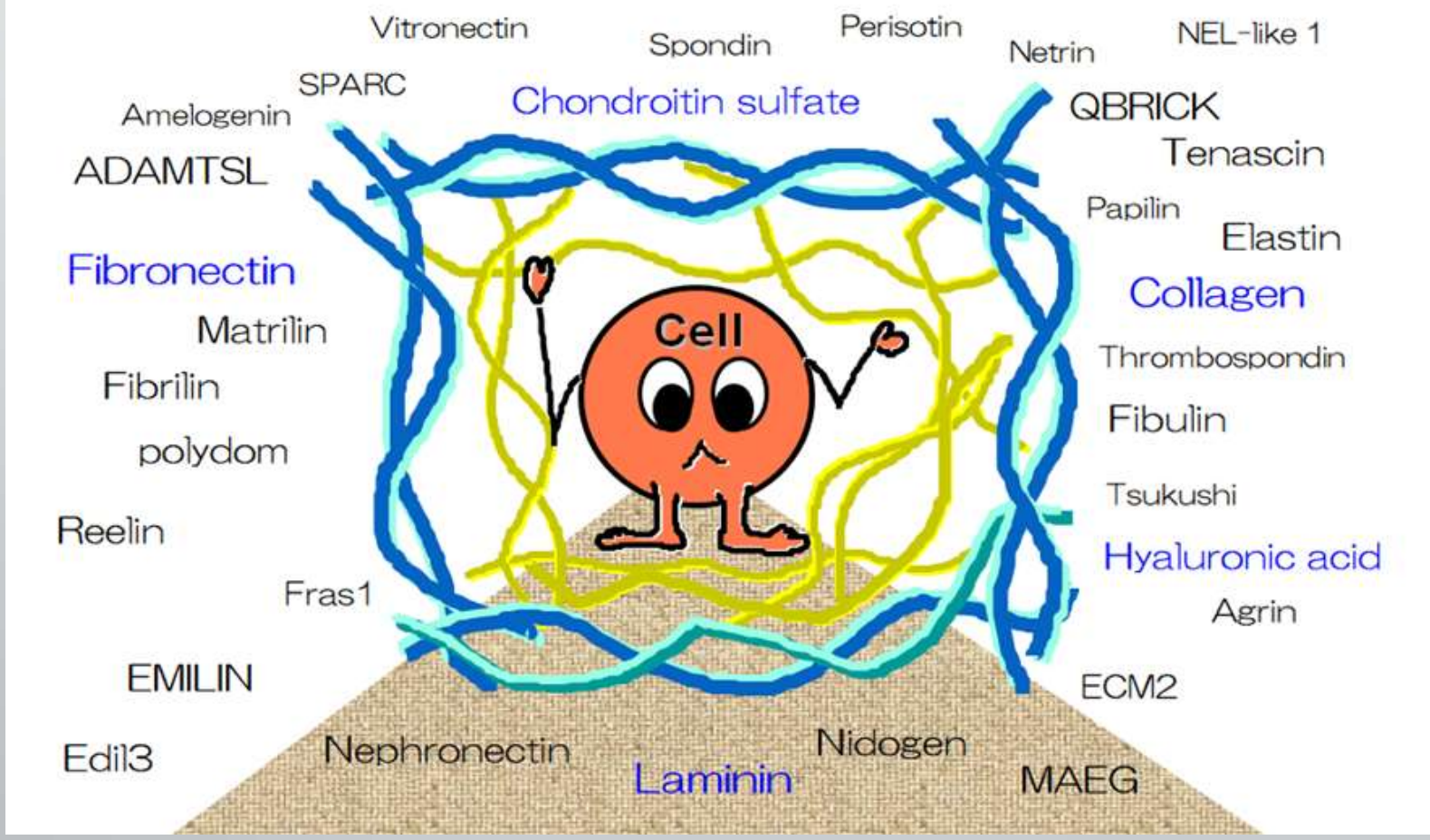
a) kollagének
b) proteoglikánok, hyaluronsav
c) elasztin
d) glikoproteinek, pl.: fibronectin, laminin, tenascin

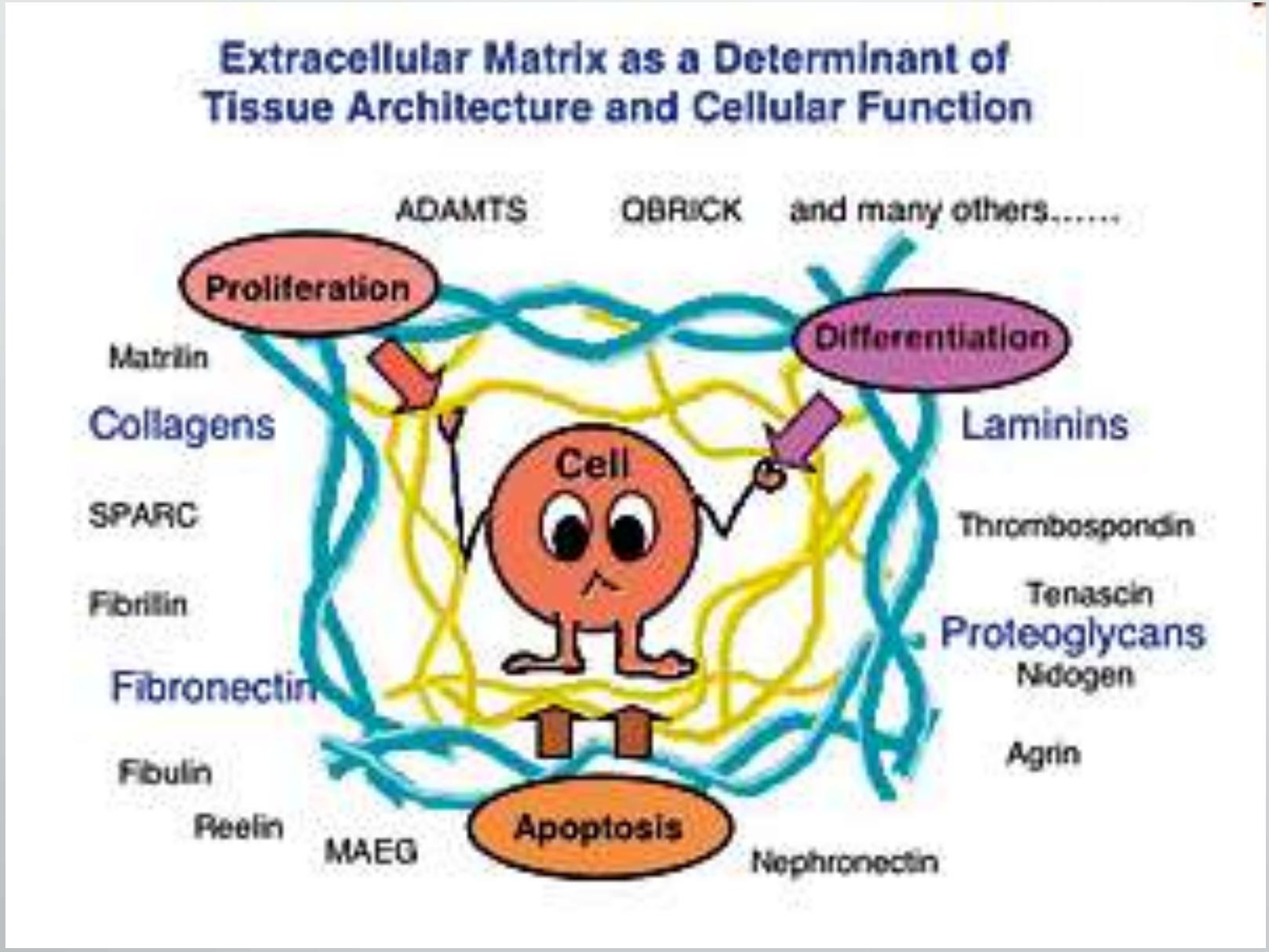
Cells secure their survival and regulate growth and differentiation through adhesive interaction with surrounding extracellular matrix



http://www.matrixome.co.jp/en/about/sekiguchi

Molecular complexity of the extracellular matrix:
There are more than 300 proteins localized in the extracellular matrix




Extracellular Matrix as a Determinant of Tissue Architecture and Cellular Function
ADAMTS
QBRICK
and many others.....
Proliferation
Differentiation
Matrilin
Collagens
SPARC
Fibrillin
Fibronectin
Fibulin
Reelin
MAEG
Cell
Apoptosis
Laminins
Thrombospondin
Tenascin
Proteoglycans
Nidogen
Agrin
Nephronectin

Examples of positive and negative regulation of differentiation by ECM proteins in vitro

Matrix component	Cell type	Reference
POSITIVE		
Laminin	epithelial conversion of kidney mesenchyme	Klein et al., 1988
	neurite outgrowth	Sanes, 1989
	albumin synthesis by hepatocytes	Caron 1990
	milk protein production by mammary epithelial cells	Streuli et al., 1991
	tubule formation by endothelial cells	Kubota et al., 1988 Grant et al., 1989
	process formation by osteoblasts	Vukicevic et al., 1990
	myoblast fusion	von der Mark and Öcalan, 1989
Thrombospondin	neurite outgrowth	Neugebauer et al., 1991 O'Shea et al., 1991
Fibronectin	erythroblast differentiation	Patel and Lodish, 1987
Collagens	mammary epithelial morphogenesis	Hall et al., 1982 Lee et al., 1985
	colonic epithelial morphogenesis	Pignatelli and Bodmer, 1988
	tubule formation by endothelial cells	Montesano et al., 1983
Vitronectin	neurite outgrowth	Neugebauer et al., 1991
Tenascin	neurite outgrowth	Chiquet, 1989
	chondrocyte differentiation	Mackie et al., 1987
NEGATIVE		
Fibronectin	myoblast fusion	Podleski et al., 1979 von der Mark and Öcalan, 1989
	keratinocyte terminal differentiation	Adams and Watt, 1989
	chondrocyte differentiation	West et al., 1979
	adipocyte differentiation	Spiegelman and Ginty, 1983

Factors Influencing the Migration of Crest Cells

Permissive molecules

dissociation of lamina basalis of neural tube: plasminogene activator

ECM components: laminin, fibronectin, tenascin, collagene typ. IV

Cell adhesion molecules: (cadherin)

Growth factors: Mash1, endothelin-3, neurogenin, GDNF.

Inhibitory molecules

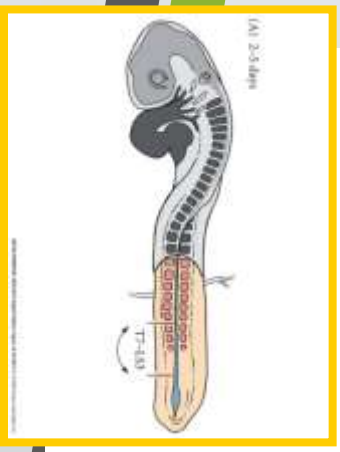
F-spondin (thrombospondin)

ECM components: chondroitin-sulphate, aggrecan, versican, collagen type IX.

Ephrin-proteins (Ephrin B2 and B1)

on Eph receptors

Neural crest cell migration in the trunk



Thrombospondin is expressed in the anterior section of sclerotomes, and cooperates with fibronectin and laminin to promote NC migration

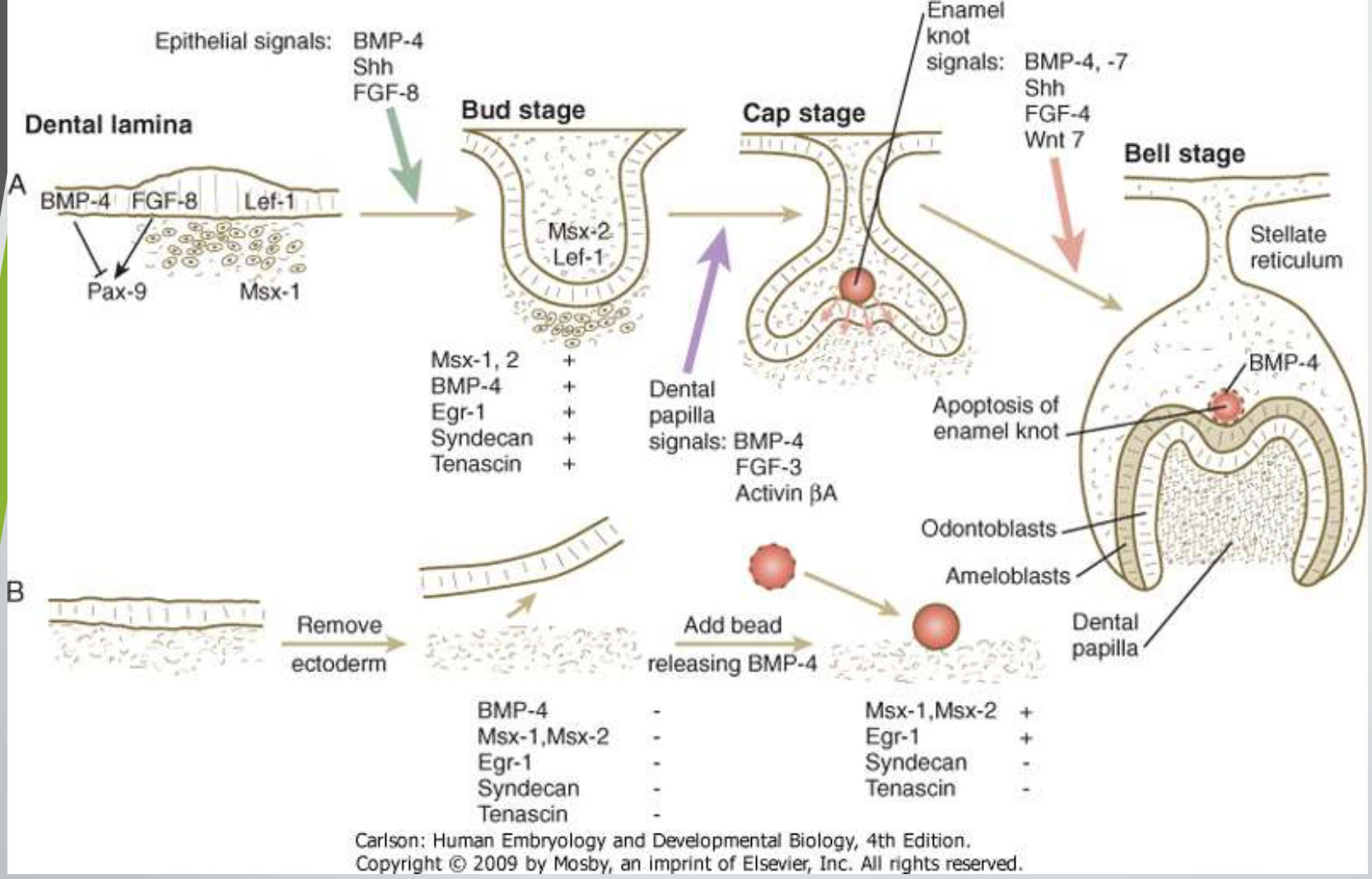
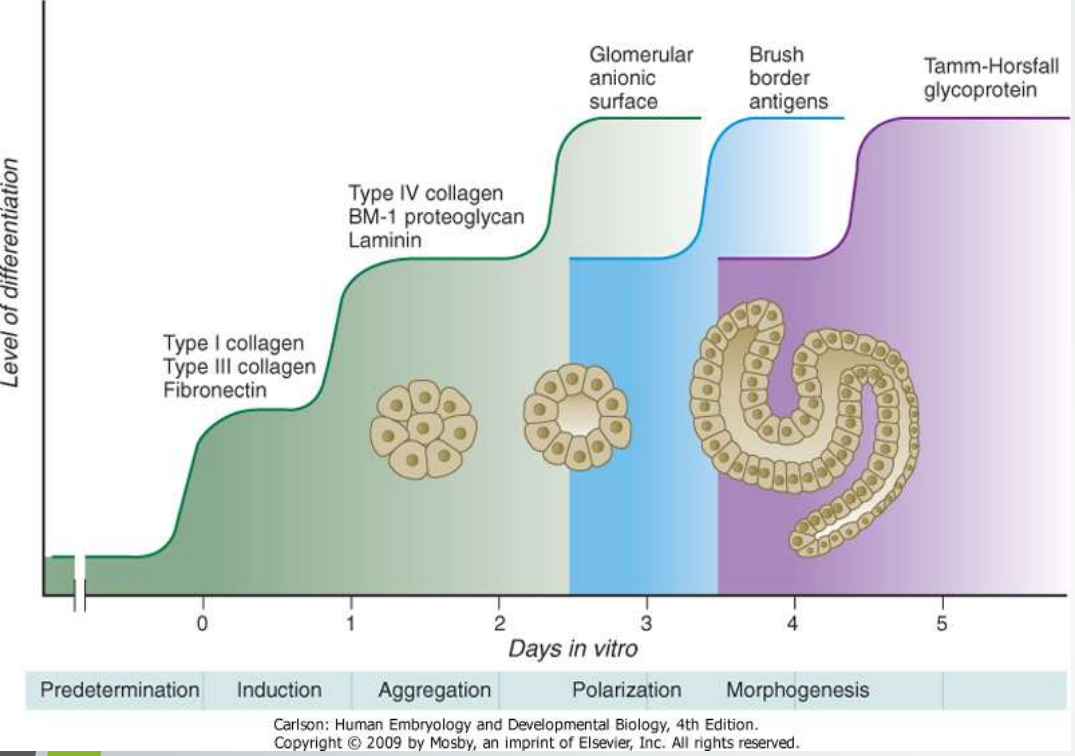


Figure 14-17 A, Inductive interactions during tooth development. Molecules associated with the *green arrow* represent components of the signal from dental lamina ectoderm to underlying neural crest mesenchyme; molecules associated with the *violet arrow* are signals from the dental papilla to the overlying ectoderm; molecules associated with the *pink arrow* are signals from the enamel knot to dental papilla. B, In vitro experiment showing that a bead releasing BMP-4 can induce dental mesenchyme to express specific markers (Msx-1, Msx-2, and Egr-1).



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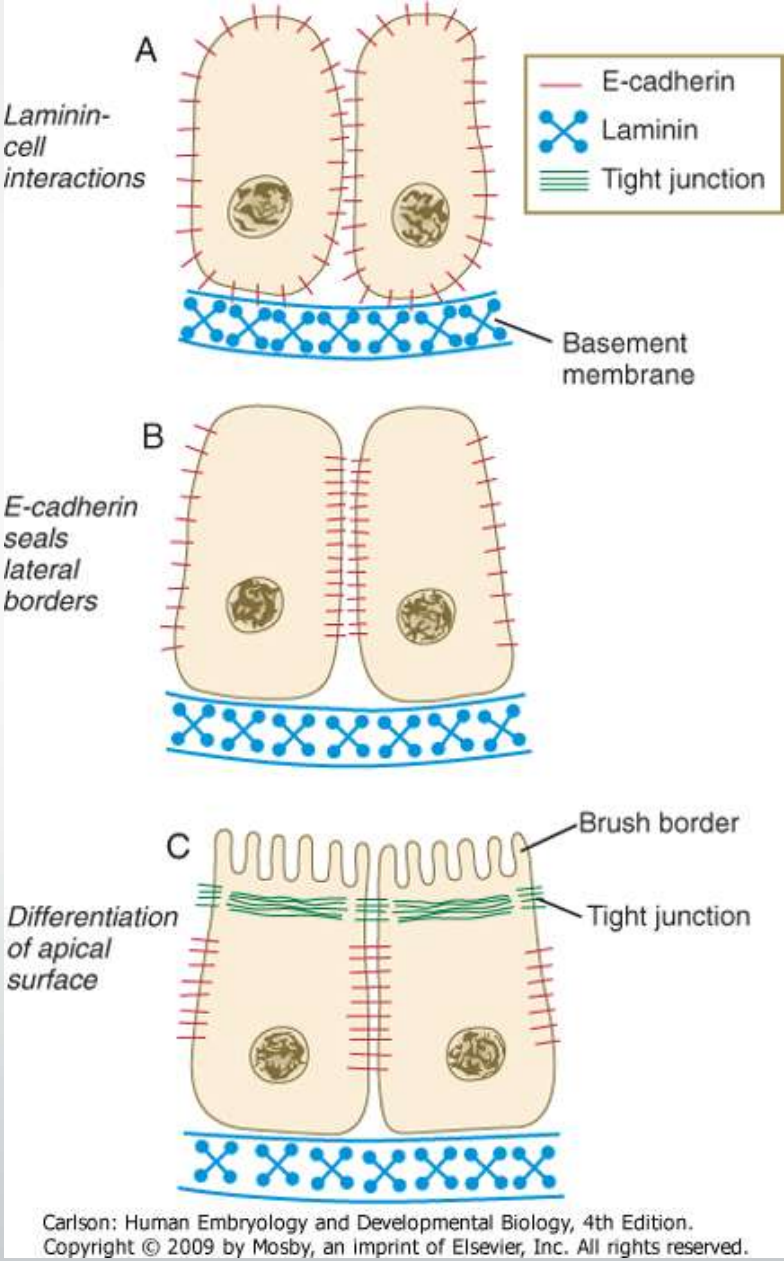

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Nephron fejlődése során expresszálódó molekulák (szövettenyészet)

Molecules expressed during the development of the nephron

Proximalis kanyarulatos csatorna falának fejlődése

Proximal convoluted tubule: development of the wall

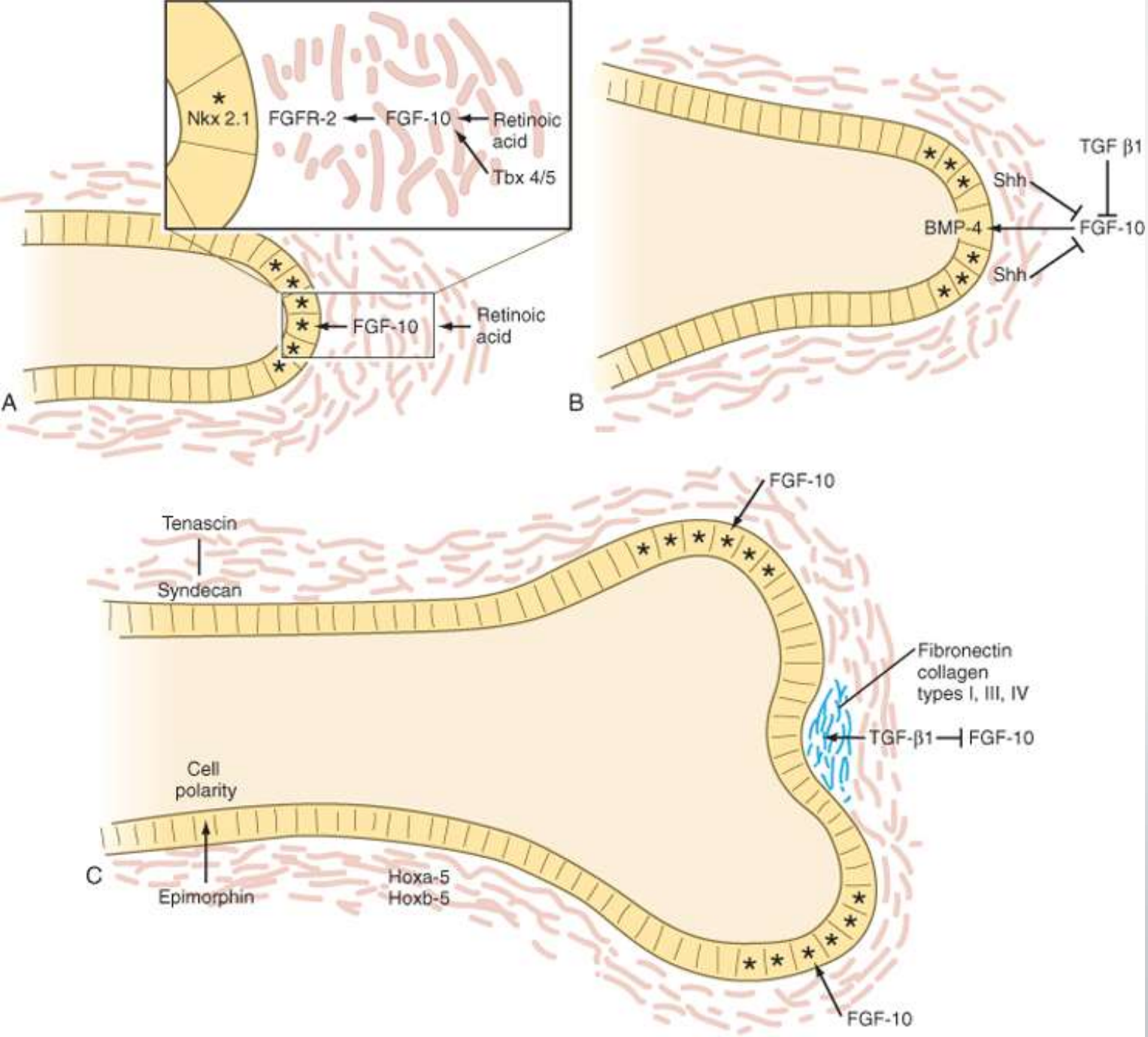

Figure 15-26 Molecular aspects of outgrowth and branching of the respiratory tree. A, The tip of an elongating respiratory duct. FGF-10 secretion in the mesenchyme stimulates the growth of the tip of the epithelial duct toward it. B, The prelude to branching. Inhibition of FGF-10 signaling at the tip of the duct leads to stabilization of that area. C, Cleft formation.

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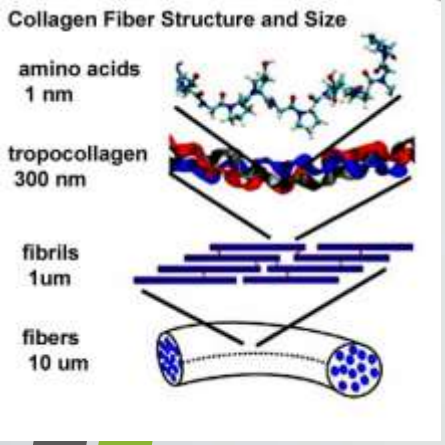
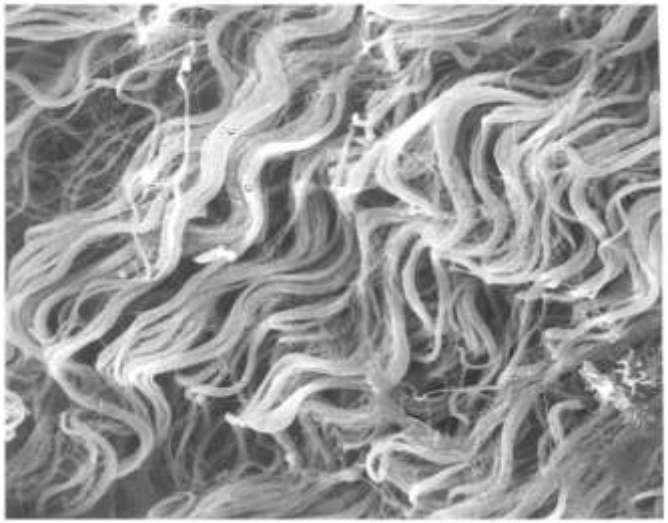
	Type	Molecular Formula	Polymerized Form	Tissue Distribution
FIBRIL-FORMING (FIBRILLAR)	I	$[\alpha1(I)]_2\alpha2(I)$	fibril	bone, skin, tendon, ligaments, cornea, intern organs (accounts for 90% of body collagen)
	II	$[\alpha1(II)]_3$	fibril	cartilage, intervertebral disc, notochord, vitreous humor of the eye
	III	$[\alpha1(III)]_3$	fibril	skin, blood vessels, internal organs
	V	$[\alpha1(V)]_2\alpha2(V)$	fibril (with type I)	as for type I
	XI	$\alpha1(XI)\alpha2(XI)\alpha3(XI)$	fibril (with type II)	as for type II
FIBRIL-ASSOCIATED	IX	$\alpha1(IX)\alpha2(IX)\alpha3(IX)$ with type II fibrils	lateral association	cartilage
	XII	$[\alpha1(XII)]_3$ with some type I fibrils	lateral association	tendon, ligaments, some other tissues
NETWORK-FORMING	IV	$[\alpha1(IV)_2\alpha2(IV)$	sheetlike network	basal laminae
	VII	$[\alpha1(VII)]_3$	anchoring fibrils	beneath stratified squamous epithelia

Kollagének

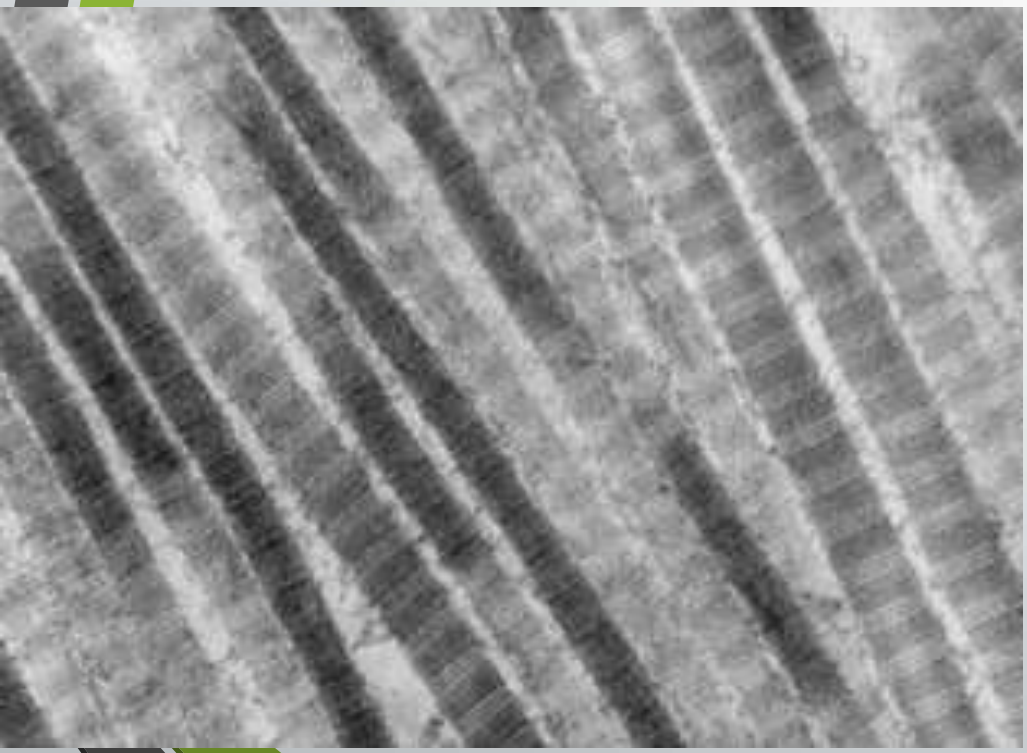
Type	Notes	Gene(s)
I	This is the most abundant collagen of the human body. It is present in scar tissue, the end product when tissue heals by repair. It is found in tendons, skin, artery walls, the endomysium of myofibrils, fibrocartilage, and the organic part of bones and teeth.	COL1A1, COL1A2
II	Hyaline cartilage, makes up 50% of all cartilage protein. Vitreous humour of the eye.	COL2A1
III	This is the collagen of granulation tissue, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized. Reticular fiber. Also found in artery walls, skin, intestines and the uterus	COL3A1
IV	basal lamina; eye lens. Also serves as part of the filtration system in capillaries and the glomeruli of nephron in the kidney.	COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6
V	most interstitial tissue, assoc. with type I, associated with placenta	COL5A1, COL5A2, COL5A3
VI	most interstitial tissue, assoc. with type I	COL6A1, COL6A2, COL6A3
VII	forms anchoring fibrils in dermal epidermal junctions	COL7A1
VIII	some endothelial cells	COL8A1, COL8A2
IX	FACIT collagen, cartilage, assoc. with type II and XI fibrils	COL9A1, COL9A2, COL9A3
X	hypertrophic and mineralizing cartilage	COL10A1
XI	cartilage	COL11A1, COL11A2
XII	FACIT collagen, interacts with type I containing fibrils, decorin and glycosaminoglycans	COL12A1
XIII	transmembrane collagen, interacts with integrin a1b1, fibronectin and components of basement membranes like nidogen and perlecan.	COL13A1
XIV	FACIT collagen	COL14A1
XV	-	COL15A1
XVI	-	COL16A1
XVII	transmembrane collagen, also known as BP180, a 180 kDa protein	COL17A1
XVIII	source of endostatin	COL18A1
XIX	FACIT collagen	COL19A1
XX	-	COL20A1
XXI	FACIT collagen	COL21A1
XXII	-	COL22A1
XXIII	MACIT collagen -	COL23A1
XXIV	-	COL24A1
XXV	-	COL25A1
XXVI	-	EMID2
XXVII	-	COL27A1
XXVIII	-	COL28A1
XXIX	epidermal collagen	COL29A1

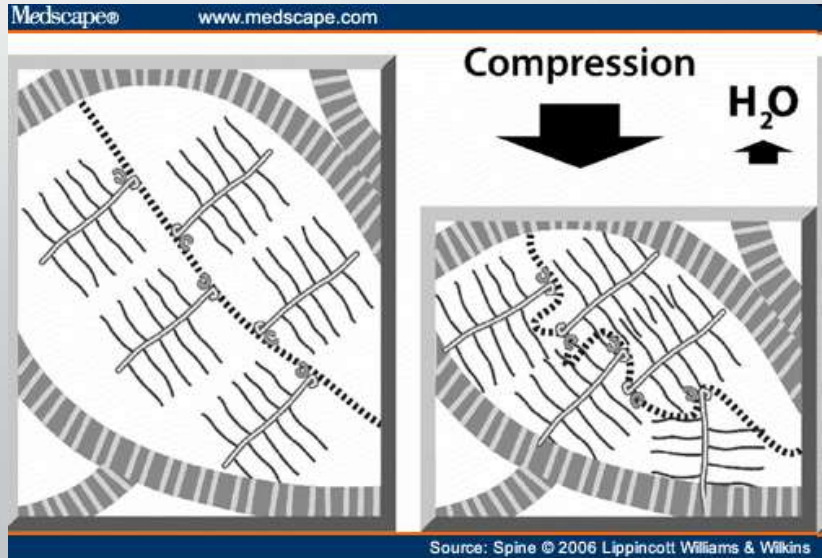
Kollagének





Artist: Julian Voss-Andreae
Sculpture shown: "Unraveling Collagen", 2005, stainless steel, height: 11'3' (3.40 m).
Location: Orange Memorial Park Sculpture Garden, City of South San Francisco, CA. Right panel shows the top.





Kollagének

Table 19–3 Some Common Proteoglycans

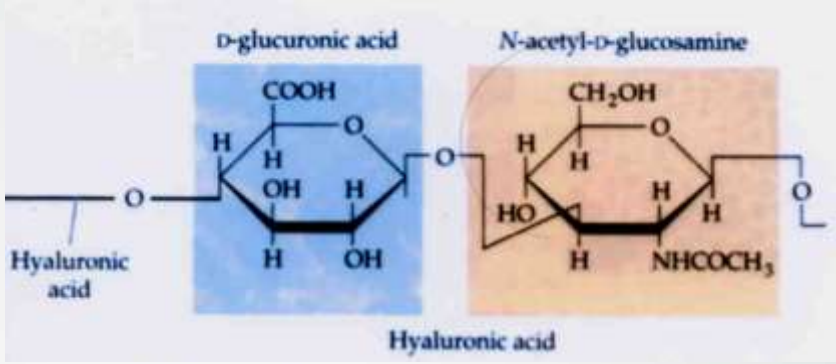
Proteoglycan	Approximate Molecular Weight of Core Protein	Type of GAG Chains	Number of GAG Chains	Location	Functions
Aggrecan	210,000	chondroitin sulfate + keratan sulfate	~130	cartilage	mechanical support; form large aggregates with hyal
Betaglycan	36,000	chondroitin sulfate/ dermatan sulfate	1	cell surface and matrix	binds TGF-β
Decorin	40,000	chondroitin sulfate/ dermatan sulfate	1	widespread in connective tissues	binds to type I collagen fibr and TGF-β
Perlecan	600,000	heparan sulfate	2–15	basal laminae	structural and filtering func in basal lamina
Serglycin	20,000	chondroitin sulfate/ dermatan sulfate	10–15	secretory vesicles in white blood cells	helps to package and store secretory molecules
Syndecan-1	32,000	chondroitin sulfate + heparan sulfate	1–3	fibroblast and epithelial cell	cell adhesion; binds FGF

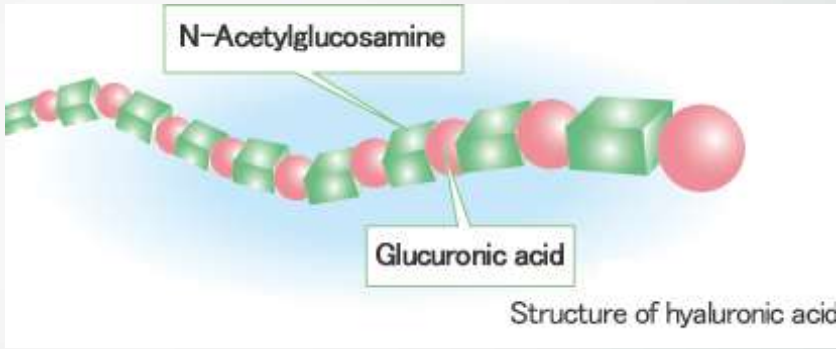
Proteoglikánok

Table 3.3 Repeating disaccharide units of the most common glycosaminoglycans of matrix proteoglycans

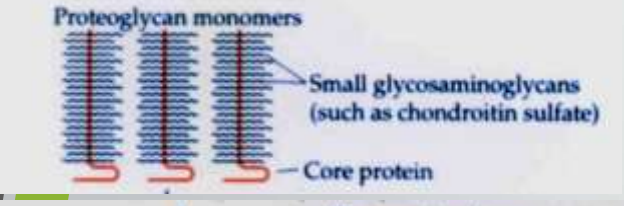
Glycosaminoglycan	Repeating disaccharide unit[a]	Distribution
Hyaluronic acid	Glucuronic acid-*N*-acetylglucosamine	Connective tissues, bone, vitreous body
Chondroitin sulfate	Glucuronic acid-*N*-acetylgalactosamine sulfate	Cartilage, cornea, arteries
Dermatan sulfate	[Glucuronic or iduronic acid]-*N*-acetylgalactosamine sulfate	Skin, heart, blood vessels
Keratan sulfate	Galactose-*N*-acetylglucosamine sulfate	Cartilage, cornea
Heparan sulfate	[Glucuronic or iduronic acid]-*N*-acetylglucosamine sulfate	Lung, arteries, cell surfaces

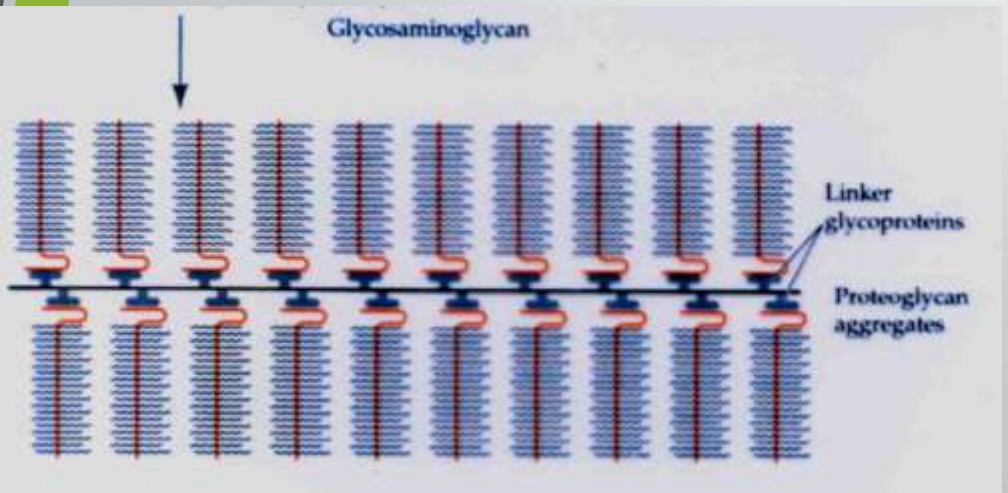
[a]These are the typical repeating units of these glycosaminoglycans. However, regions of each GAG can have slightly modified saccharides.

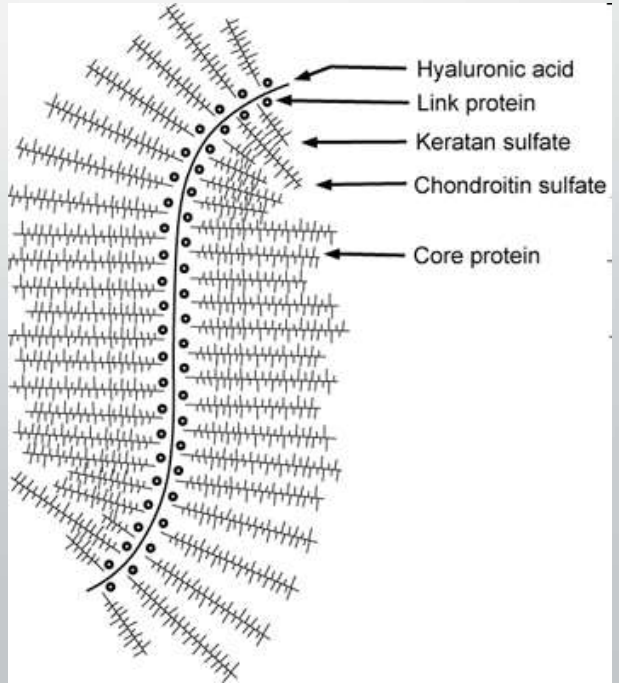


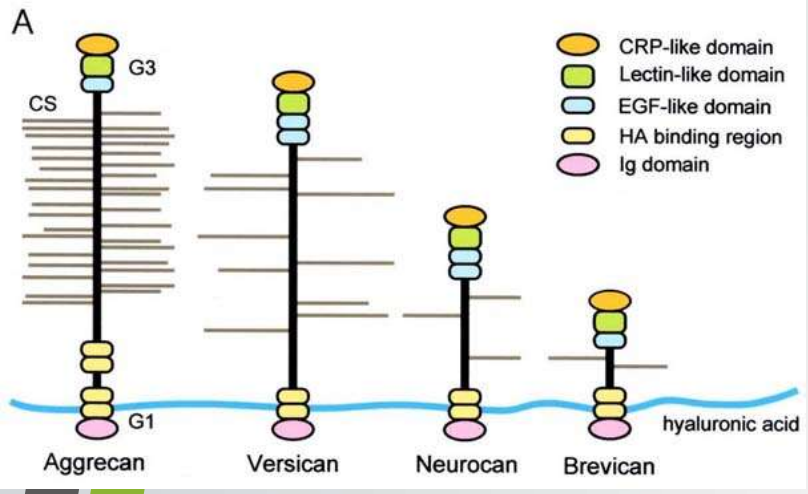


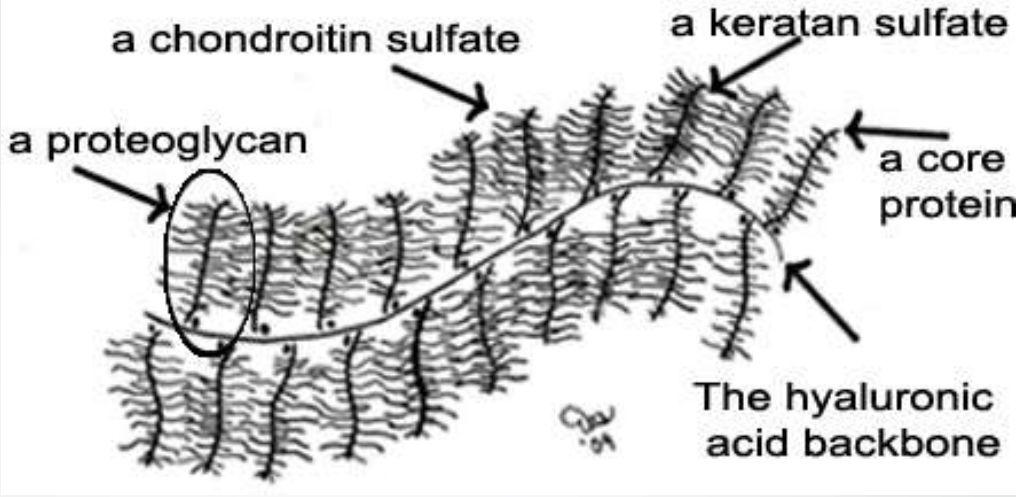
Proteoglikánok



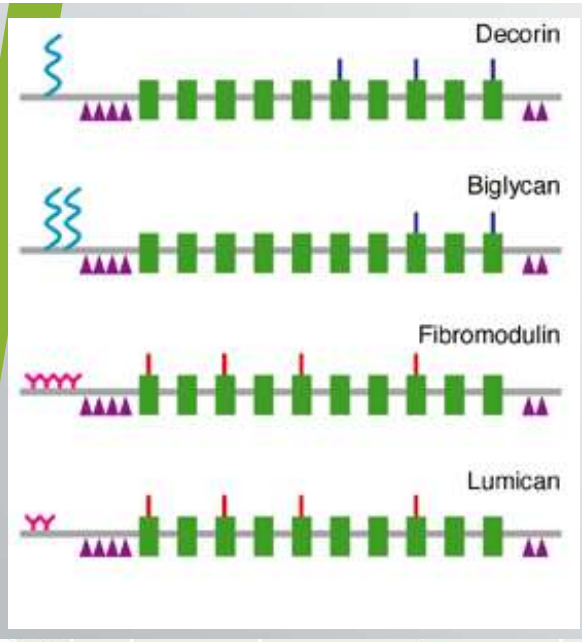


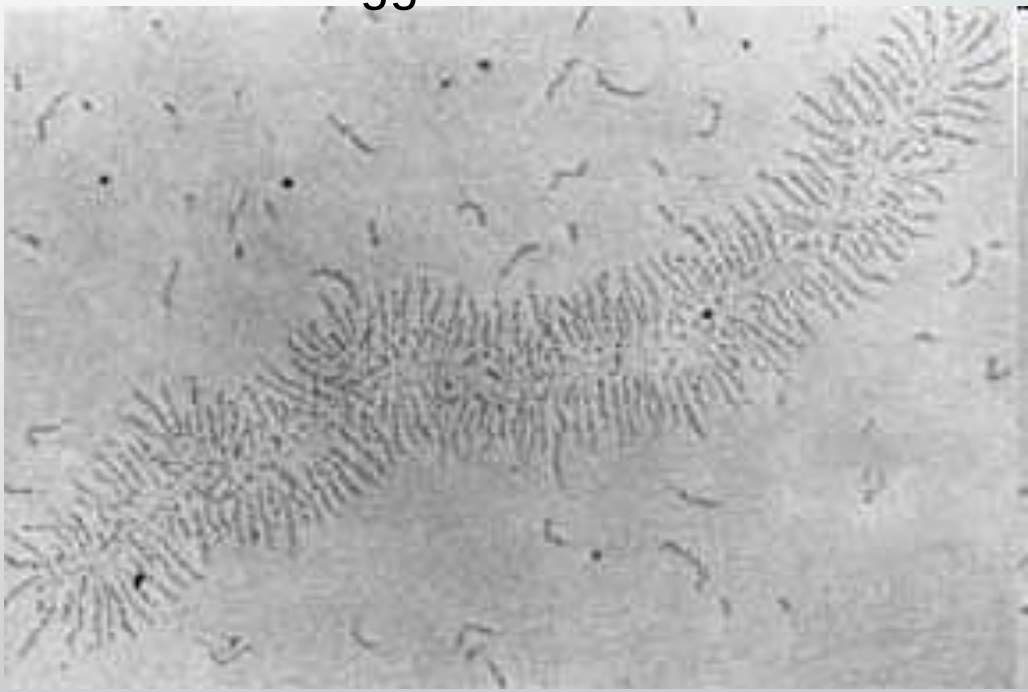


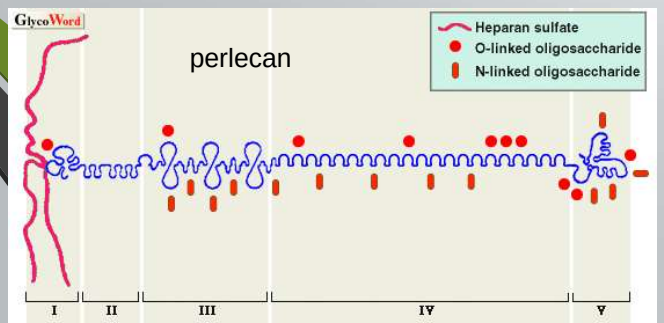




aggrecan

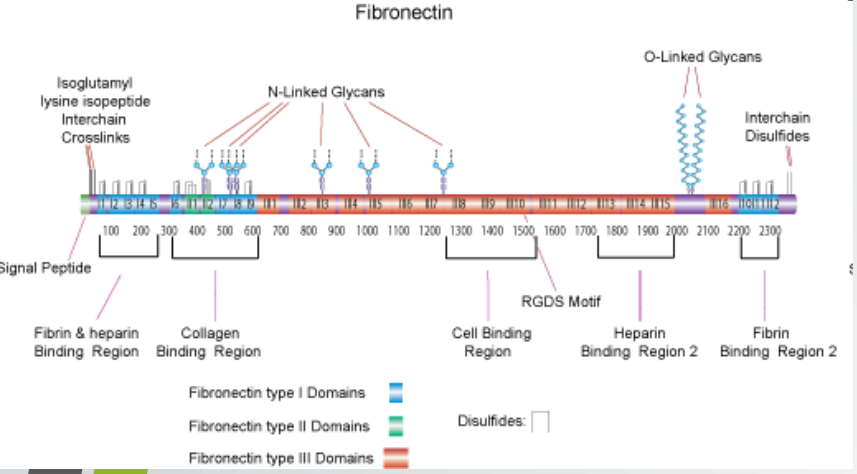


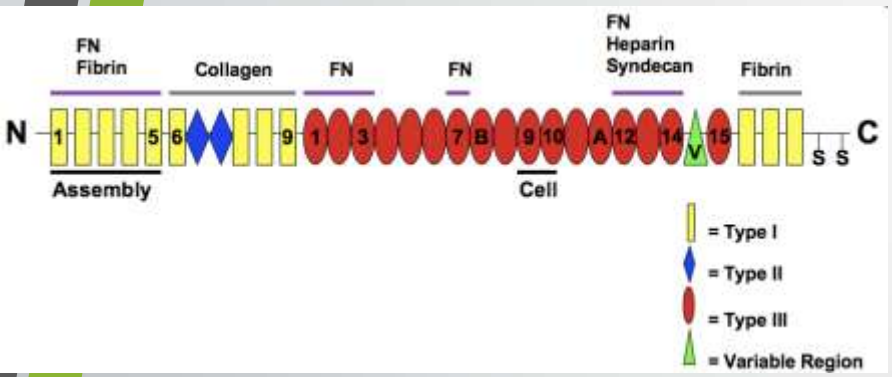


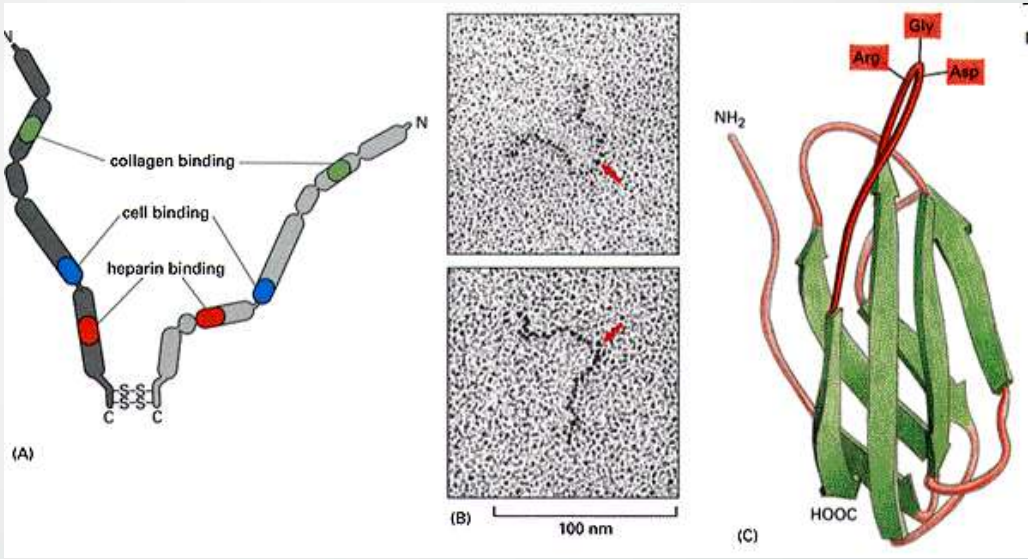


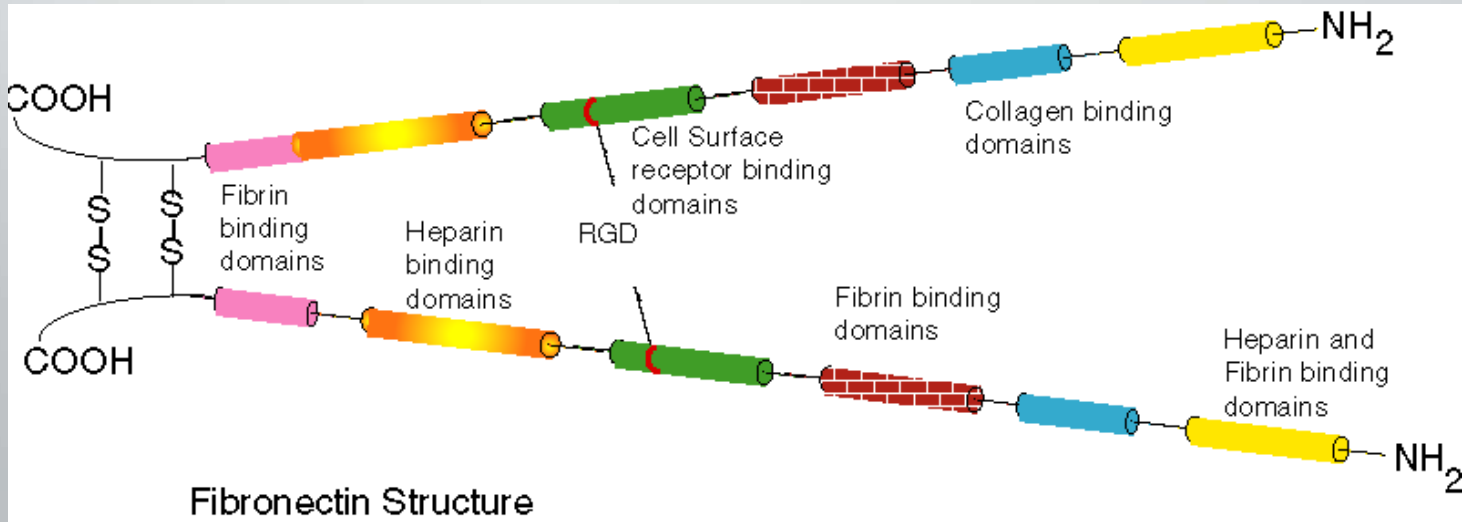
Proteoglikánok

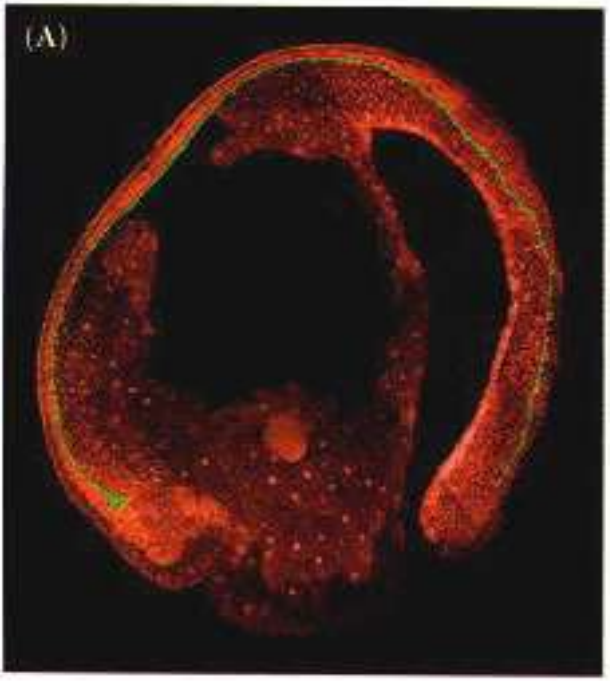
Fibronectin











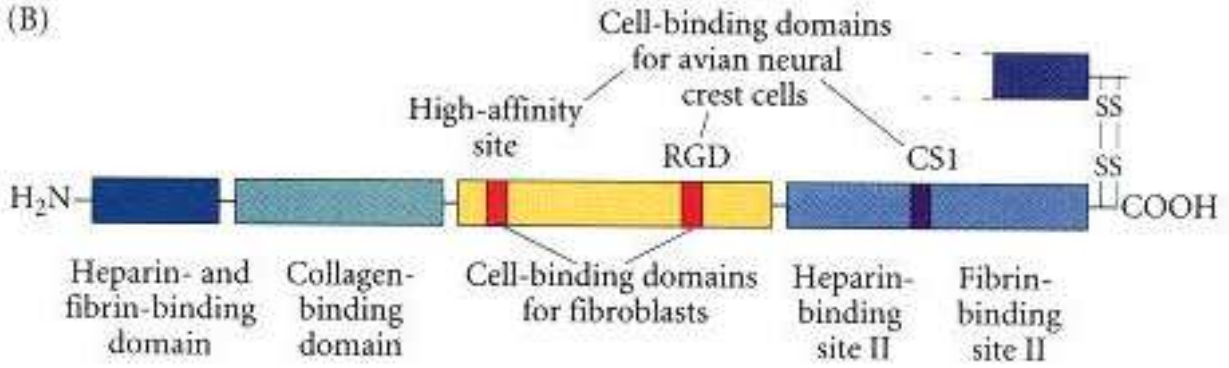


Figure 6.32.
Fibronectin in the developing frog embryo. (A) Fluorescent antibodies to fibronectin show fibronectin deposition as a green band in the *Xenopus* embryo during gastrulation. The fibronectin will orient the mesoderm movements of the cells. (B) Structure and binding domains of fibronectin. The rectangles represent protease-resistant domains. The fibroblast-binding domain consists of two units, the RGD site and the high-affinity site, both of which are essential for cell binding. Avian neural crest cells have another site that is necessary for them to migrate on a fibronectin substrate. Other regions of fibronectin enable it to bind to collagen, heparin, and other molecules of the extracellular matrix.

Lamina basalis, membrana basalis

membrana basalis / lamina basalis

•a hámszövetek lamina basalishoz kötődnek.

•lamina basalis sejtmentes matrix

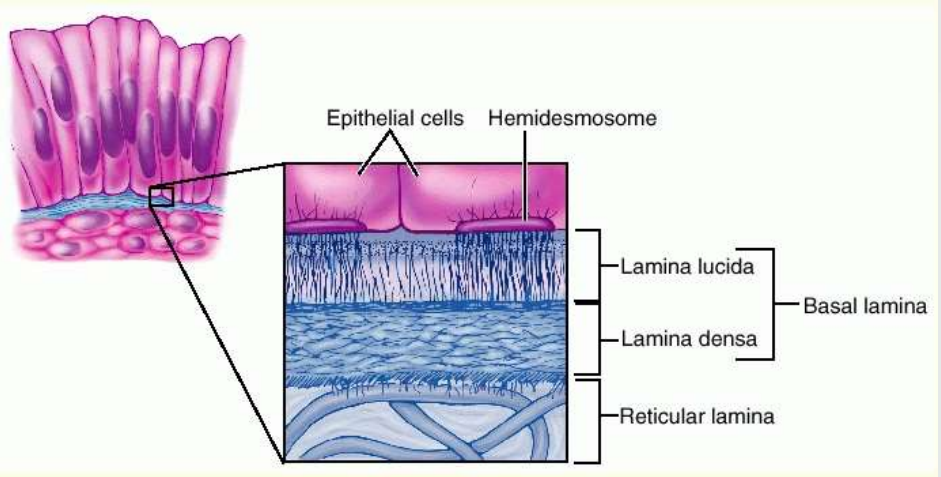
•a lamina basalis vékony

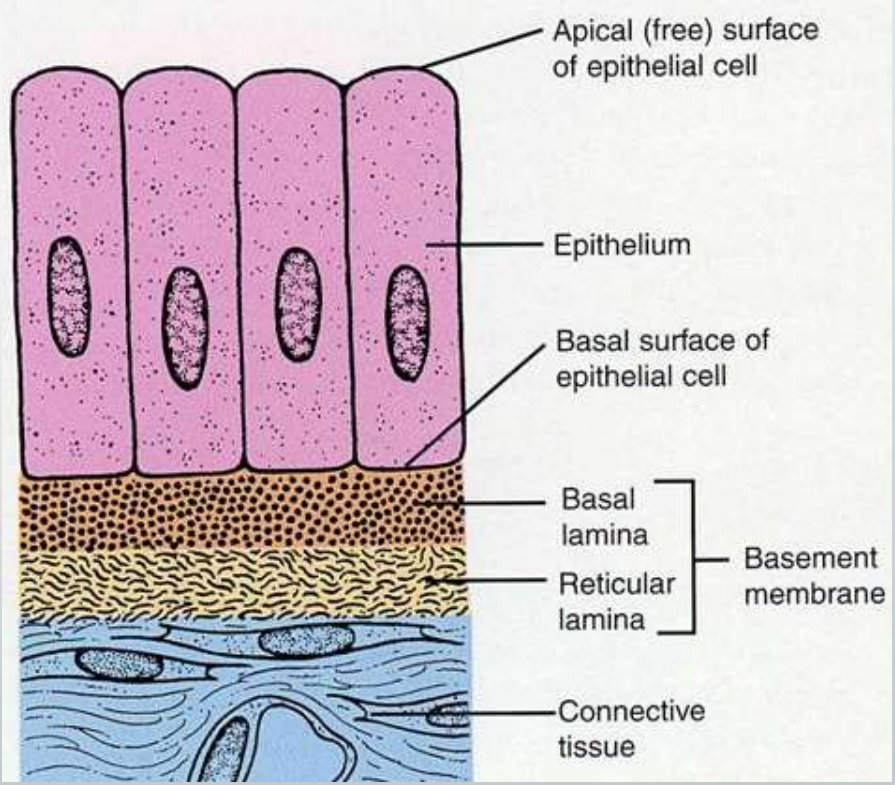
szerepe:

sejtpolaritás befolyásolása

proliferáció szabályozása

szűrő funkció





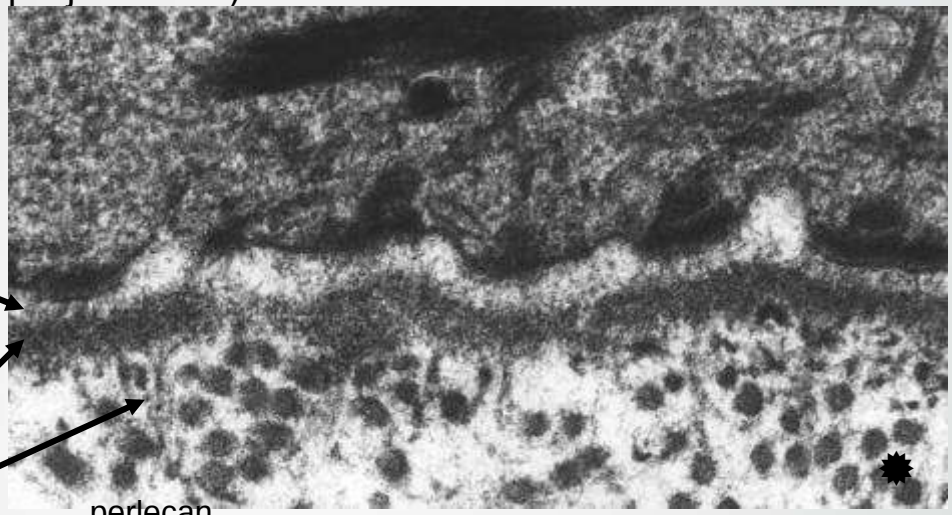
Lamina basalis

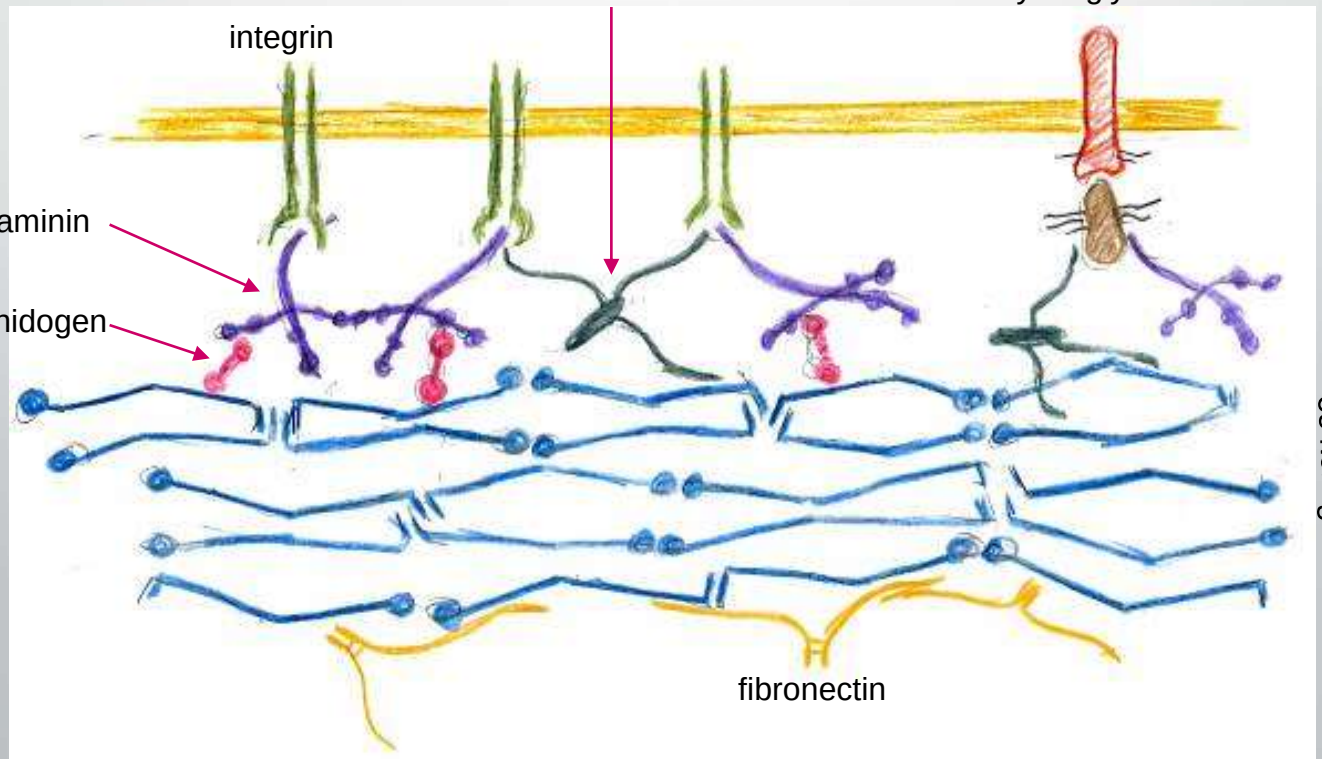
A hámréteg basalis felszínéhez illeszkedő vékony réteg (40-120 nm vastag, fénymikroszkóppal alig, elektronmikroszkóppal jól látható).

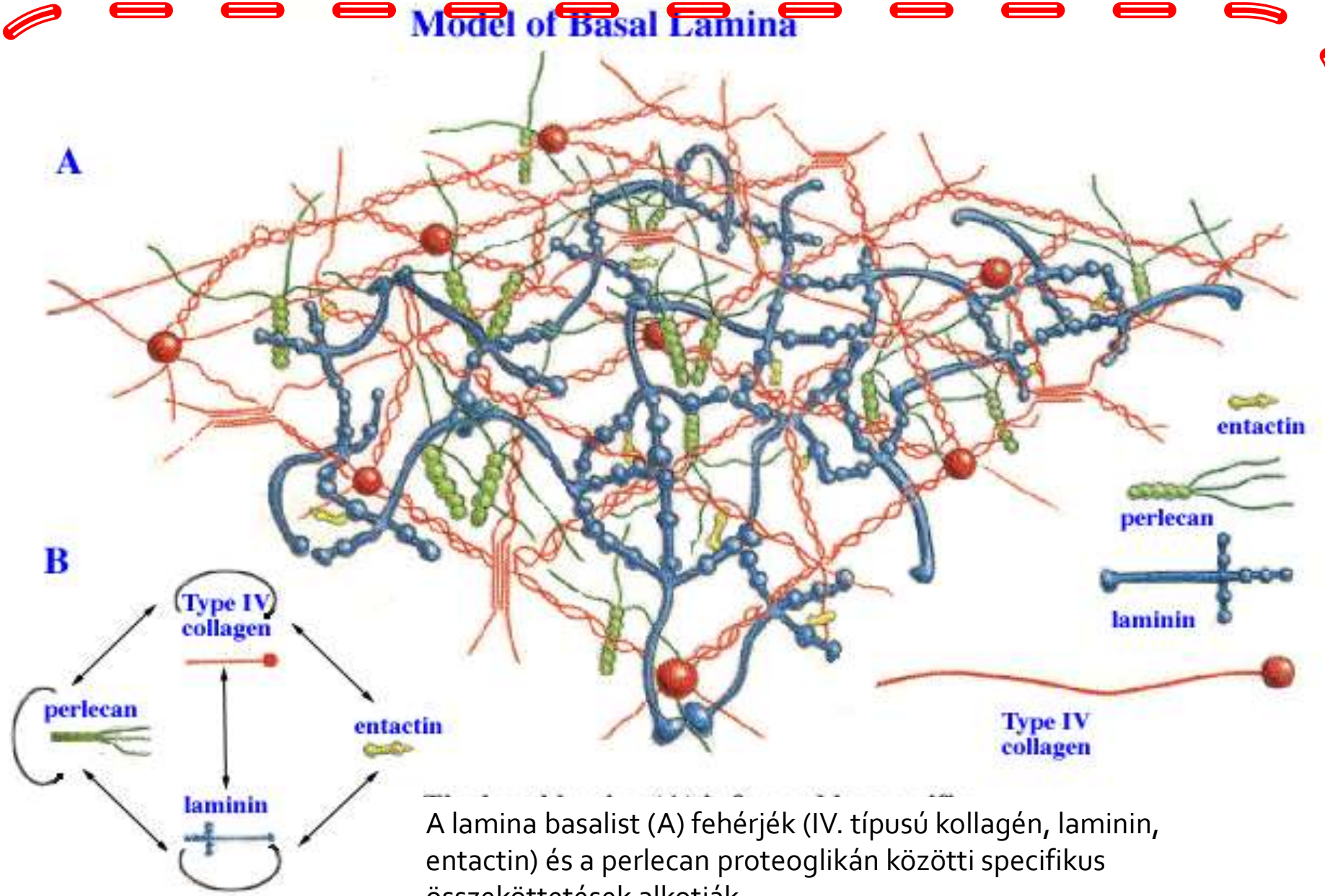
EM: két rétegből áll

lamina rara (sejtmembránhoz közelebb)

lamina densa

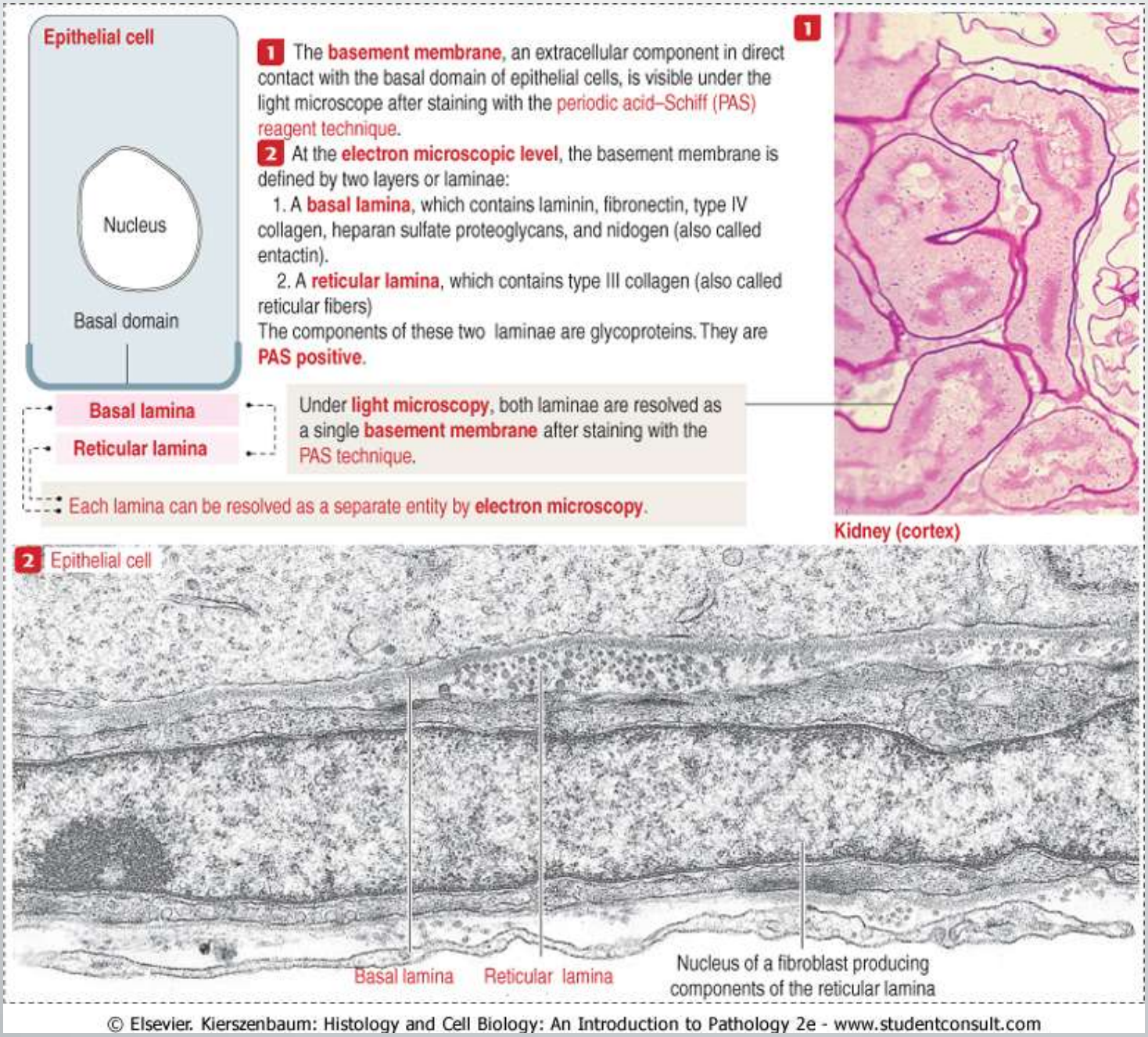






A lamina basalist (A) fehérjék (IV. típusú kollagén, laminin, entactin) és a perlecan proteoglikán közötti specifikus összeköttetések alkotják
A (B) ábra nyilai azt mutatják, mely molekulák tudnak közvetlenül egymáshoz kapcsolódni

Lamina basalis



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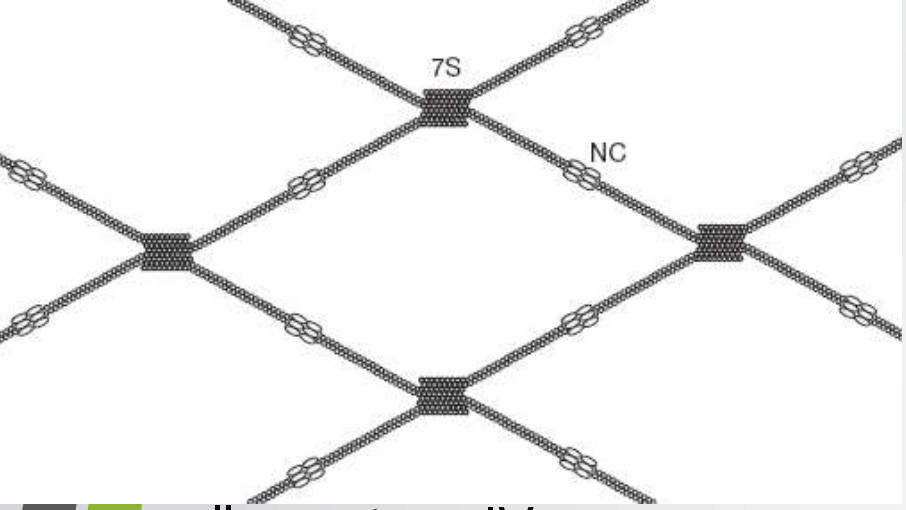
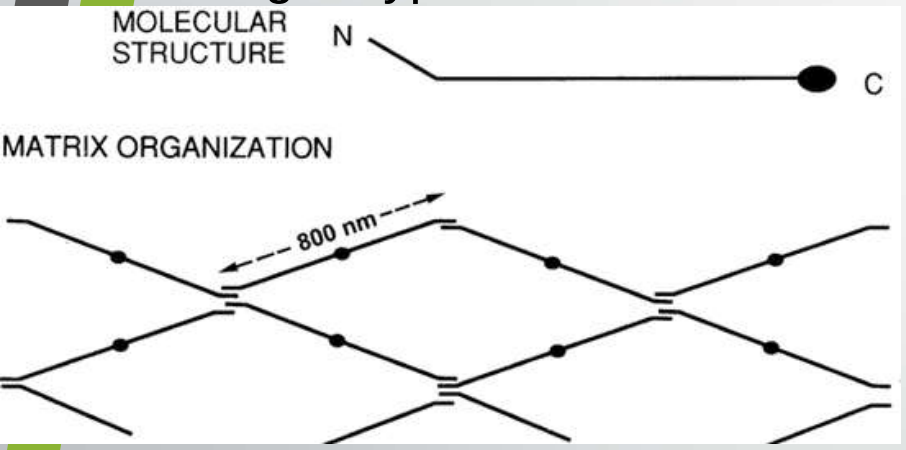
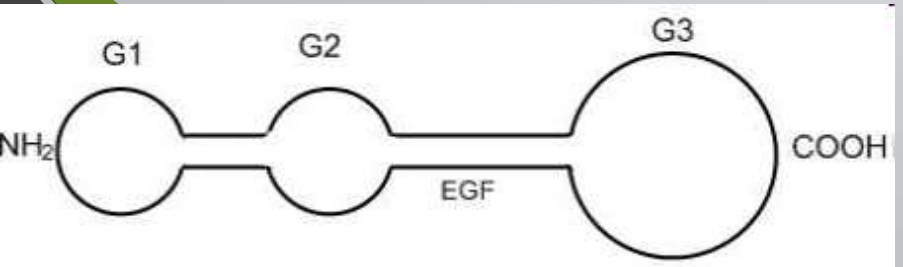
Lamina basalis

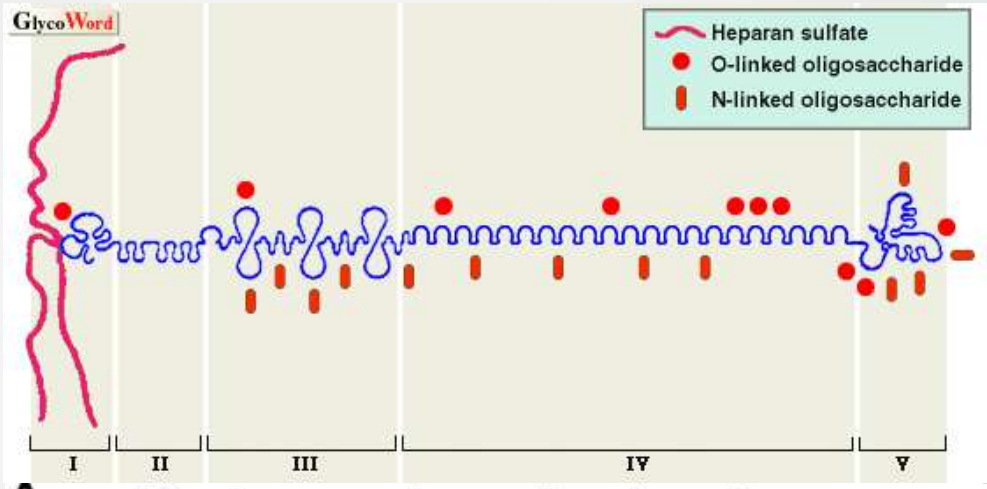


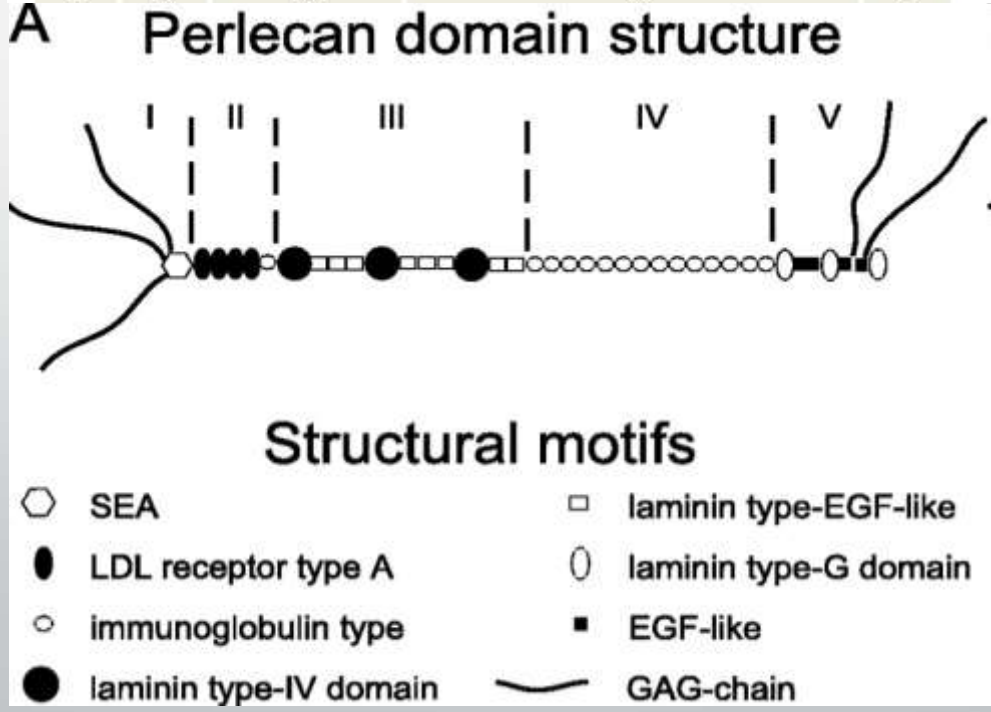
collagen type IV.

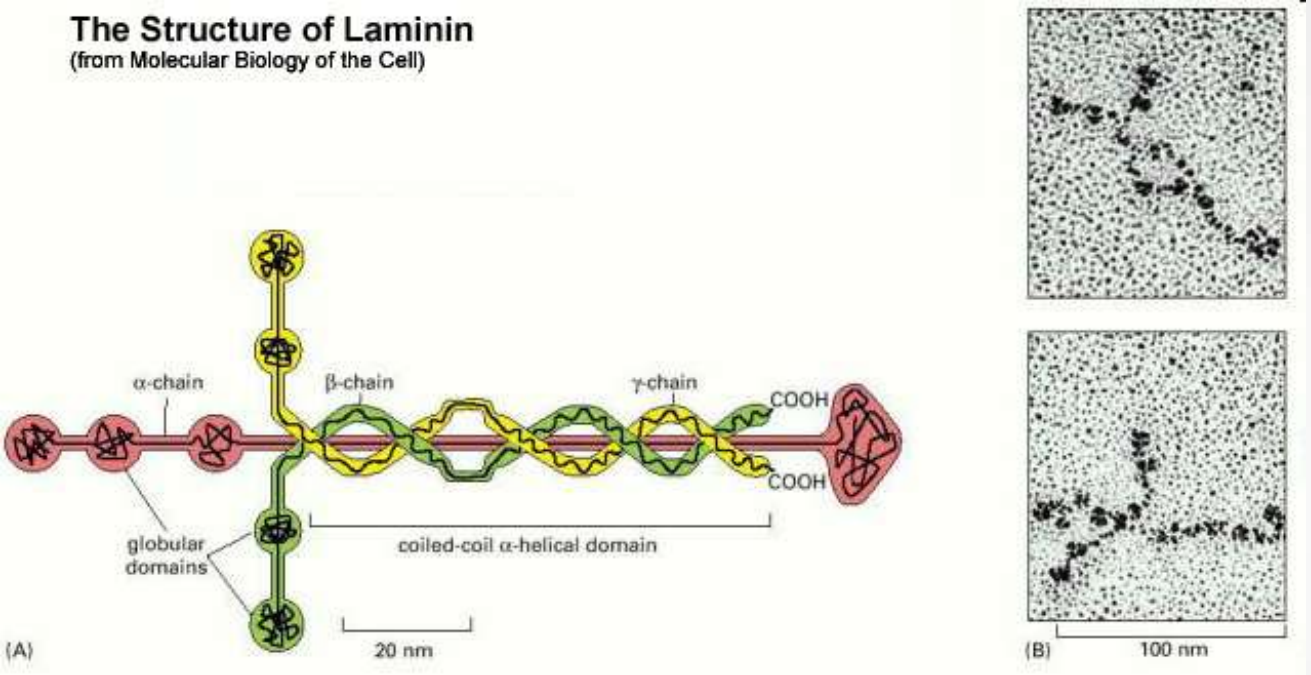


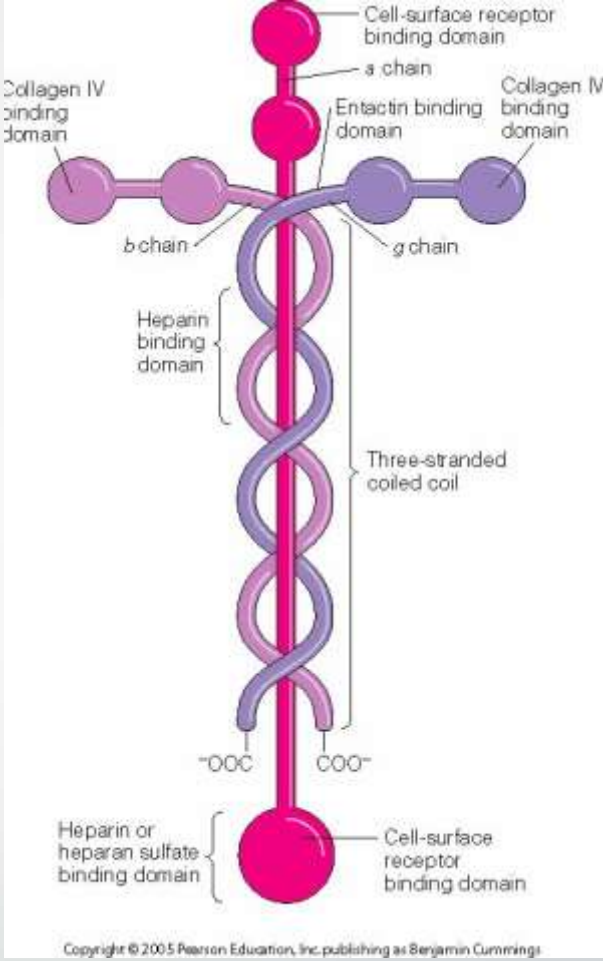
nidogen/entactin

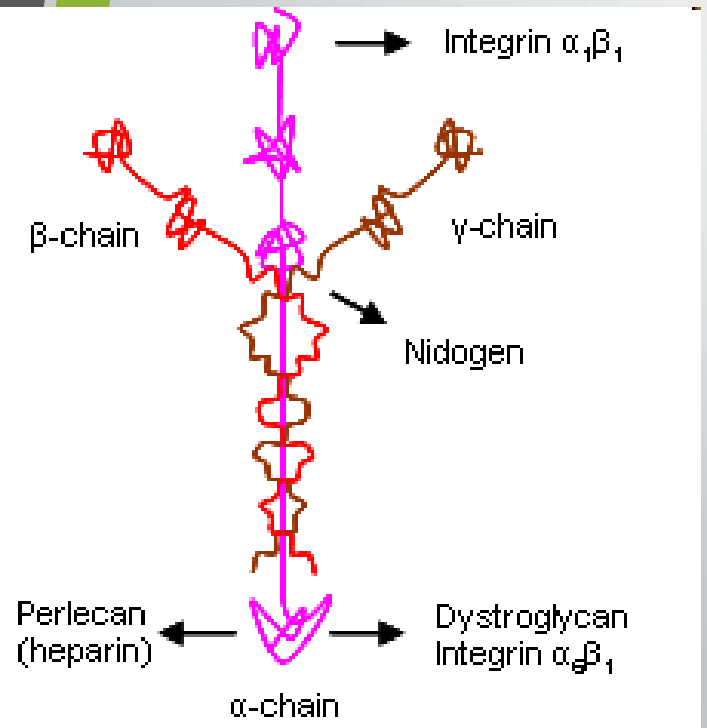






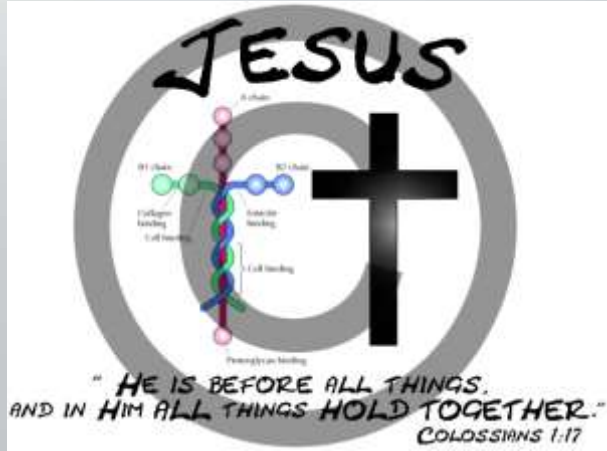






Ln-1	α1β1γ1
Ln-2	α2β1γ1
Ln-3	α1β2γ1
Ln-4	α2β2γ1
Ln-5	α3β3γ2
Ln-6	α3β1γ1
Ln-7	α3β2γ1
Ln-8	α4β1γ1
Ln-9	α4β2γ1
Ln-10	α5β1γ1
Ln-11	α5β2γ1

Laminin



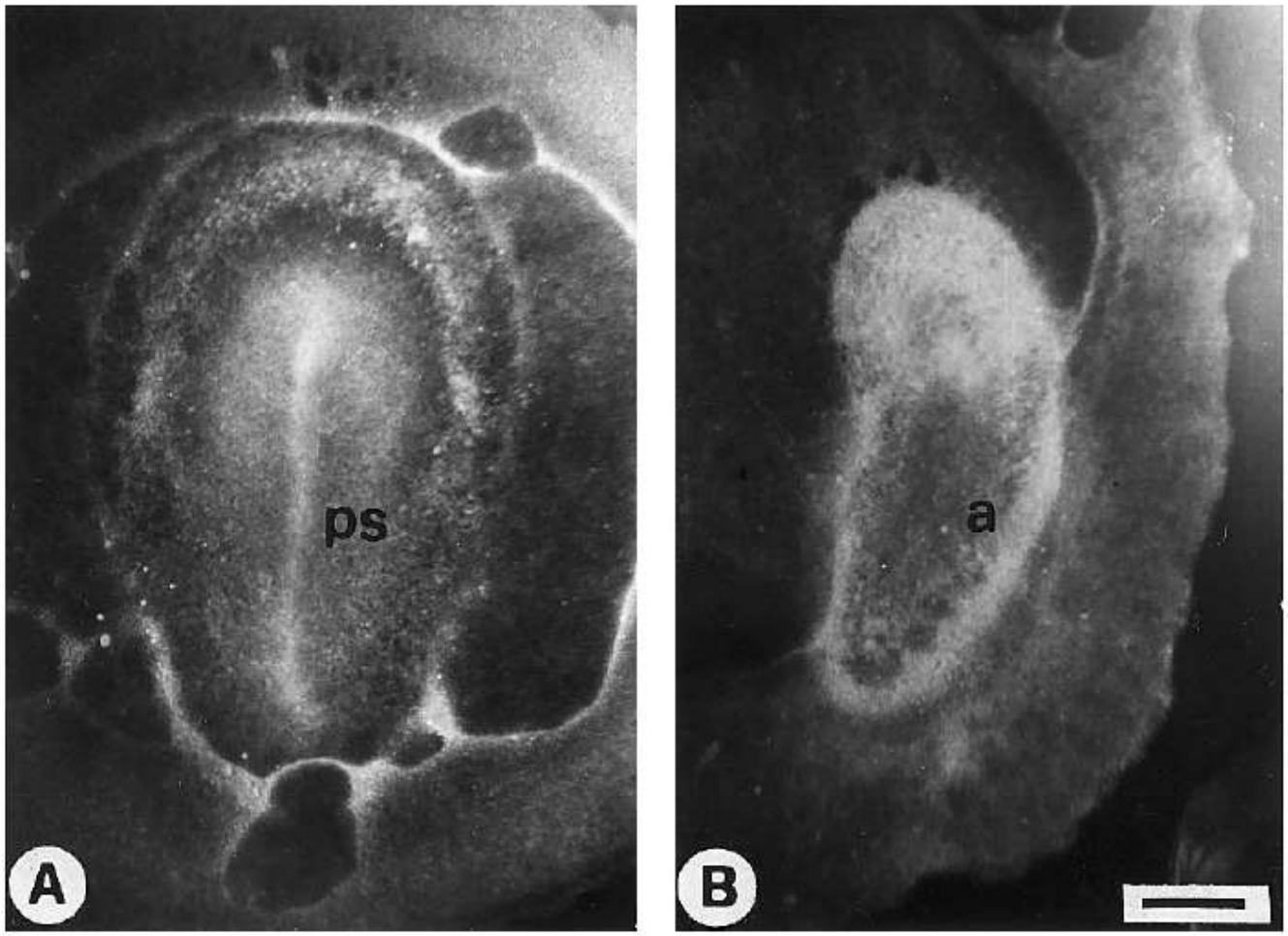


Fig. 3. Antibodies to laminin perturb morphogenetic movements of early chick embryo. Chick embryos at the morula stage (st. X) cultured in plain Ringer solution (A) or in Ringer solution containing laminin antibodies (B) for 4 h, then cultured for 22 h in plain egg albumen (methods as in Zagris and Chung, 1990). Photomicrographs of embryos at the end of culture. a, an atypical primitive streak; ps, primitive streak. Bar = 500 μm.

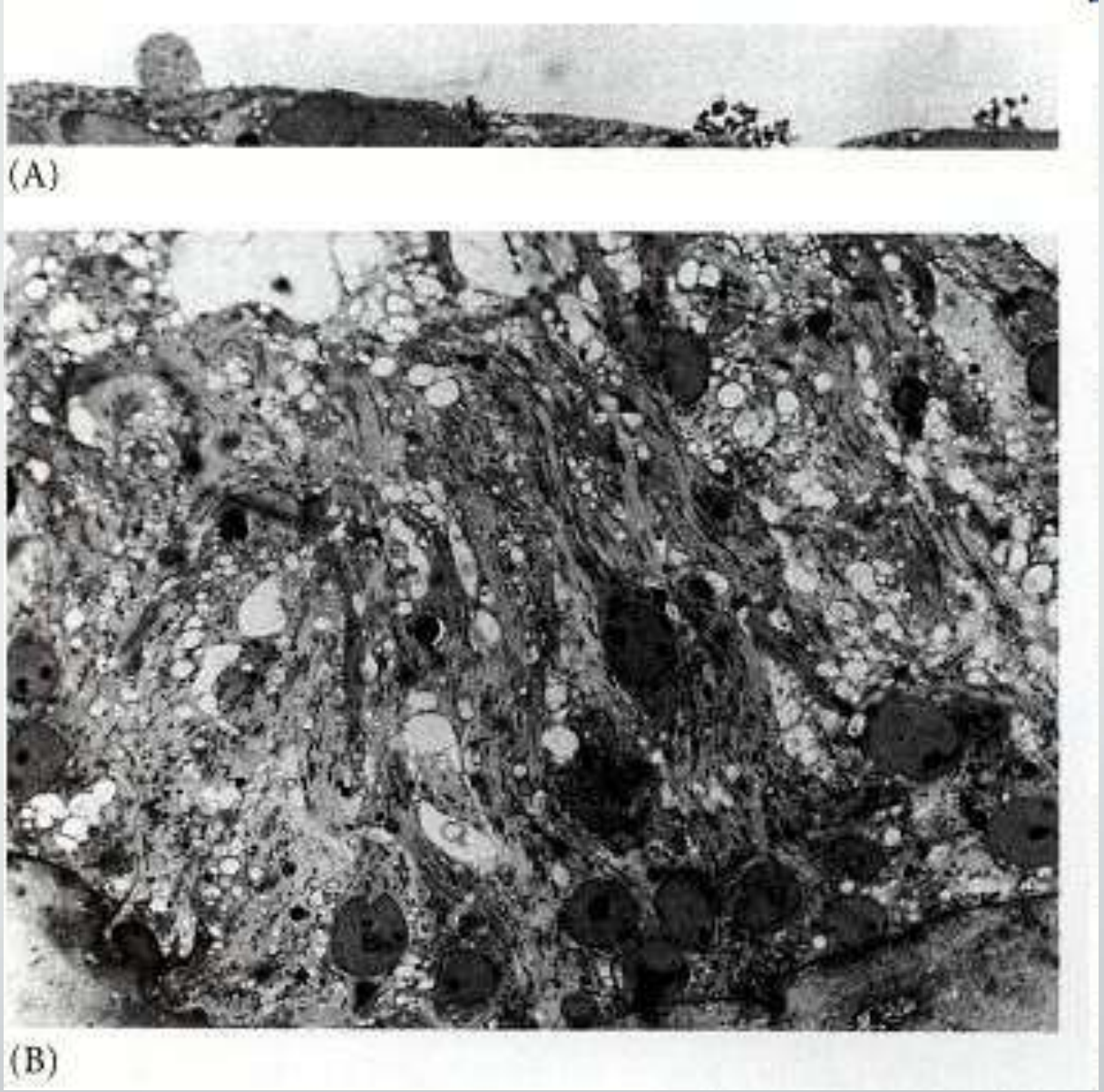


Figure 6.35.
Role of the extracellular matrix in cell differentiation. Light micrographs of rat Sertoli testis cells grown for two weeks (A) on tissue culture plastic dishes and (B) on dishes coated with basal lamina. The two photographs were taken at the same magnification, 1200×.

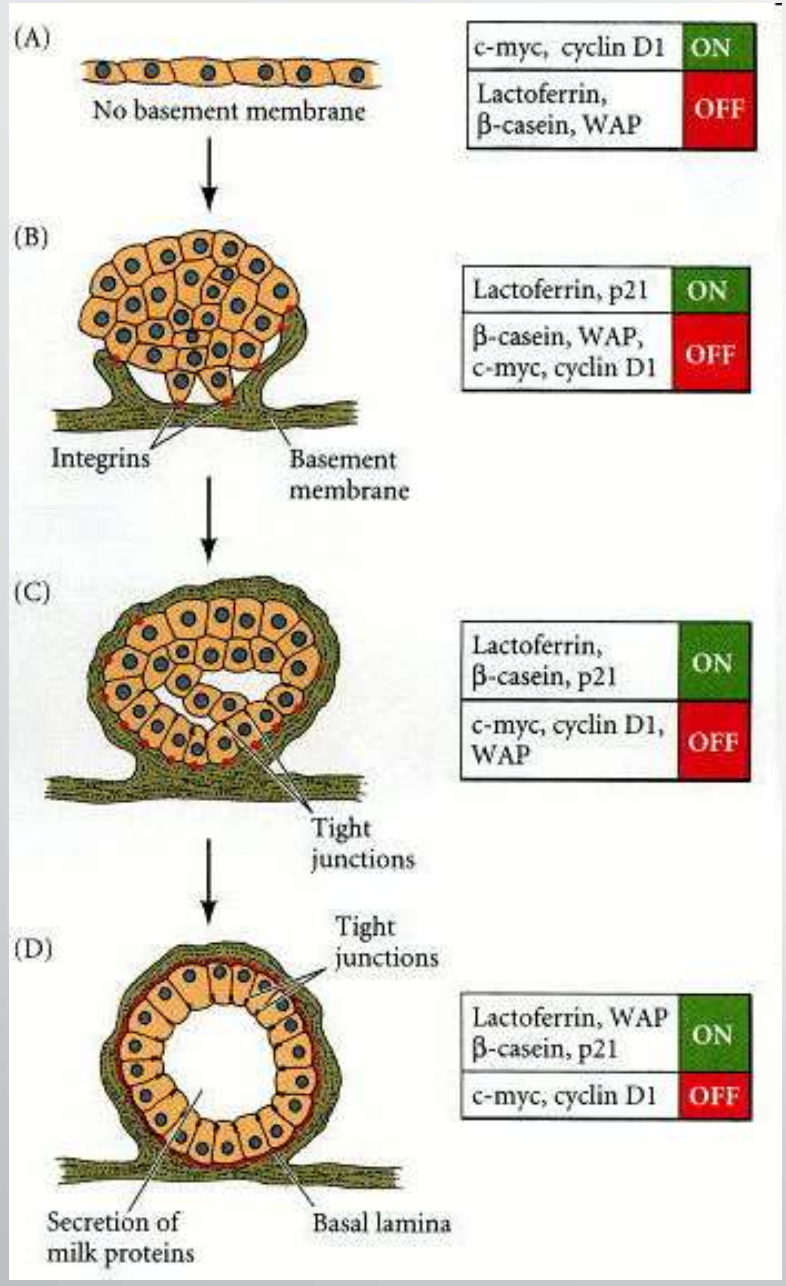
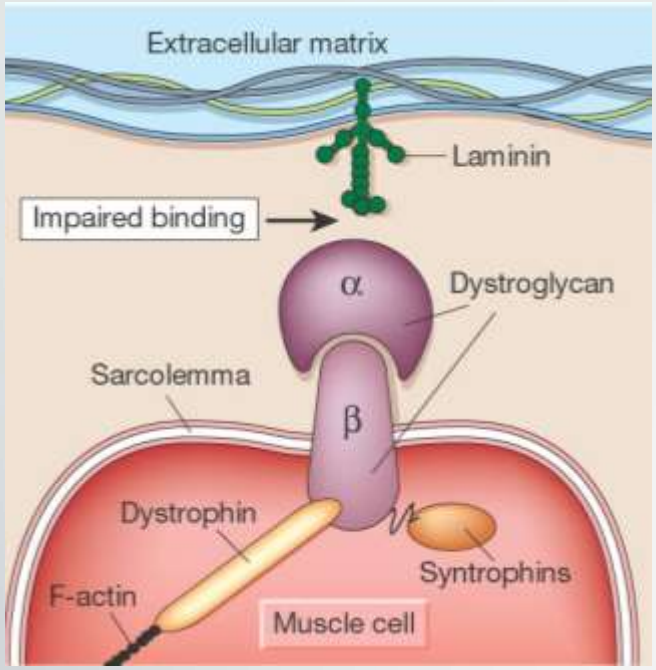
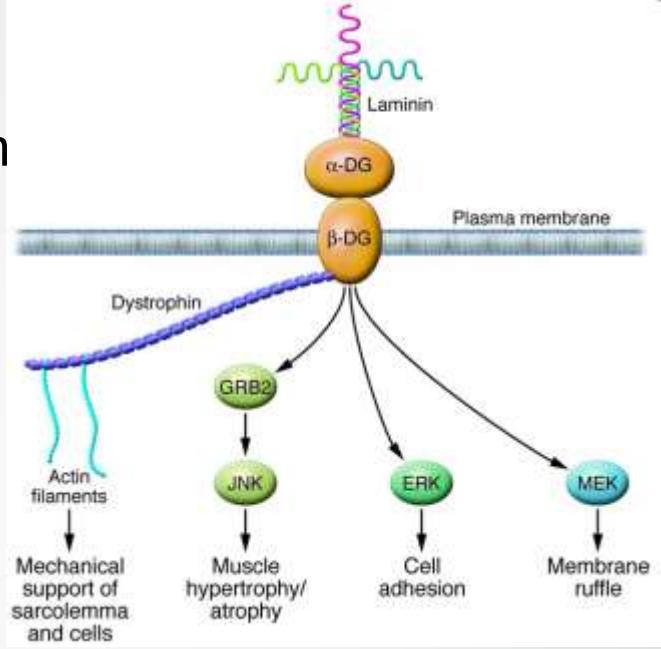
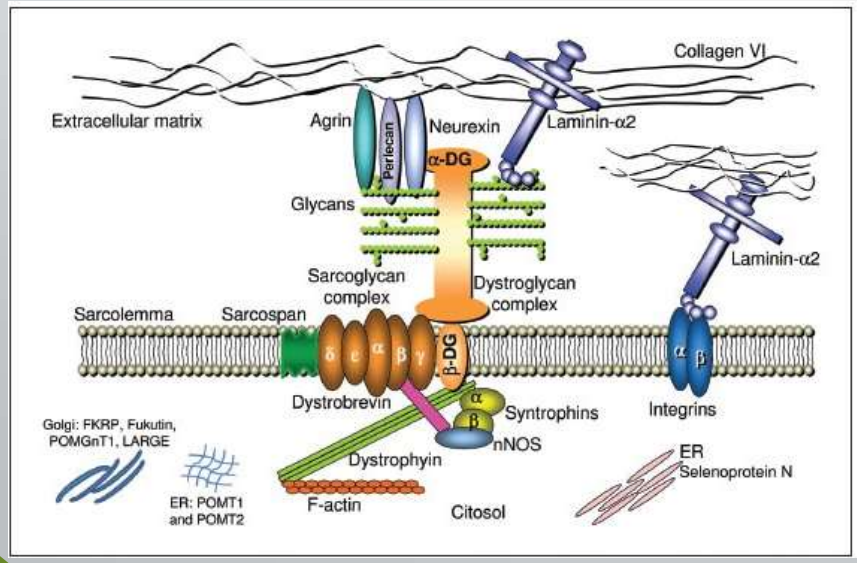


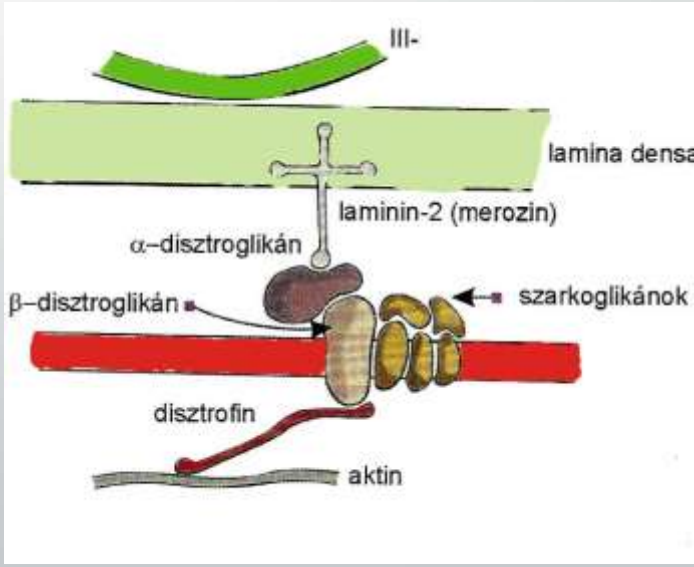
Figure 6.36.
Basement membrane-directed gene expression in mammary gland tissue. (A) Mouse mammary gland tissue divides when placed on tissue culture plastic. Cell division genes are on, and the genes capable of synthesizing the differentiated products of the mammary gland (lactoferrin, casein, whey acidic protein) are off. (B) When presented with basement membrane that contains laminin, the genes for cell division proteins are turned off, while the gene inhibiting cell division (p21) and the gene for lactoferrin are turned on. (C, D) Mammary gland cells wrap the basement membrane about them, forming a secretory epithelium. The genes for casein and whey protein are sequentially activated.

Dystroglycan

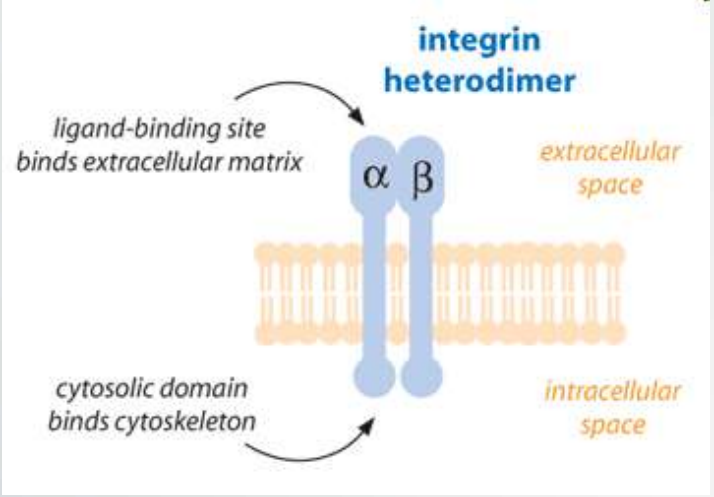






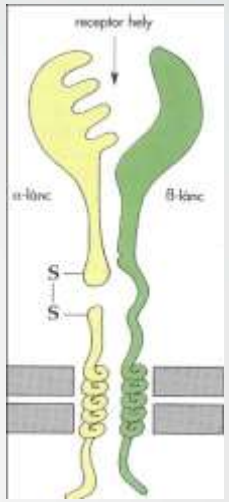


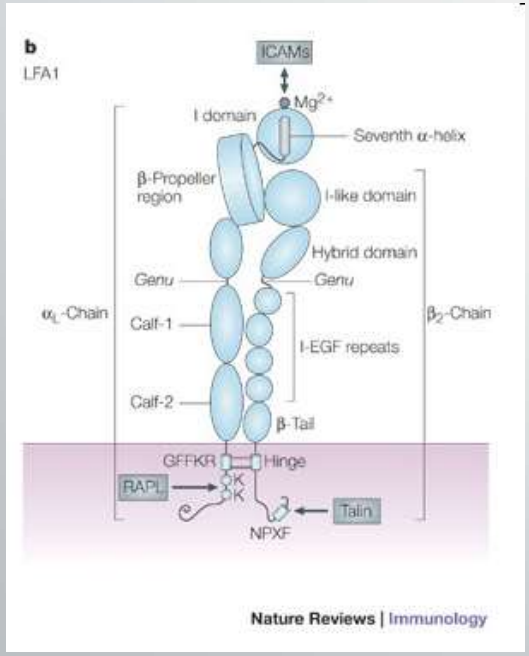
Integrinek
Sejt-matrix kapcsolatok

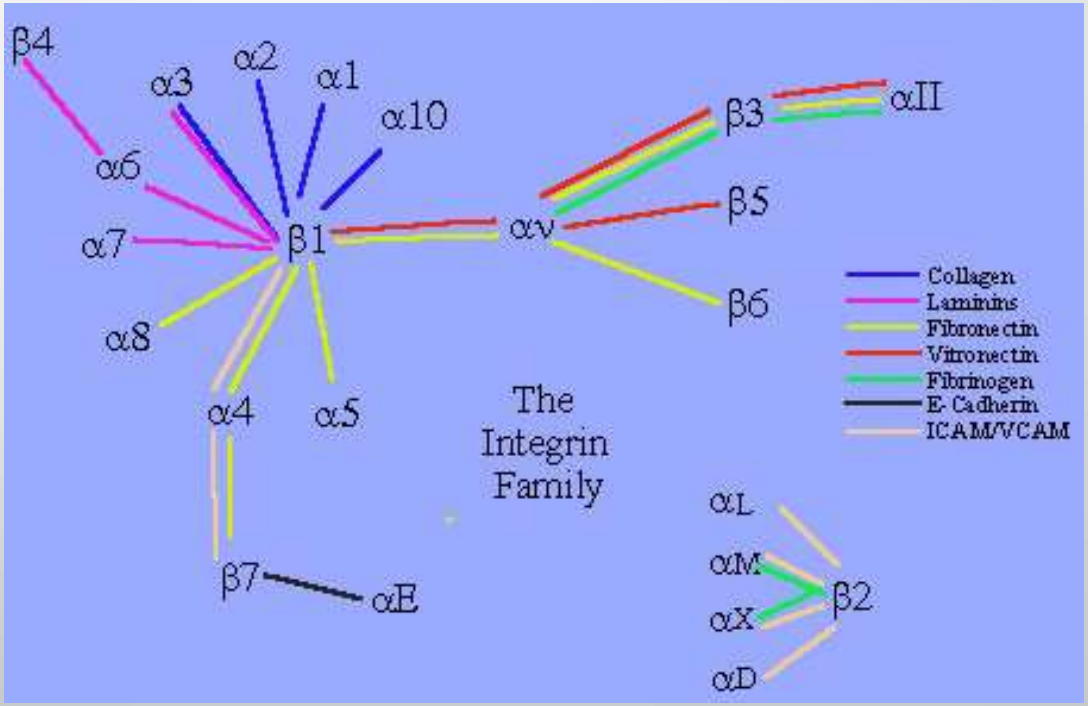


Integrinek

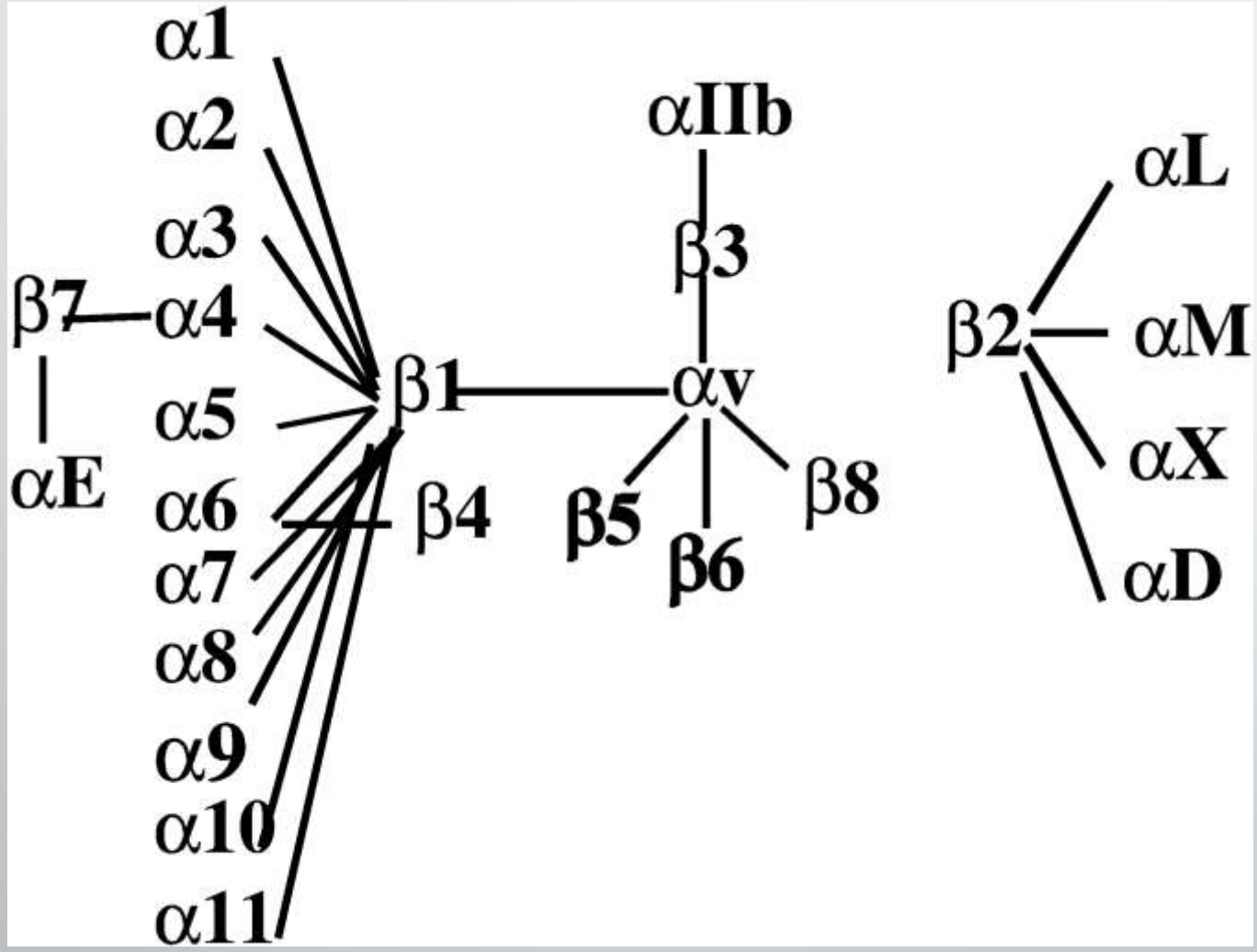
arg-gly-asp (RGD)







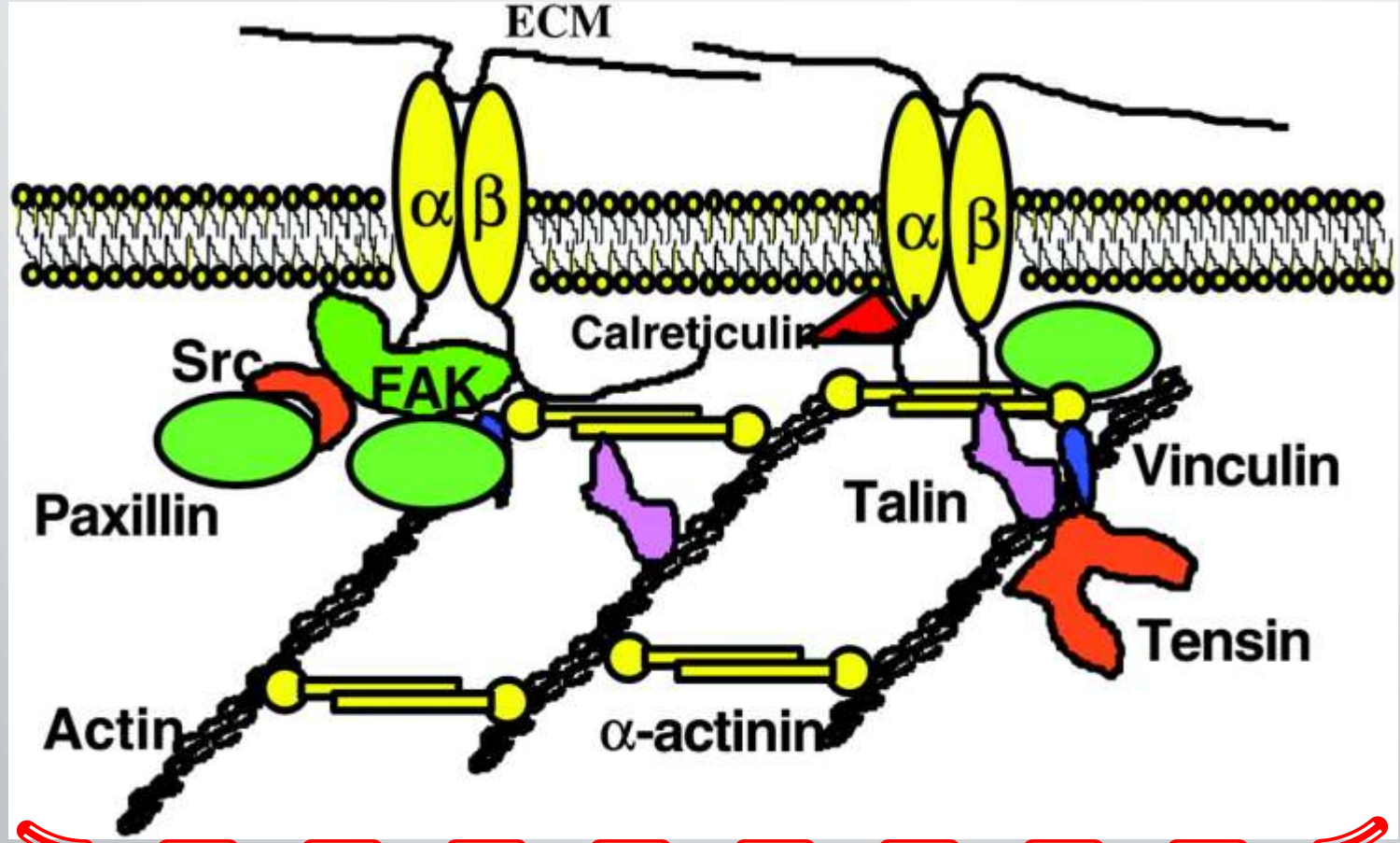
The integrin family.



DEAN SHEPPARD Physiol Rev 2003;83:673-686

Physiological Reviews

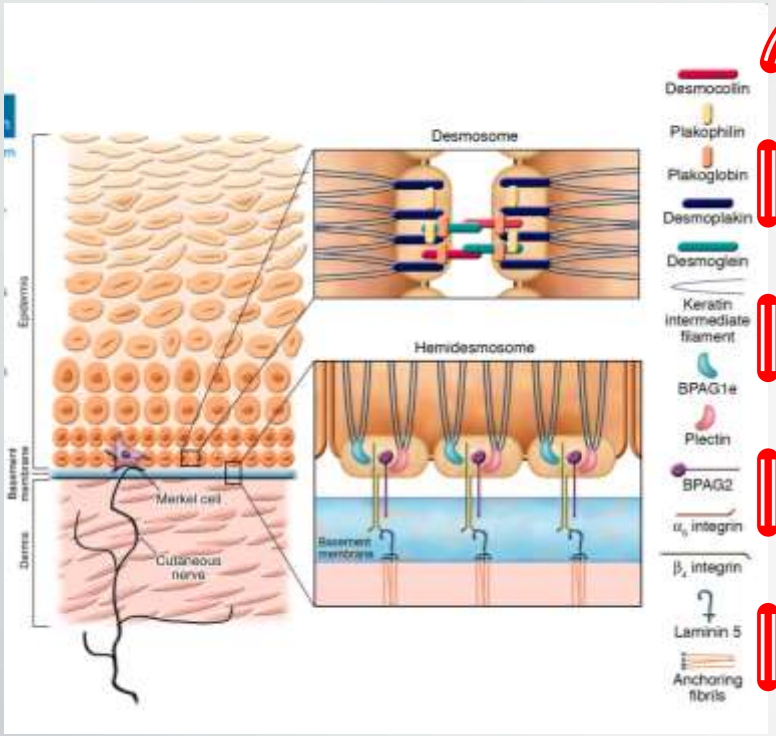
Simplified model of integrin signaling complexes.

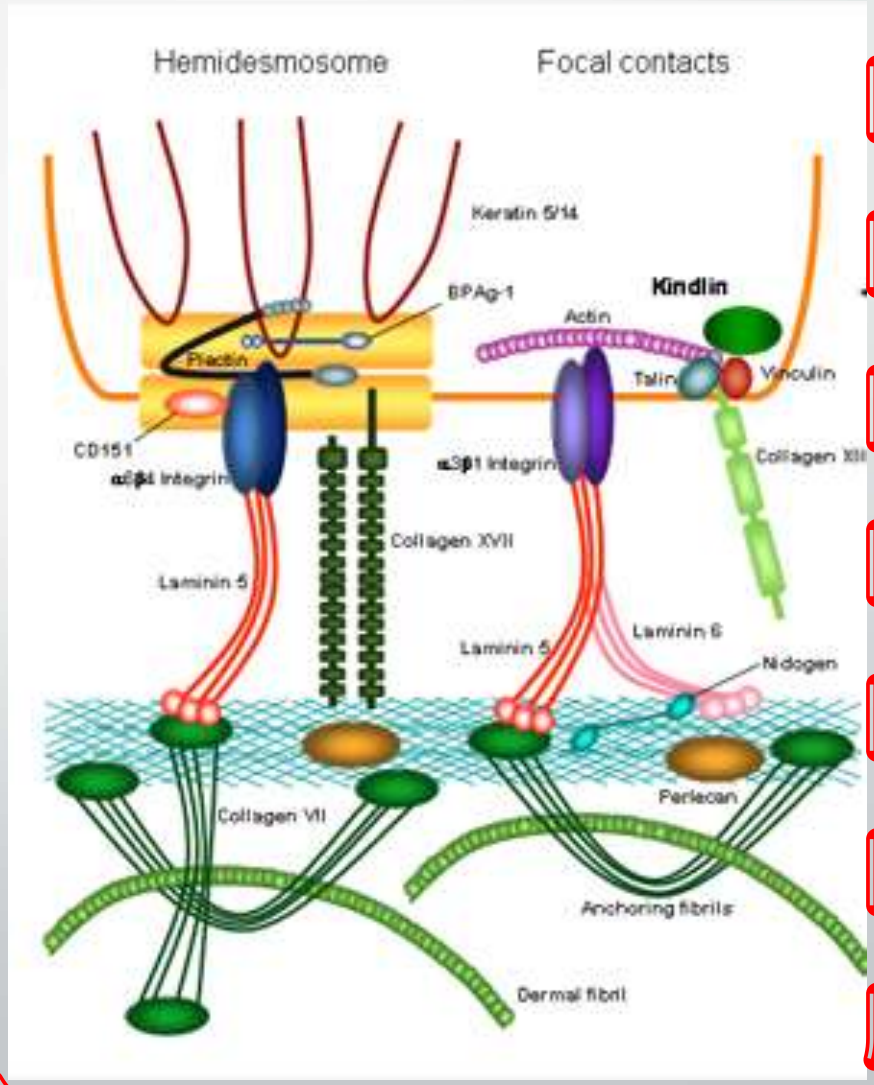


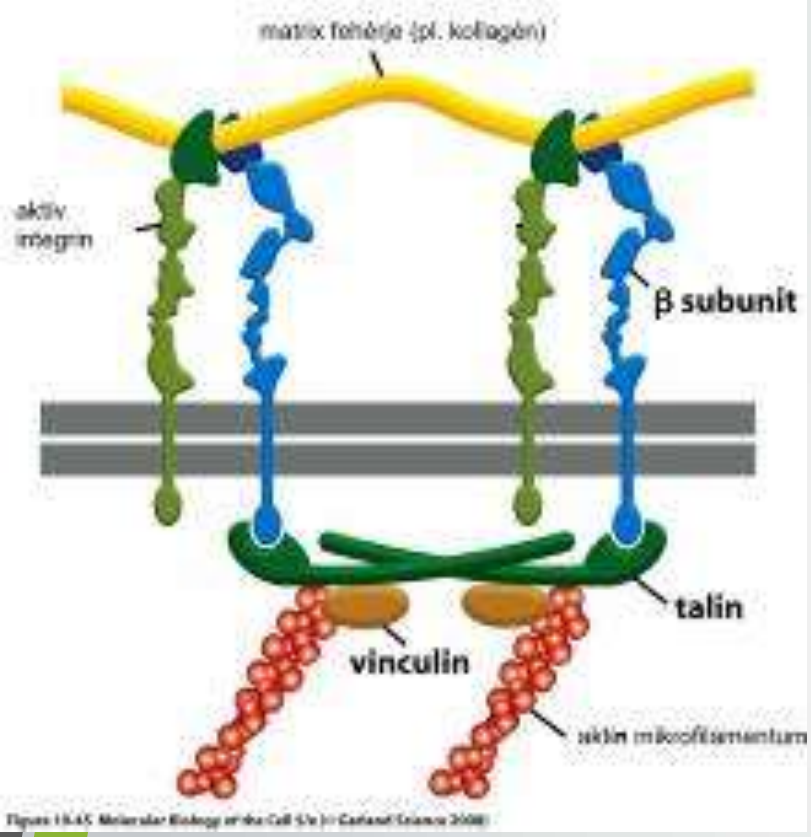
DEAN SHEPPARD Physiol Rev 2003;83:673-686

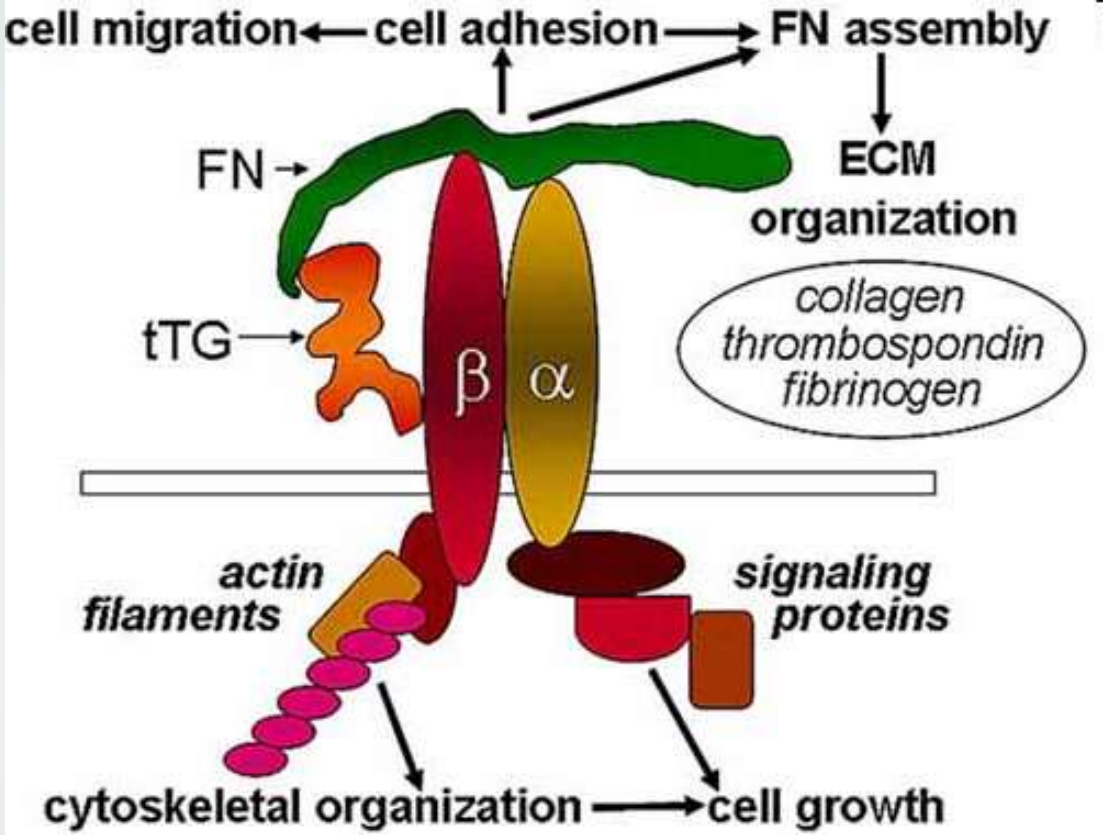
Physiological Reviews

Hemidesmosoma, focalis contactus

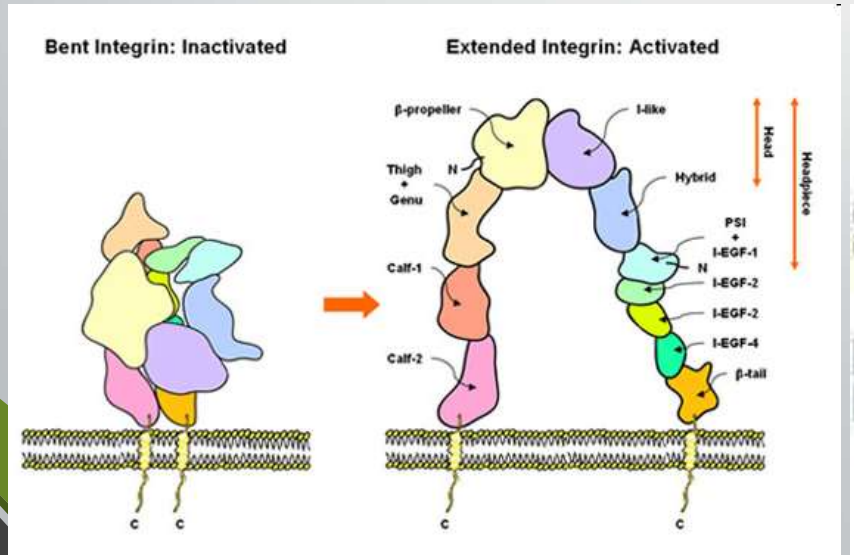


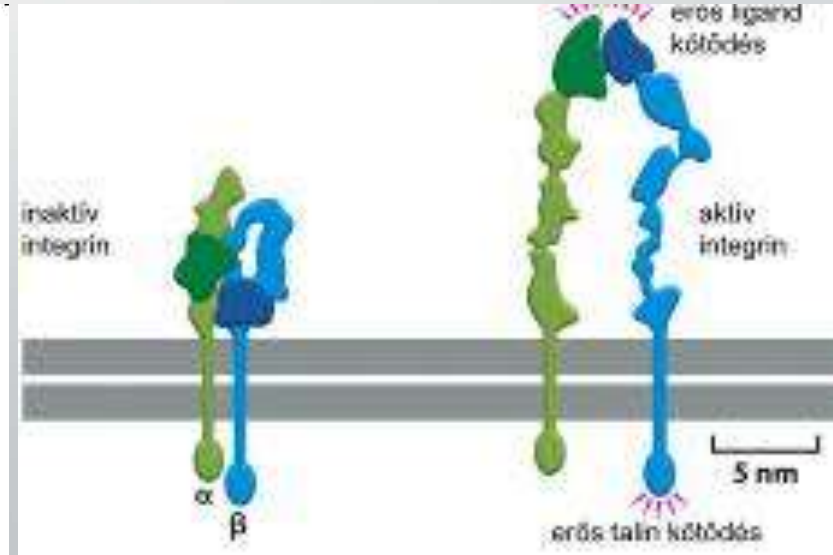



aktív integrin
β subunit
talin
vinculin


cell migration
cell adhesion
FN assembly
FN
ECM organization
tTG
β
α
collagen
thrombospondin
fibrinogen
actin filaments
signaling proteins
cytoskeletal organization
cell growth

Integrinek


Bent Integrin: Inactivated
Extended Integrin: Activated
β-propeller
I-like
Hybrid
Thigh + Genu
N
Calf-1
Calf-2
PSI + I-EGF-1
I-EGF-2
I-EGF-2
I-EGF-4
β-tail
Head
Headpiece
C
C
C
C


erős ligand kötődés
inaktív integrin
aktív integrin
5 nm
α
β
erős talin kötődés

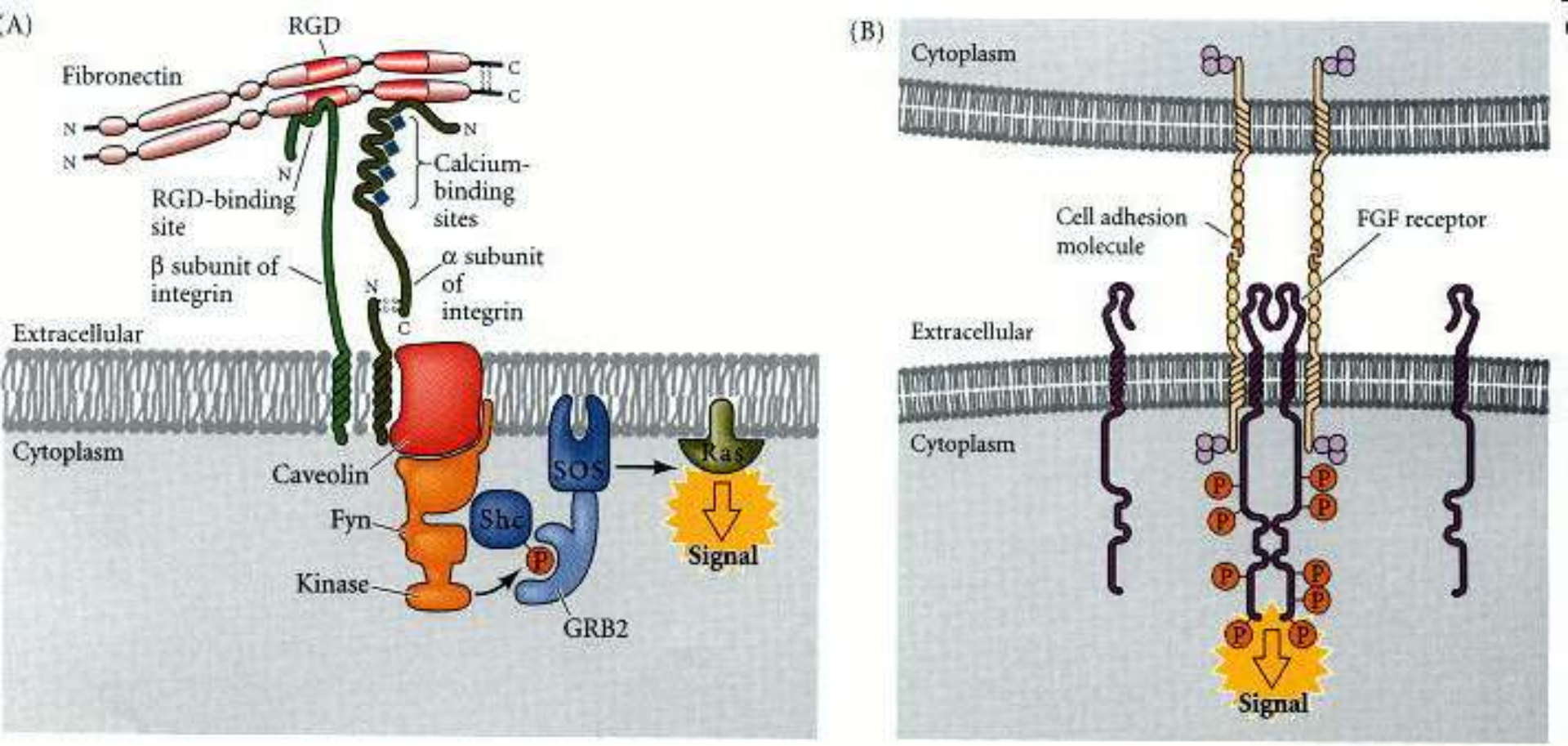


Figure 6.37.
Two types of activation by cell adhesion molecules. (A) Cell-substrate adhesion molecules such as integrins may transmit a signal from the cytoplasmic portion of the integrin protein to the Ras G protein through a cascade involving caveolin and Fyn proteins. (B) The FGF receptors may be “hijacked” by cell adhesion molecules and dimerized. They may be brought together by the interaction of opposite cell adhesion molecules, or the “crosslinking” of FGF receptors by the apposing cell membrane may activate their kinase domains.

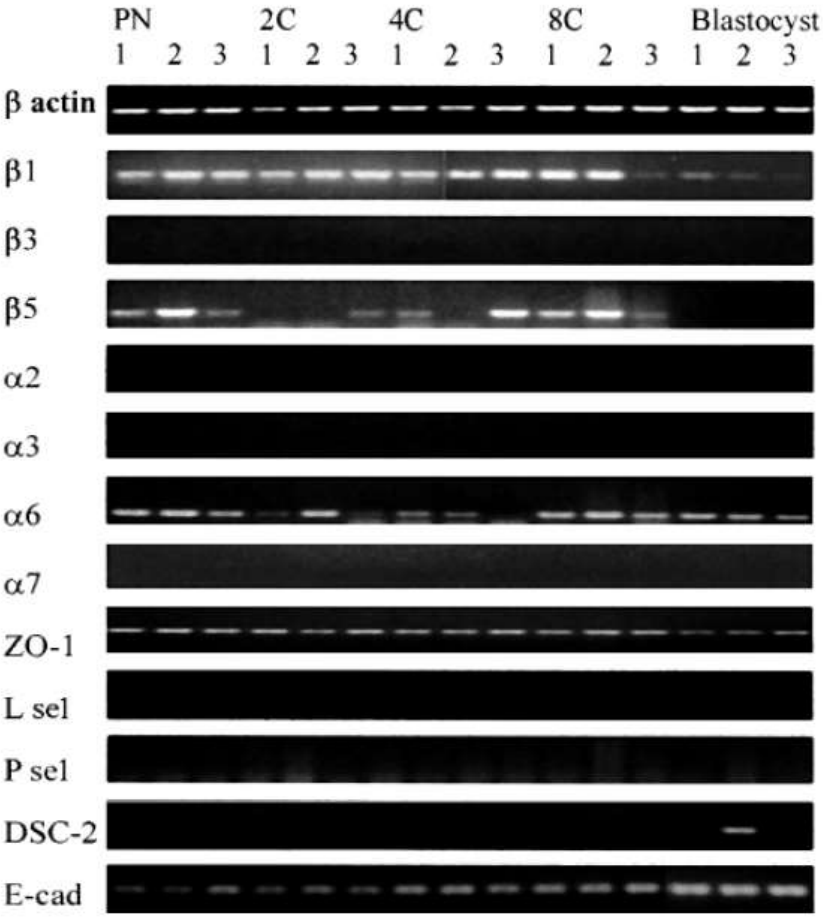


Figure 1. PCR amplification of β actin, integrins β1, β3, β5, α2, α3, α6 and α7, ZO-1, L selectin (L sel), P selectin (P sel), DSC-2 and E-cadherin (E-cad) from cDNAs amplified from three individual embryos (1,2,3) at each of the pronucleate (PN), 2-cell (2C), 4-cell (4C), 8-cell (8C) and blastocyst stages of development.

integrins in the preimplantation embryos

Expression of cell adhesion molecules during human preimplantation embryo development.
Bloor DJ[1], Metcalfe AD, Rutherford A, Brison DR, Kimber SJ.
Mol Hum Reprod. 2002 Mar;8(3):237-45.

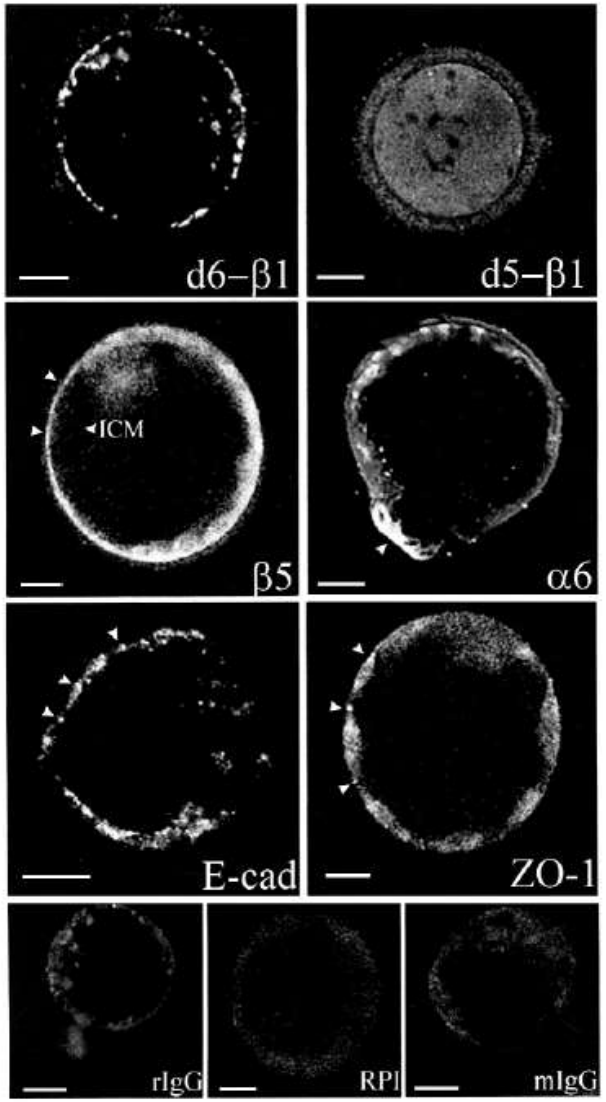


Figure 2. Confocal images of fixed human blastocysts showing protein localization of β1 (expanded blastocyst, d6 and cavitating embryo, d5) and β5 integrin subunits (indicating position of inner cell mass and arrowheads showing cell surface localization of β5 on polar trophectoderm), α6 integrin (arrowhead indicates staining on the trophectoderm at site of hatching from the zona pellucida), E-cadherin (E-cad) and ZO-1 (arrowheads indicate localisation of signal at cell junctions). Negative control images of blastocysts incubated with rat IgG (rIgG), mouse IgG (mIgG) or rabbit pre-immune serum (RPI). Scale bars = 25 μm.

Sejt-migráció

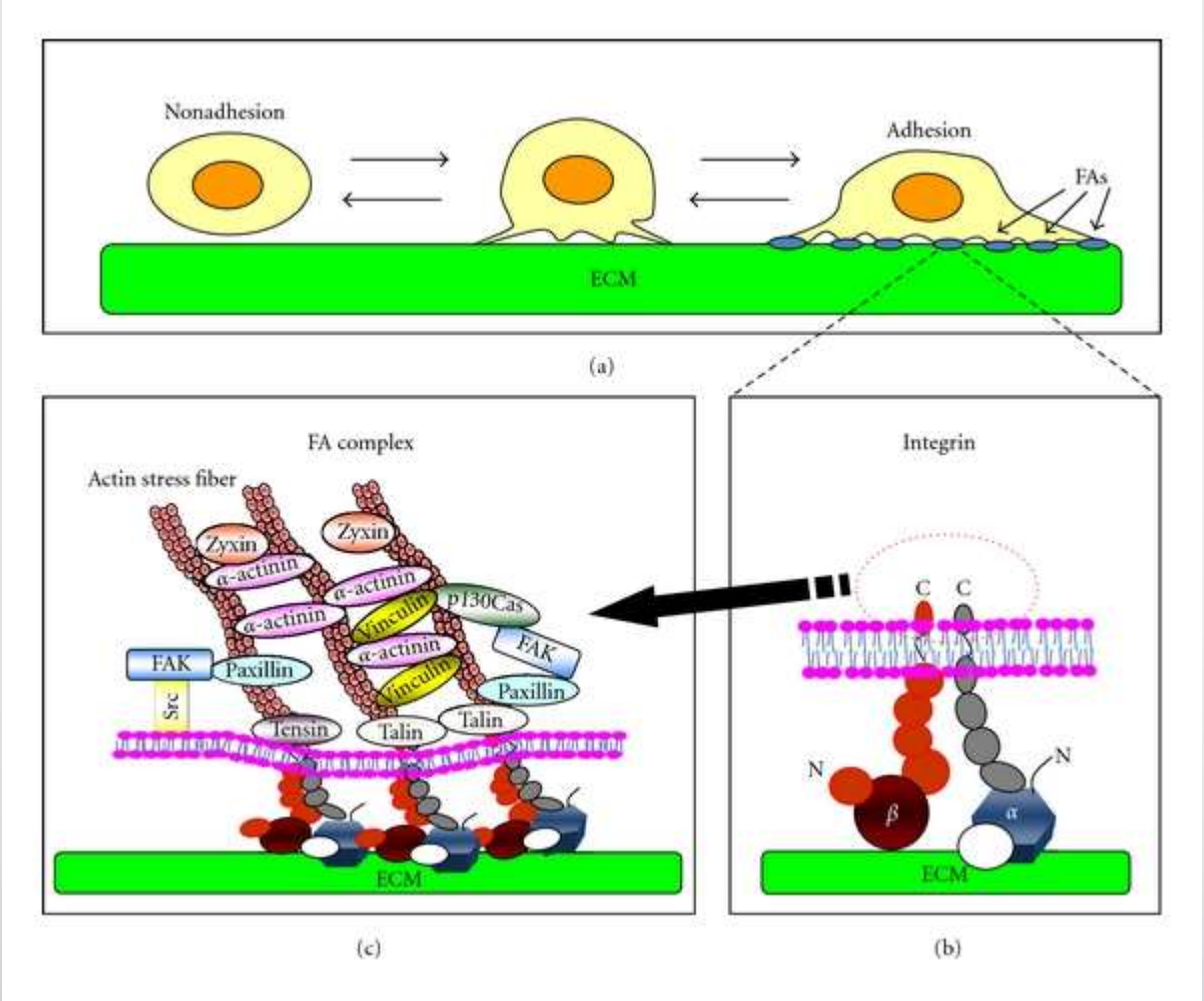
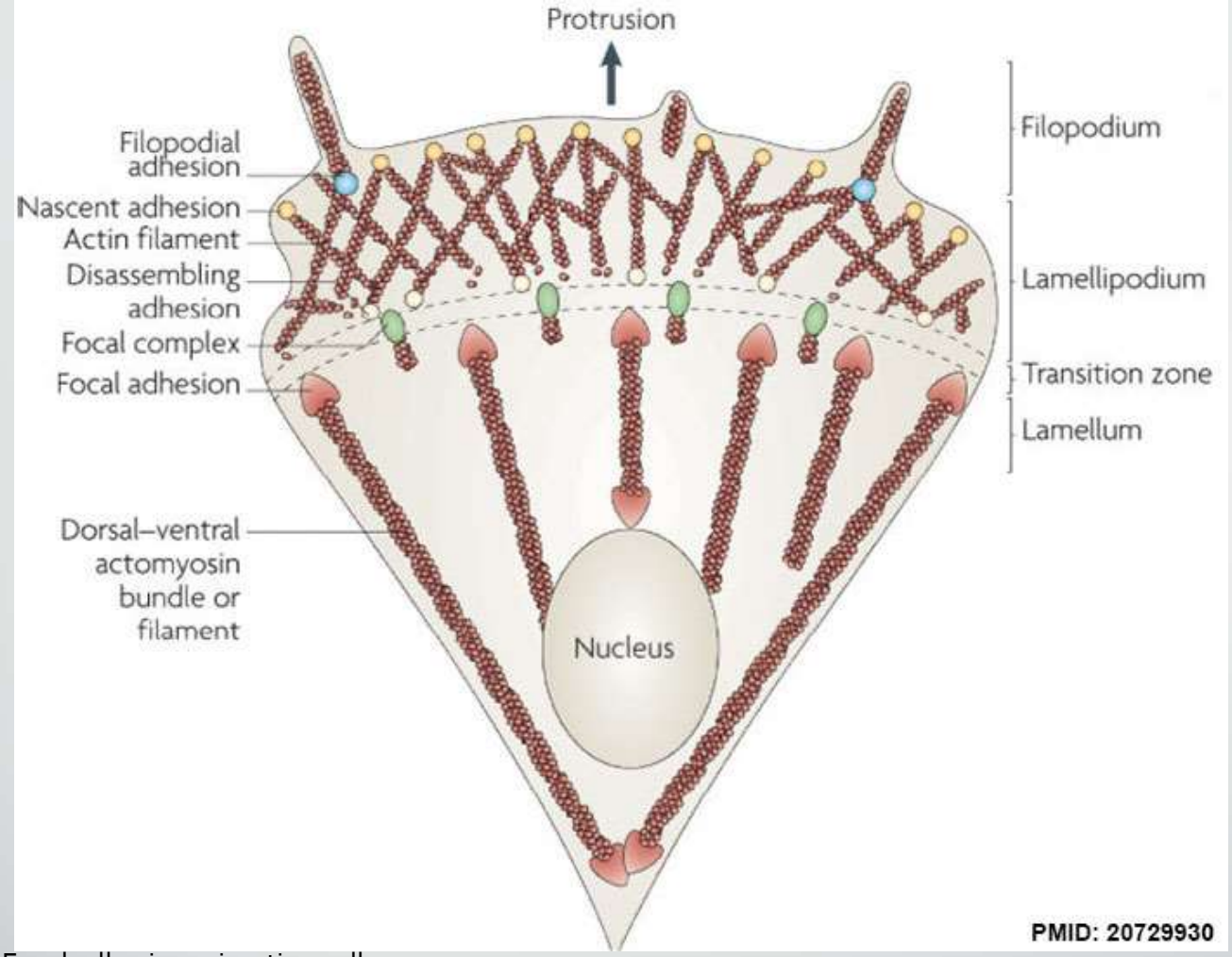


Figure 1: Integrin-mediated cell adhesion to the ECM. (a) Suspended cells adhere to the surface of ECM via integrins. Some of the nascent adhesion contacts grow and form mature focal adhesions (FAs). (b) Integrins function as a heterodimer composed of α- and β-chains. (c) The cytoplasmic portions of integrins recruit multiple cellular proteins and form cross-linked platforms to regulate both the actin cytoskeleton and signal transduction.

https://www.hindawi.com/journals/ijcb/2012/310616/fig1/



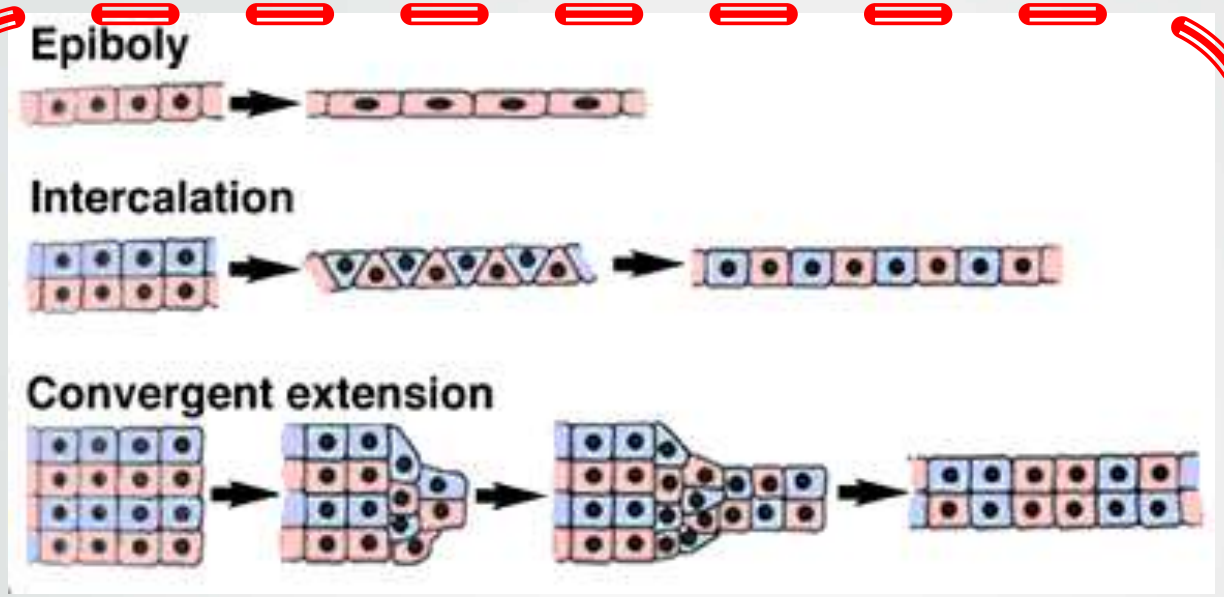
Focal adhesion migrating cell

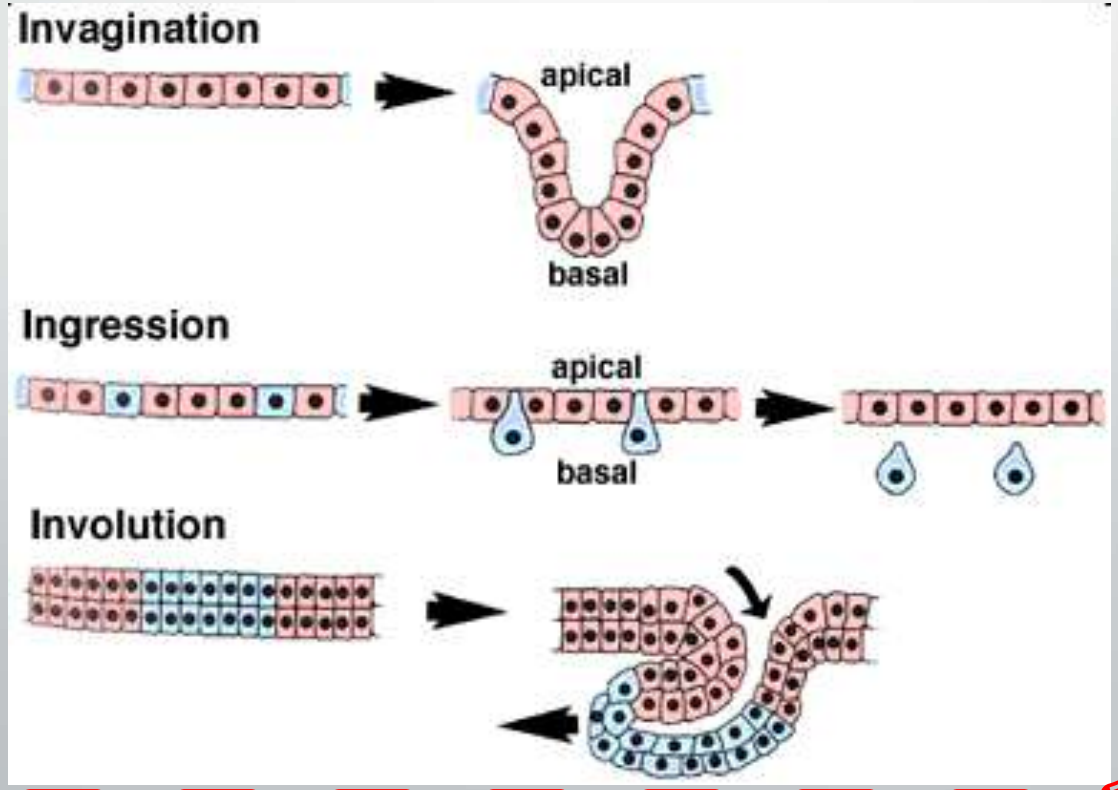
Adhesion is closely coupled with the protrusions of the leading edge of the cell (filopodia and lamellipodia). Adhesions (nascent adhesions) initially form in the lamellipodium (although adhesions may also be associated with filopodia) and the rate of nascent adhesion assembly correlates with the rate of protrusion. Nascent adhesions either disassemble or elongate at the convergence of the lamellipodium and lamellum (the transition zone). Adhesion maturation to focal complexes and focal adhesions is accompanied by the bundling and cross-bridging of actin filaments, and actomyosin-induced contractility stabilizes adhesion formation and increases adhesion size.

Reference

J Thomas Parsons, Alan Rick Horwitz, Martin A Schwartz **Cell adhesion: integrating cytoskeletal dynamics and cellular tension.** Nat. Rev. Mol. Cell Biol.: 2010, 11(9);633-43 PubMed 20729930

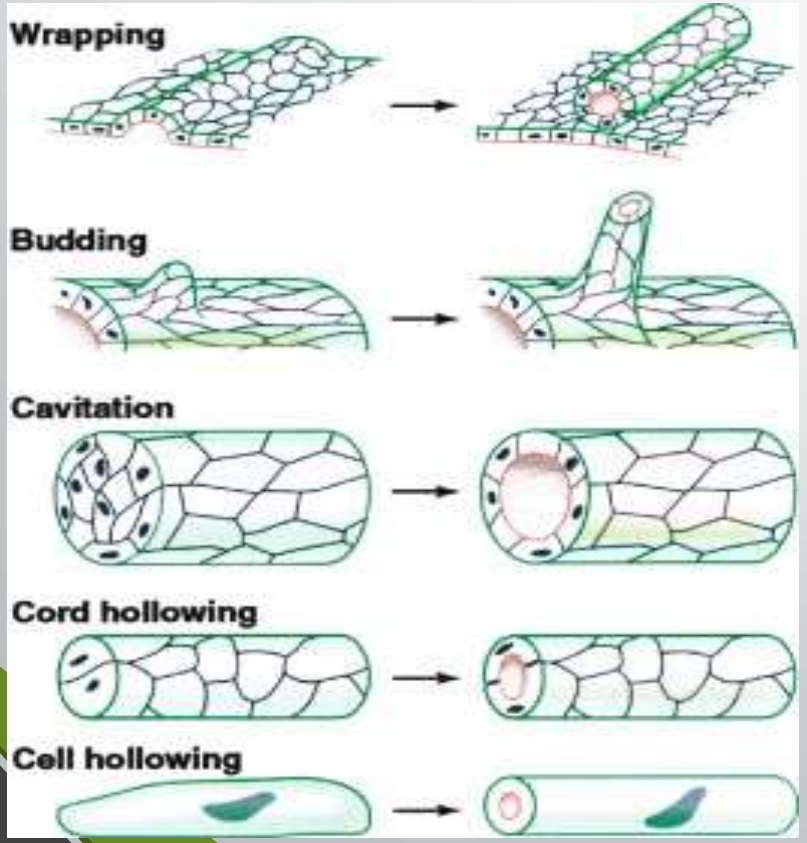
Epithelialis transformatio, tubulus képződés különböző fajtái

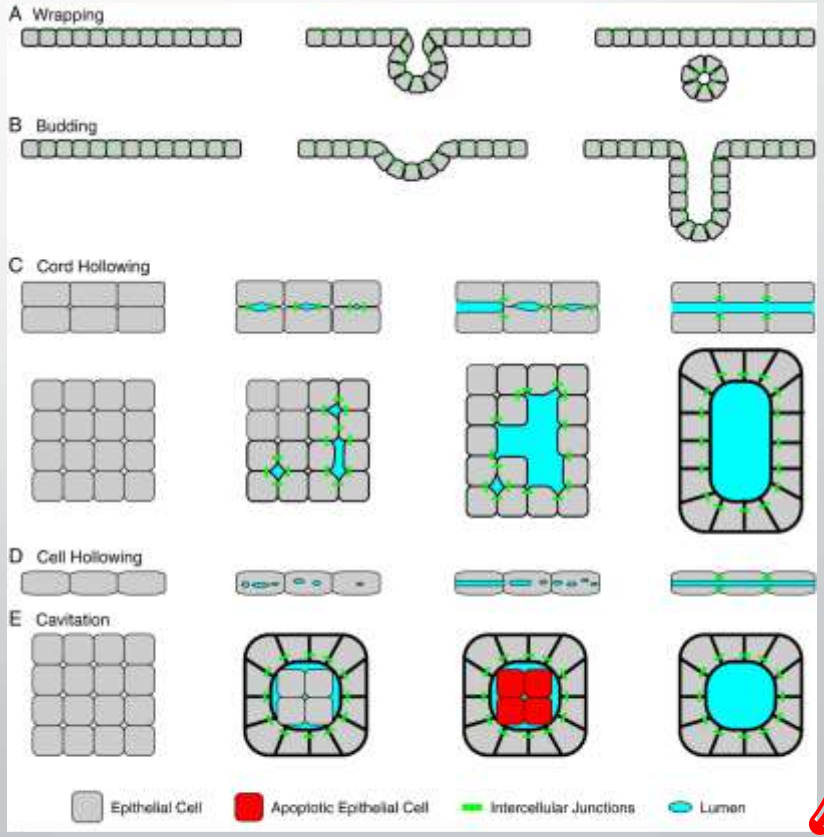

Epiboly
Intercalation
Convergent extension


Invagination
apical
basal
Ingression
apical
basal
Involution

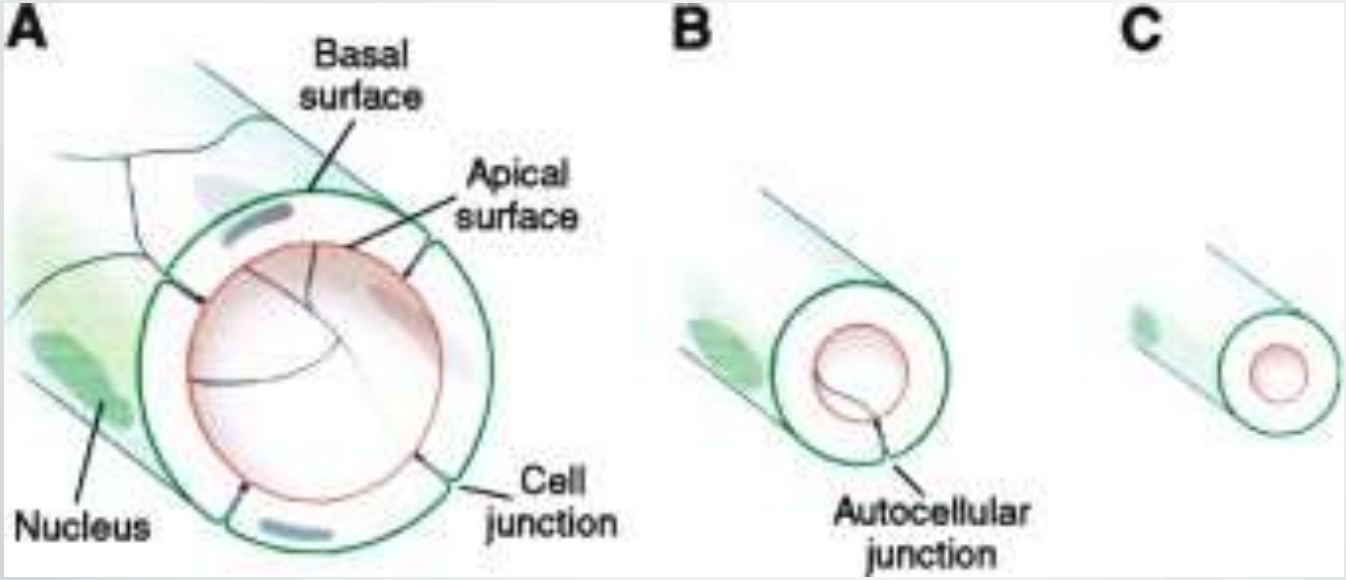
Morphological Processes of Tube Formation

Wrapping: a portion of an epithelial sheet invaginates and curls until the edges of the invaginating region meet and seal, forming a tube that runs parallel to the plane of the sheet.
Budding: a group of cells in an existing epithelial tube (or sheet) migrates out and forms a new tube as the bud extends. The new tube is a direct extension of the original tube.
Cavitation: the central cells of a solid cylindrical mass of cells are eliminated to convert it into a tube.
Cord hollowing: a lumen is created de novo between cells in a thin cylindrical cord.
Cell hollowing: a lumen forms within the cytoplasm of a single cell, spanning the length of the cell.
caption





Tubulus képződés



Types of Simple Epithelial Tubes

Tube walls are formed by polarized epithelial cells with their apical membrane surface (red) facing inward toward the lumen space, and their basal surface (green) exposed to the extracellular matrix.

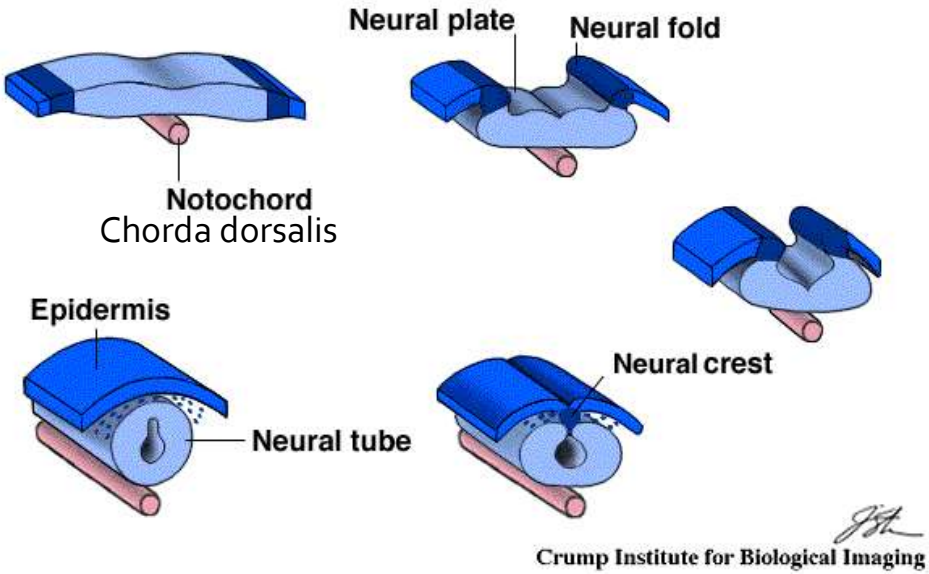
(A) A multicellular tube with four curved cells in the cross-section of the tube.

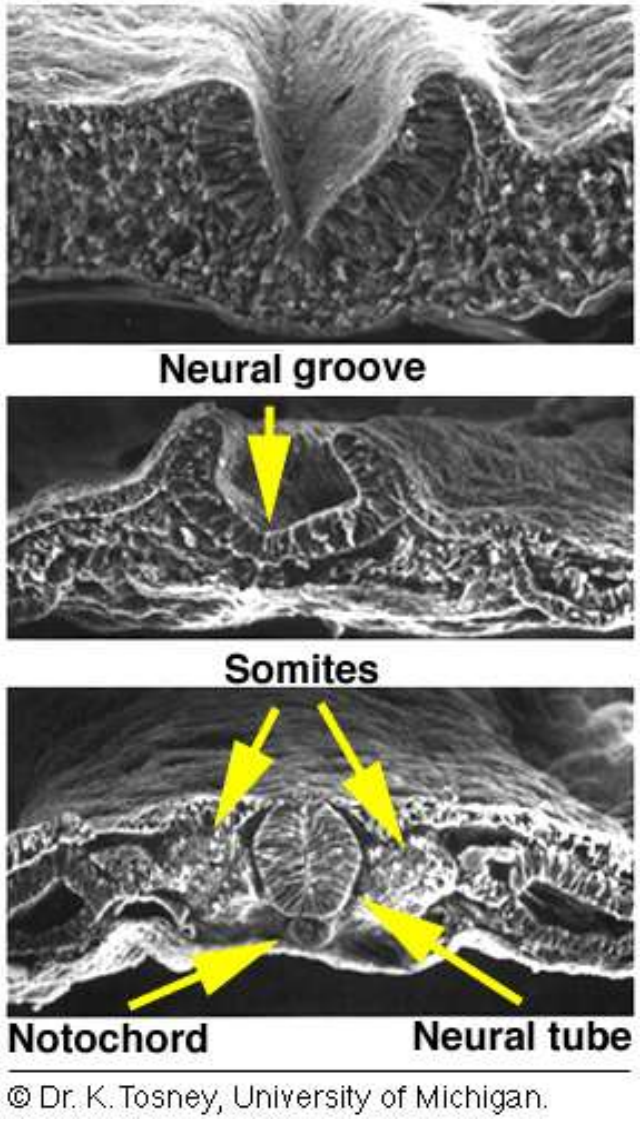
(B) A unicellular tube formed by a single cell, rolled up to enclose the lumen, and sealed with an autocellular junction.

(C) A unicellular tube with the lumen in the cytoplasm of the cell. There is no autocellular junction; the tube is "seamless."

Neurulation

Neuruláció

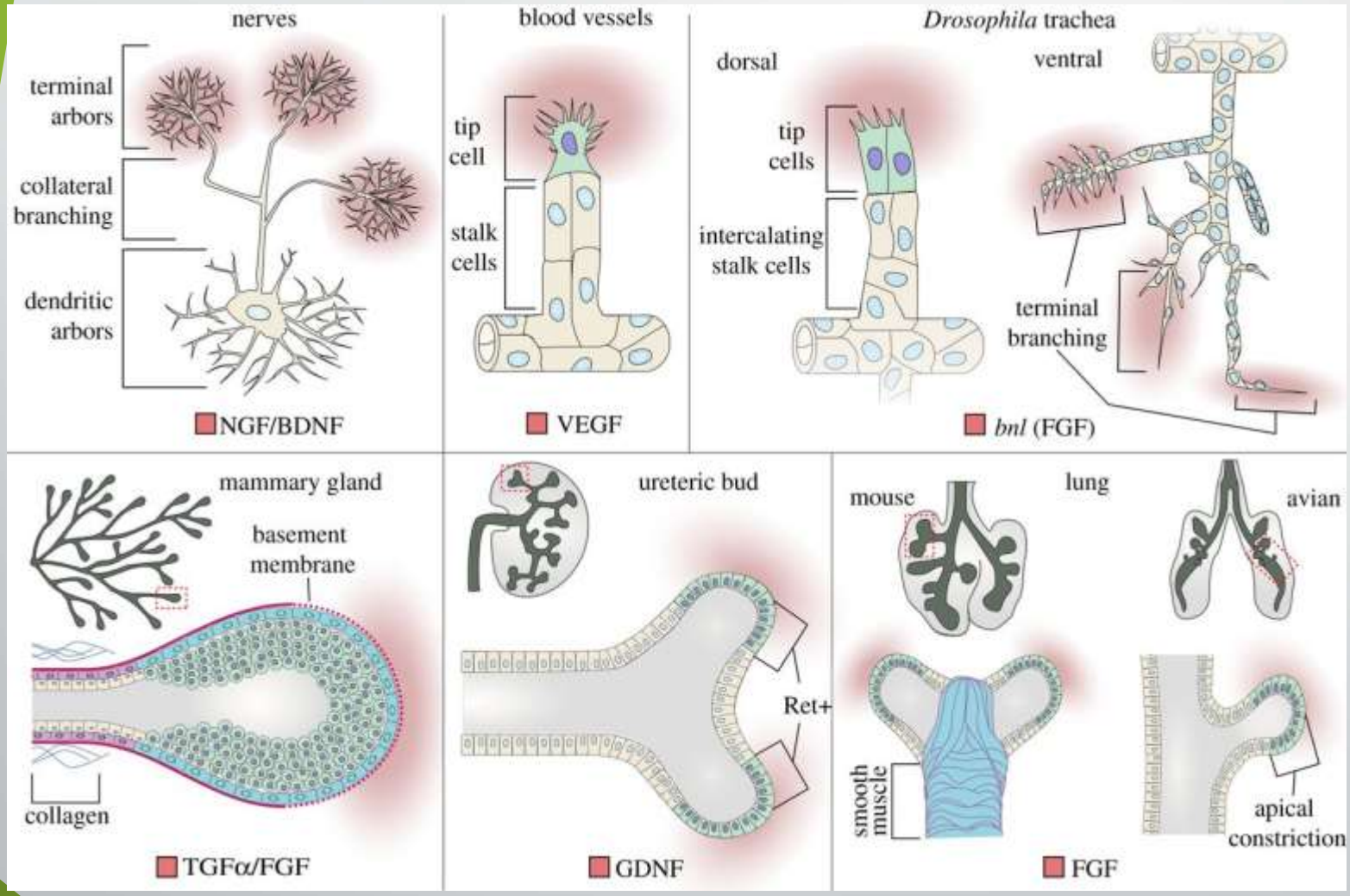




http://biology.kenyon.edu/courses/biol114/Chap14/chick_scan_EM.gif

Elágazódások (branching) különböző formái

Branching morphogenesis drives the development of multiple organs.



James W. Spurlin III, and Celeste M. Nelson Phil. Trans. R. Soc. B 2017;372:20150527

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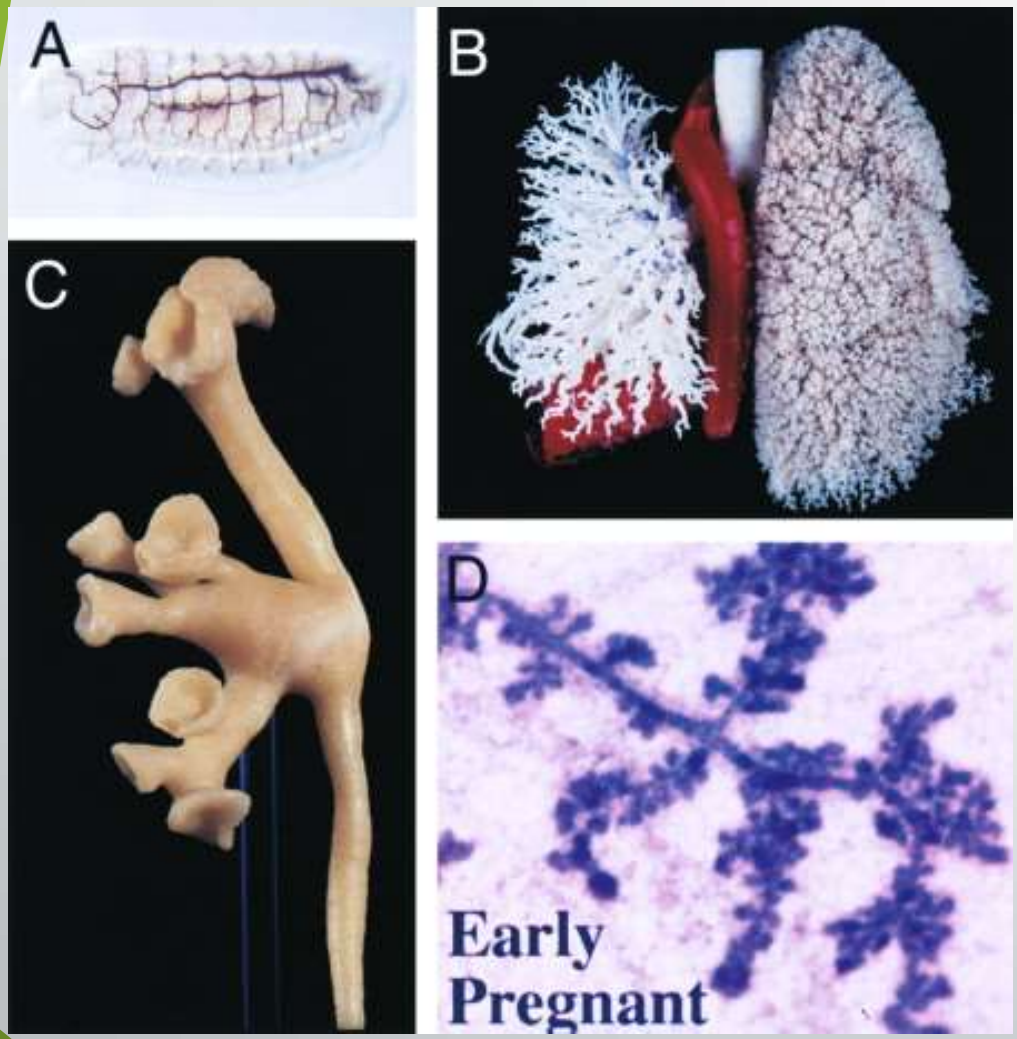
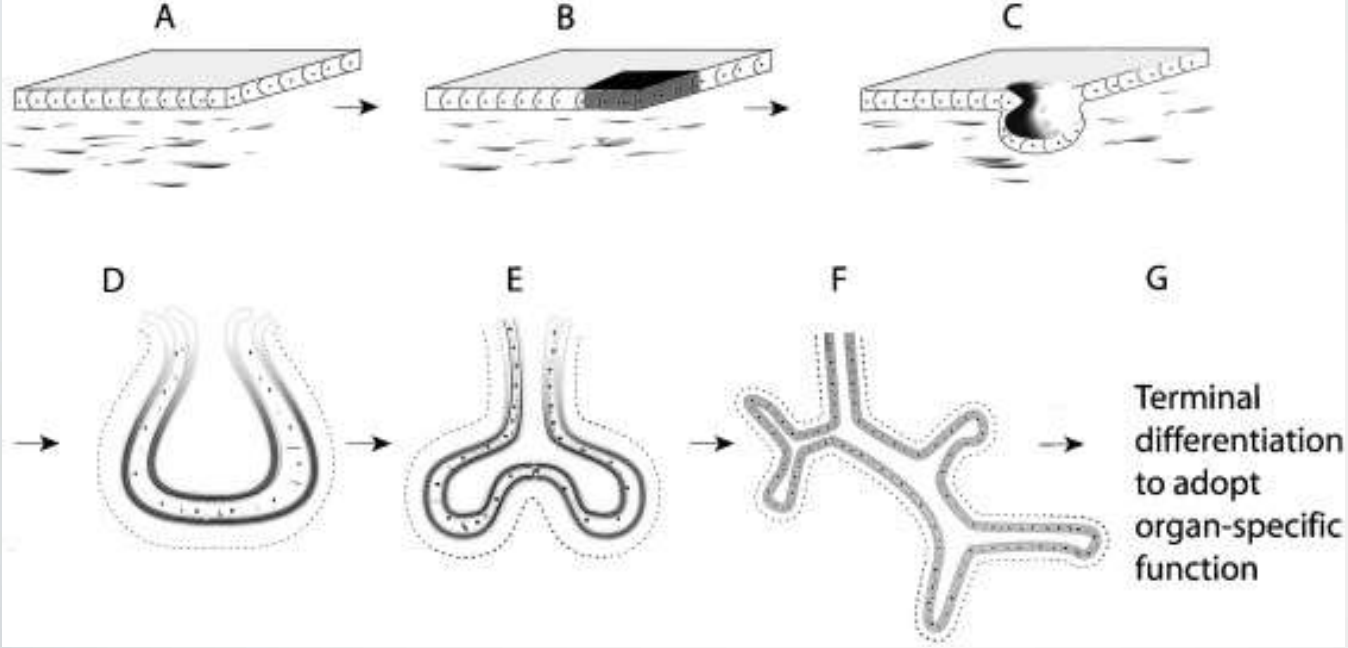
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Branching morphogenesis

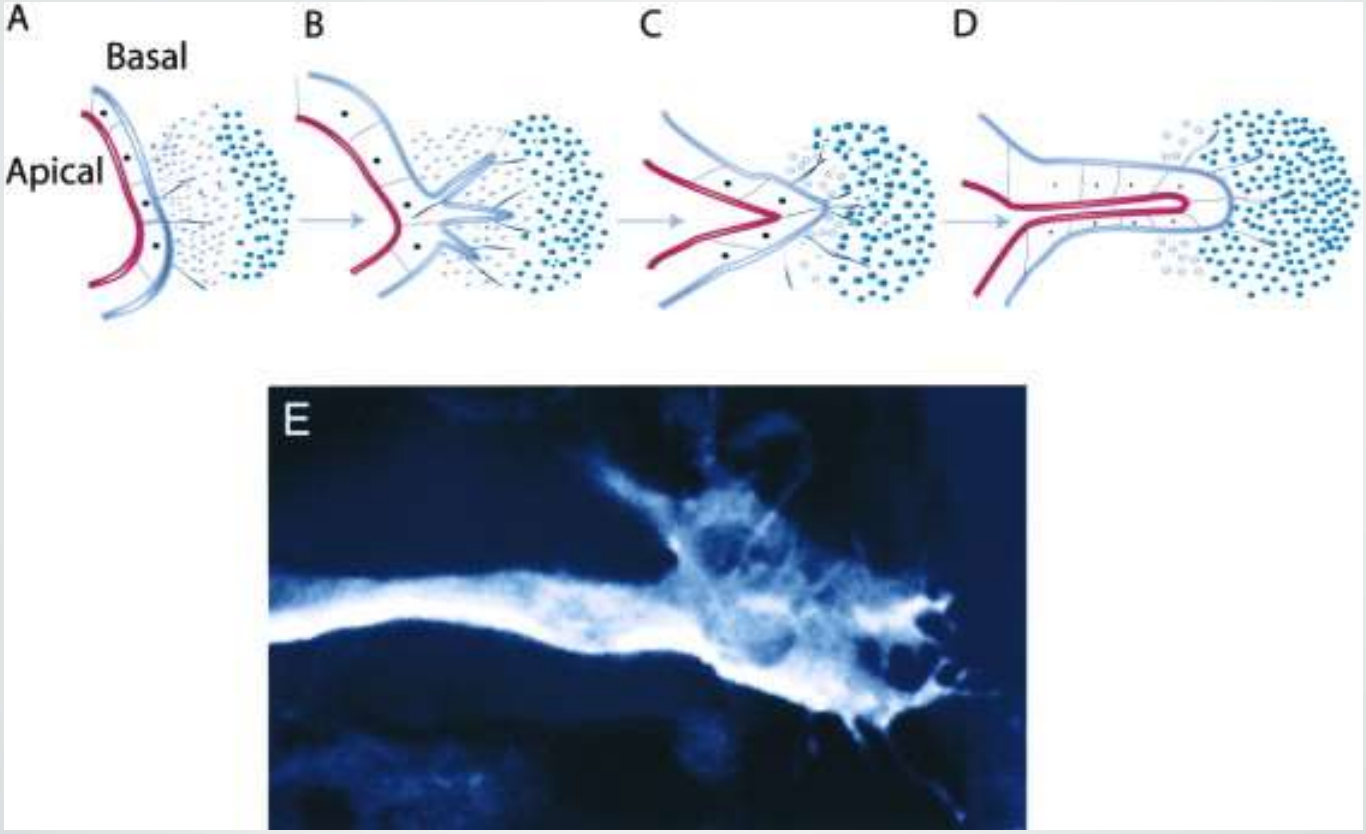


(A) The tracheal system of a stage 15 embryo, as visualized with a luminal antibody, 2A12.
(B) In white, preparation of the lung of an adult human using acryl polyester to fill in the airways. View from behind. The left lung has been filled less than the right half. Courtesy of H. Kurz, Anatomical Museum, University of Basel, Switzerland. In red, the descending aorta is visible.
(C) Collecting ducts of an adult kidney derived from the branched ureteric bud, filled with colored polyester. Courtesy of H. Kurz, Anatomical Museum, University of Basel, Switzerland.
(D) Branching in the mammary gland of a mouse in early pregnancy.



Branching Morphogenesis at the Cellular Level

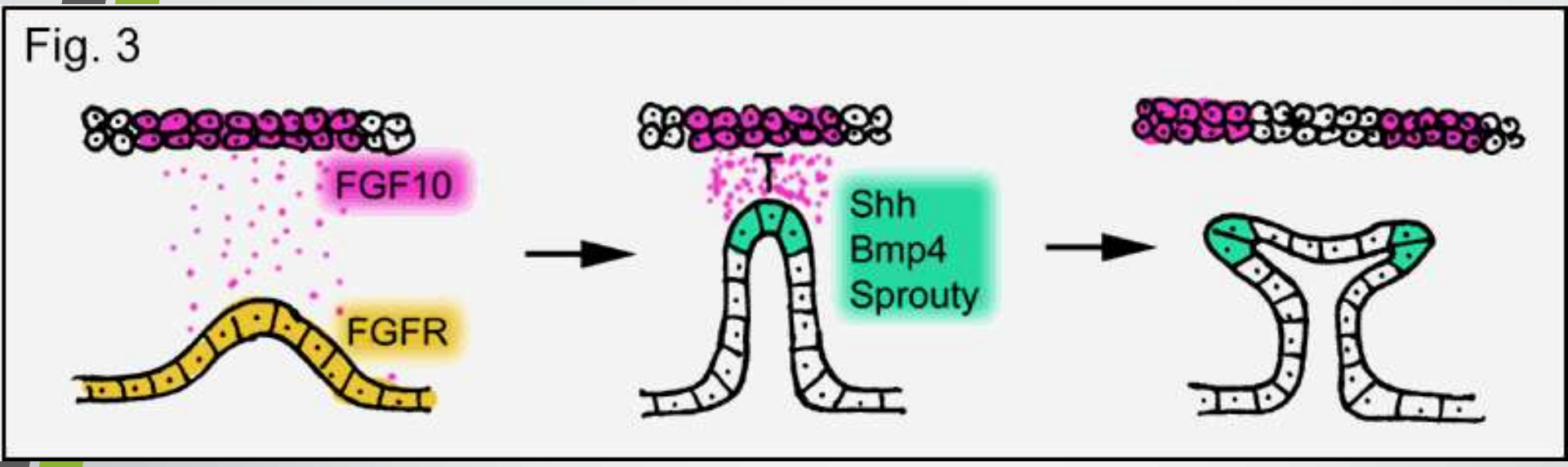
Schematic representation of a typical branching process. In many cases, a subgroup of cells (schematically illustrated in black in [B]) of a preexisting epithelium (A) is assigned to undergo branching morphogenesis by the expression of a specific subset of transcription factors and/or signaling mediators. As a consequence of this determination step, these cells invaginate or form a primary bud (C). Branch formation is then initiated in the invaginated (or budded) structure (from [D] to [E]) and the branching process can be reiterated numerous times (F). In addition, lateral branches can be induced. After the branching process, complex processes lead to the development of specialized terminal structures, a process that is different in different branched organs. Because the development of the vascular system does not in general follow the scheme outlined in this figure, we have excluded in this review a description of how the branched aspects of the arterial and venous network arises.



Branching Morphogenesis at the Subcellular Level

Control of branch formation at the subcellular level in the Drosophila tracheal system. The FGF receptor tyrosine kinase Breathless is expressed in all tracheal cells. The activation of the receptor in the cells at the tip of the outgrowing branches, presumably due to their proximity to the localized source of the FGF ligand Branchless (blue), leads to the formation of filopodial cell extensions (A). Cells at the tip of the bud subsequently form broader cell extensions (B), and ultimately move toward the Bnl source (C and D). In (E) is shown a confocal image of a tracheal branch of a stage 14 Drosophila embryo expressing a membrane-bound version of GFP specifically in tracheal cells. One can clearly see that only the two leading cells produce filopodia (see also Sutherland et al. 1996 and Ribeiro et al. 2002).

Development of mammalian's lung



The underlying principle is again a mesenchymal-epithelial cell-cell interaction mediated by FGF. Epithelial cells, expressing *FGF receptor*, respond to the secretion of FGF from nearby mesenchyme by bud formation and bud extension towards the FGF source. Exposure of the branch tip to high concentrations of FGF induces the expression of secondary genes in the tip such as bone morphogenetic protein 4 *(BMP4)*, sonic hedgehog *(Shh)* and a mammalian sprouty ortholog *(Sprouty 2)*, thus, turning the tips of the bronchial branches into signaling centers. BMP_4 inhibits epithelial cell proliferation limiting branch extension. Shh is proposed to inhibit *FGF10* expression in the mesenchyme near the tip, which splits *FGF10* expression promoting the next round of branching and Sprouty2 (like drosophila *sprouty)* restricts branching to the tip of the branch.

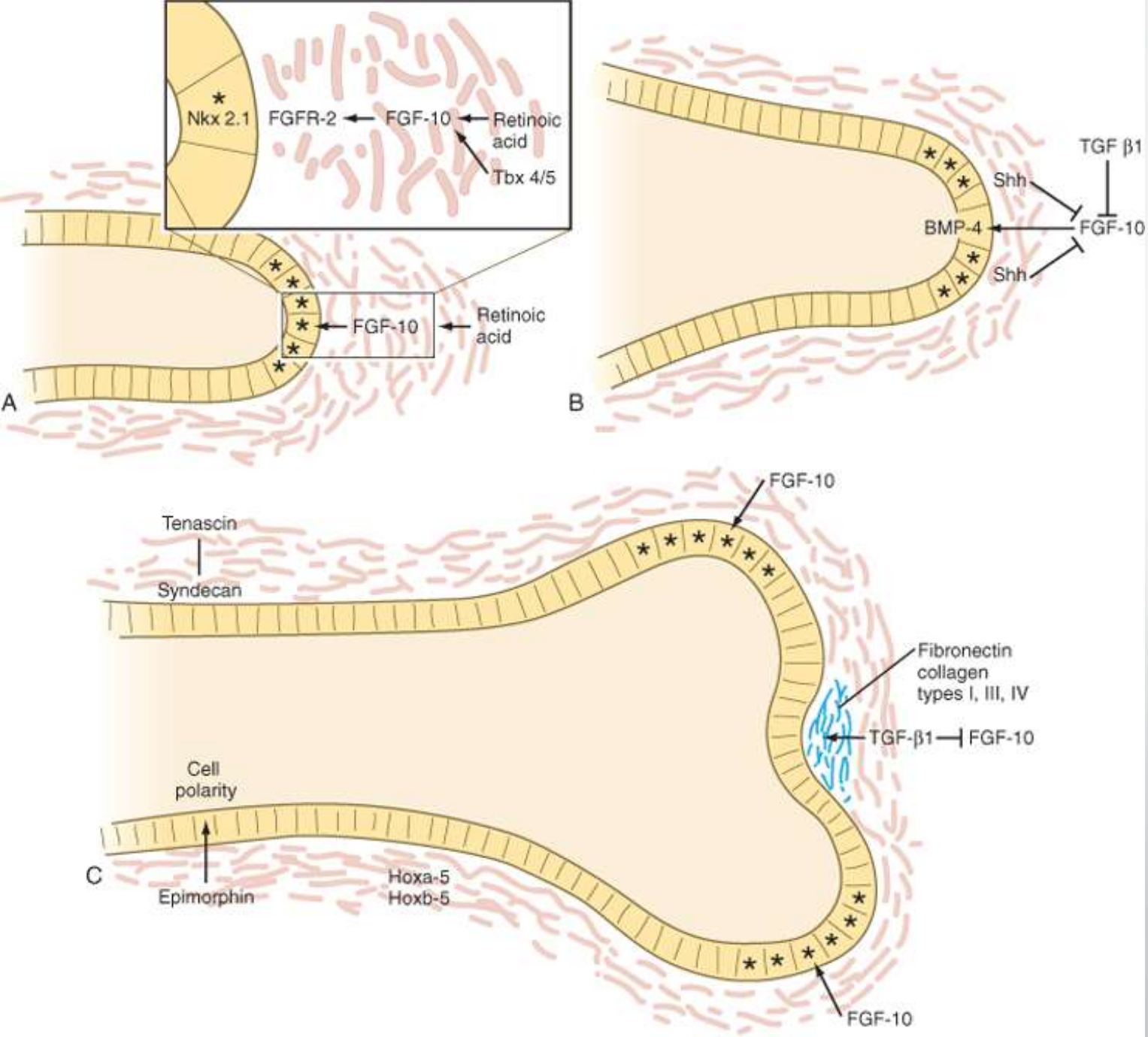


Figure 15-26 Molecular aspects of outgrowth and branching of the respiratory tree. A, The tip of an elongating respiratory duct. FGF-10 secretion in the mesenchyme stimulates the growth of the tip of the epithelial duct toward it. B, The prelude to branching. Inhibition of FGF-10 signaling at the tip of the duct leads to stabilization of that area. C, Cleft formation.

Carlson: Human Embryology and Developmental Biology, 4th Edition.
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