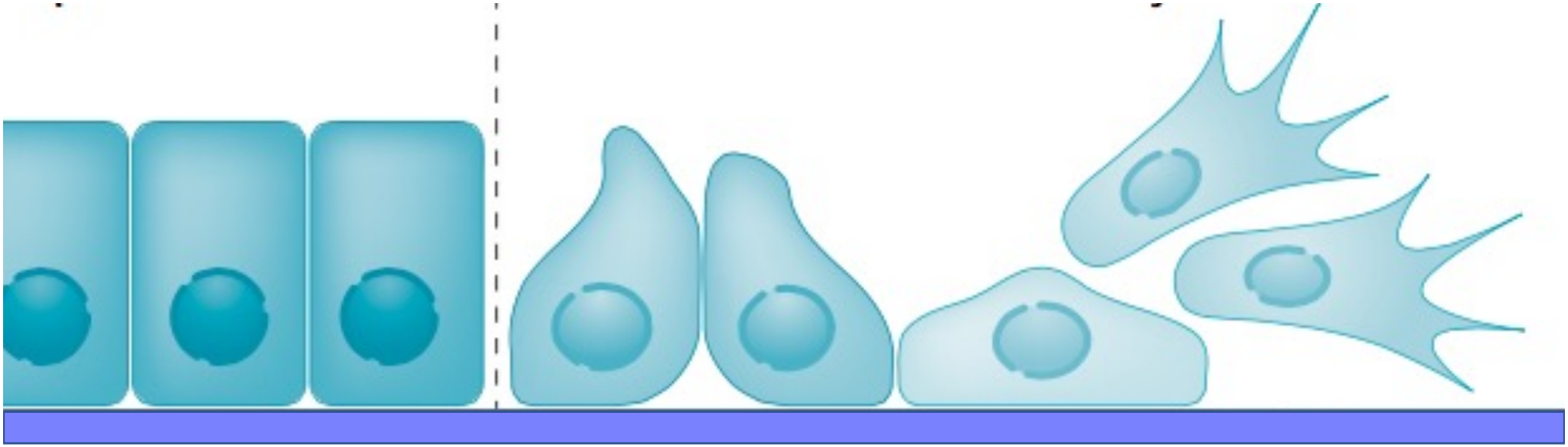
Migration, polarity, EMT, metastasis



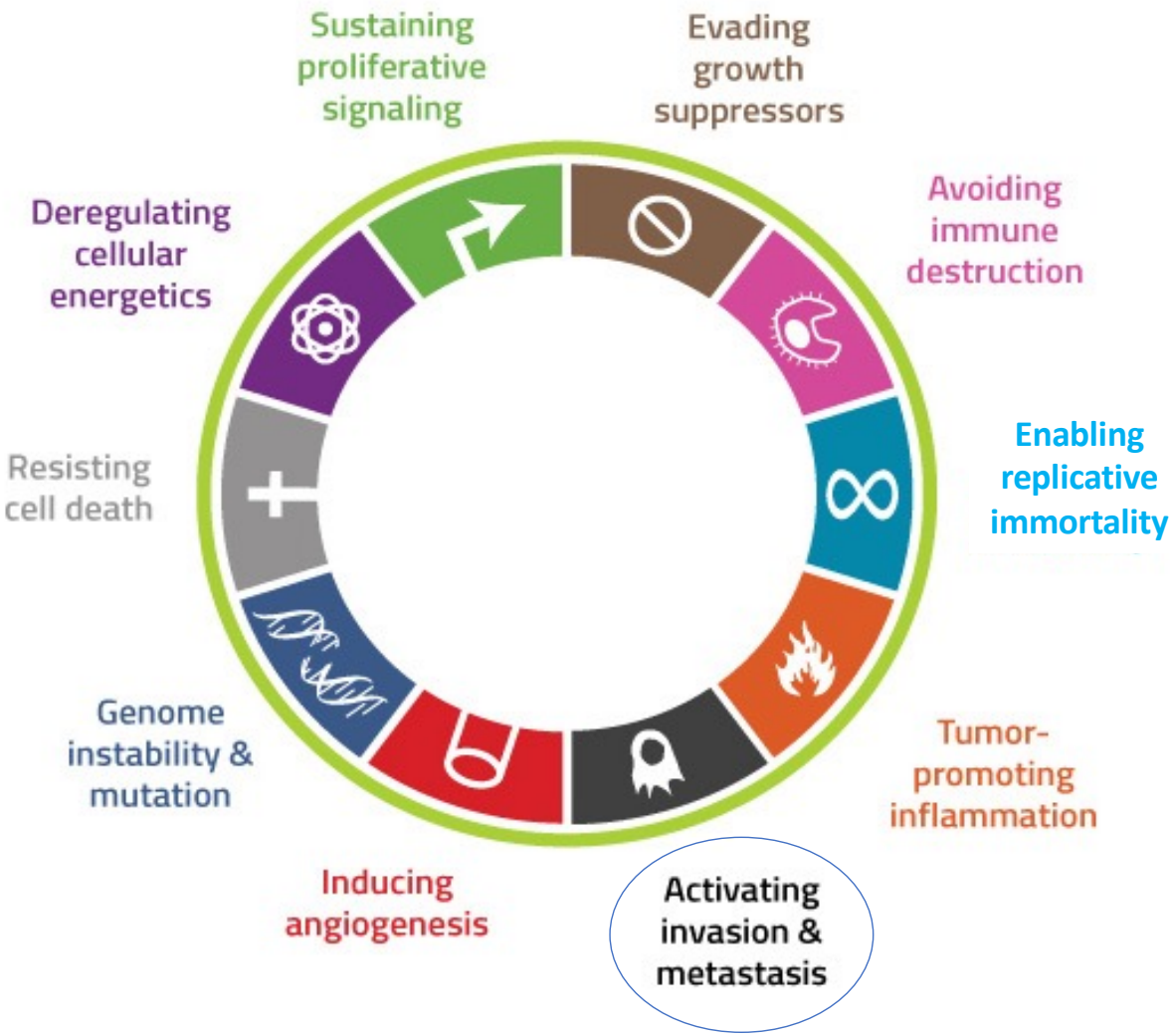
M1 International, Cancer Cell Biology, TU n°05

université PARIS-SACLAY
GRADUATE SCHOOL
Health and
Drug Sciences

d2hp

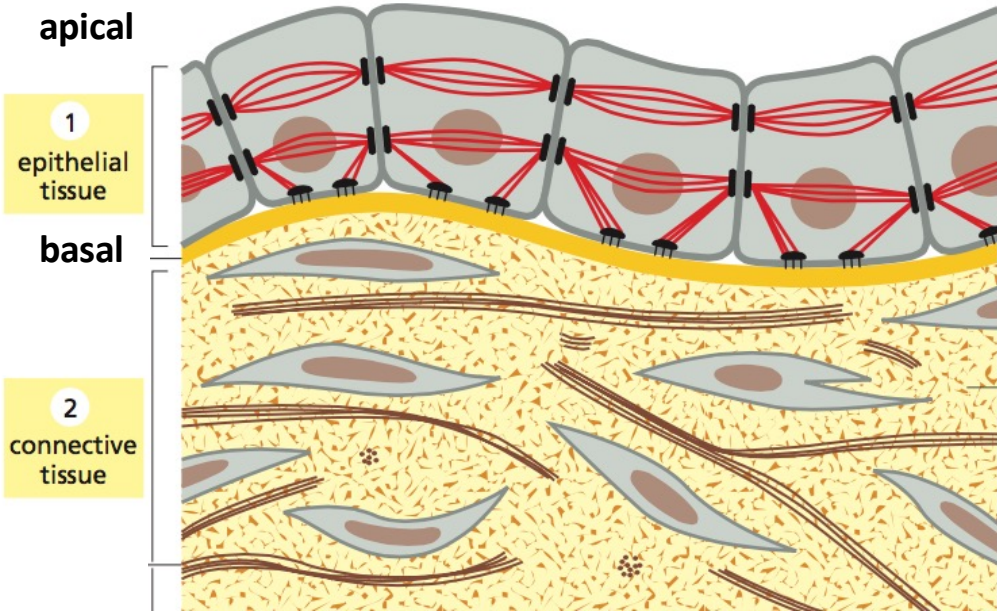
université PARIS-SACLAY
FACULTÉ DE
PHARMACIE

Hallmarks of cancer



Adapted from Hanahan et Weinberg. Cell 2011

Epithelial cells hold together and to the extra cellular matrix



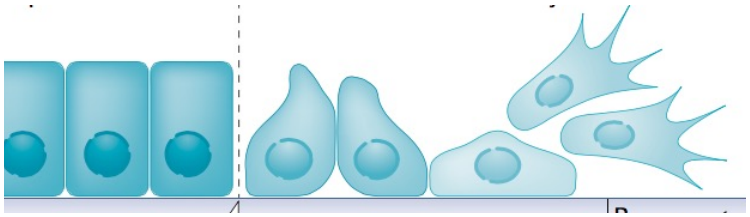
cytoskeleton linked to junctions

basal lamina

extracellular matrix (ECM)
+ cells
(+ vascularization)

EMT :
Epithelial-mesenchymal transition

MET :
Mesenchymal-epithelial transition



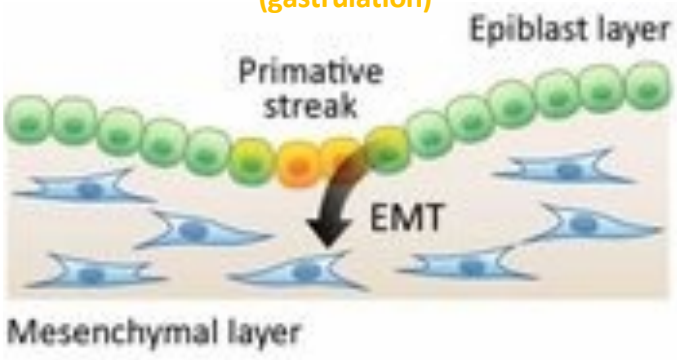
EMT & MET = Normal during development, but abnormally reactivated during metastasis

EMT
- **Junctions altered**
- **Polarity switch**
- **Epithelial fate lost (mesenchymal)**
- **ECM modified**
- **migration/invasion**

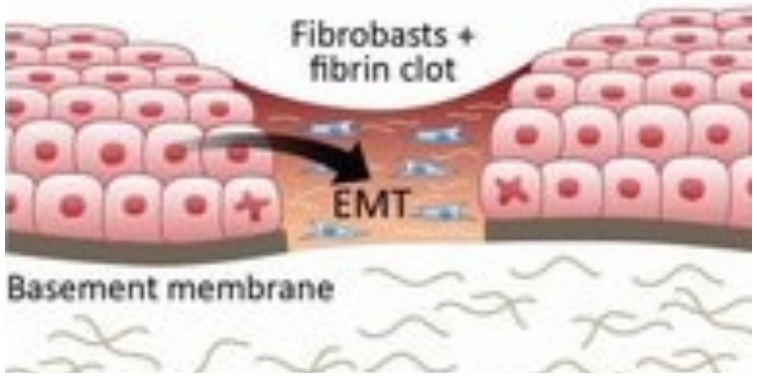
Figure 19-1 & 20-16, Molecular Biology of the Cell 6th
Yamada & Sixt,Mol Cell Biol, 2019

EMT / MET in physiopathology

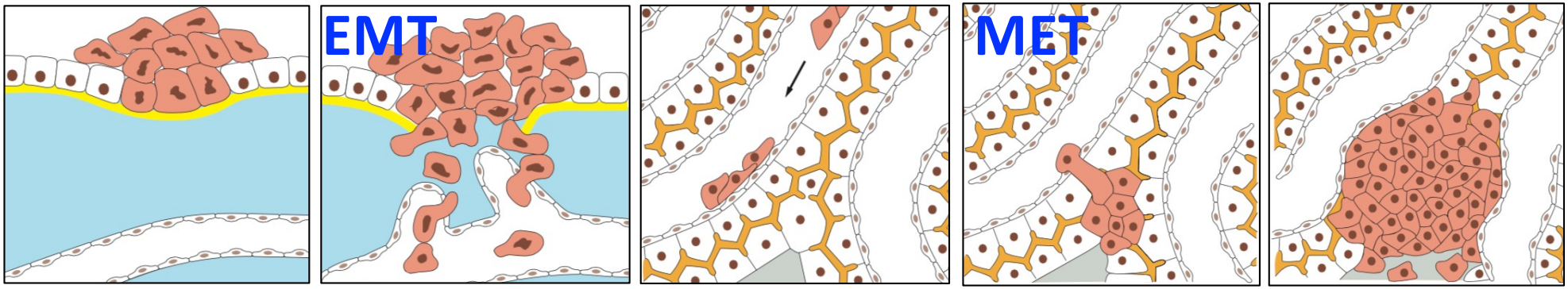
Embryonic development
(gastrulation)



Wound healing

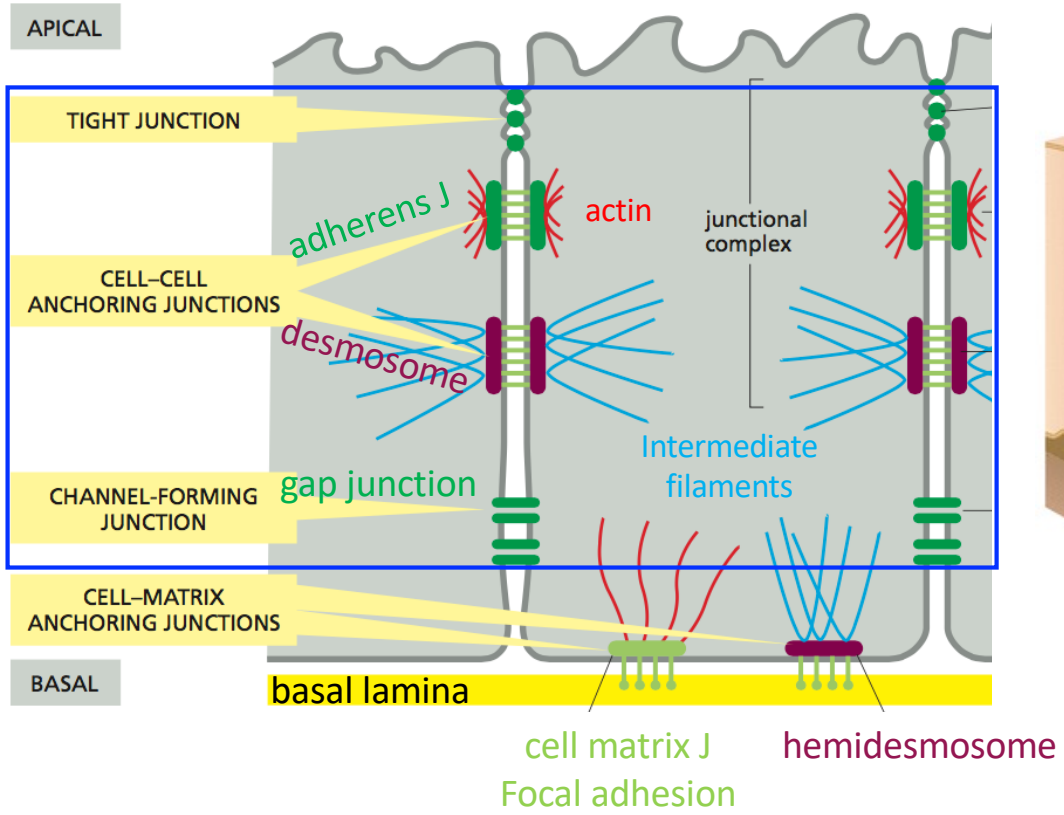


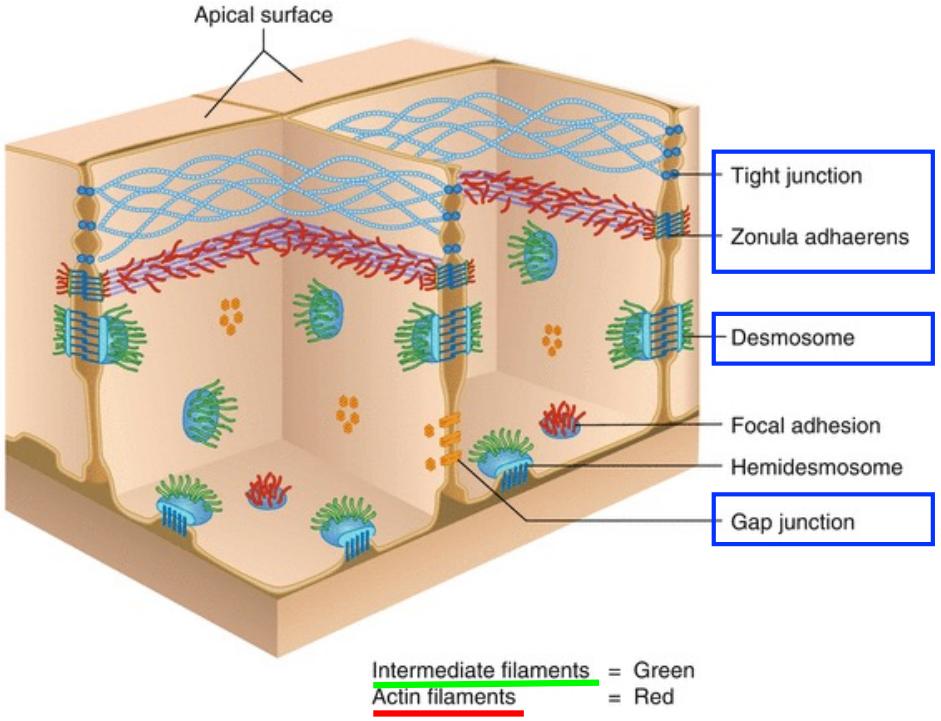
Cancer metastasis



Scanlon, 2014
Adapted from igure 20-16, Molecular Biology of the Cell 6th

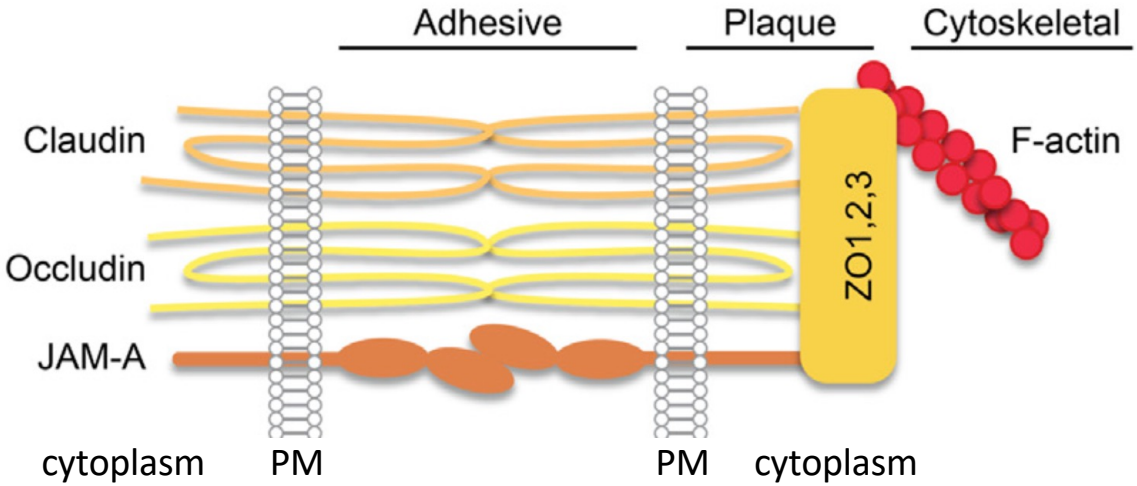
6 types of junctions in epithelial cells : 4 are cell-cell junctions





Adapted from figure 19-2, Molecular Biology of the Cell 6th

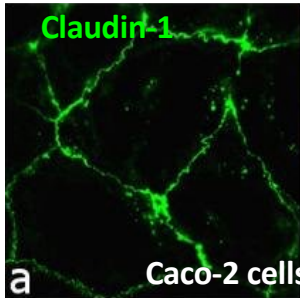
1. Tight junctions : claudins / occludins / JAMs



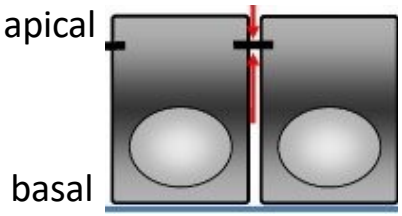
JAM : Junctionnal Adhesion Molecule (immunoglobulin super family)
ZO : Zonula Occludens proteins
PM : plasma membrane

transmembrane homophilic adhesion proteins
+ cytoplasmic scaffold proteins

immunofluorescence

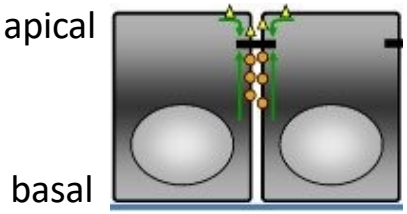


Barrier for extracellular matrix



no fluid permeability (selective ions)

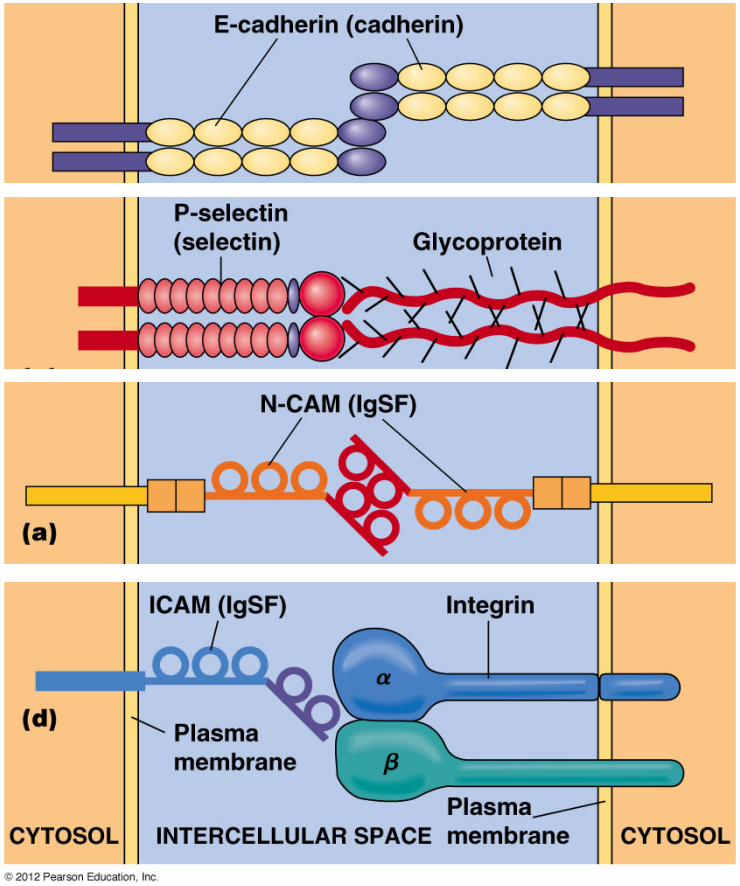
Fence in plasma membrane



Prevent protein diffusion in PM

Thermofisher
Sawada, Path. International, 2012

2. & 3. Cell-cell anchoring junctions : cell adhesion molecules (CAMs)



Cadherins / tissue integrity (homophilic, Ca2+ dpt)
Adherens junctions
(non classical cadherins in desmosomes)

Selectins / transient binding to glycoproteins (Ca2+ dpt)
Transient junctions (heterophilic)

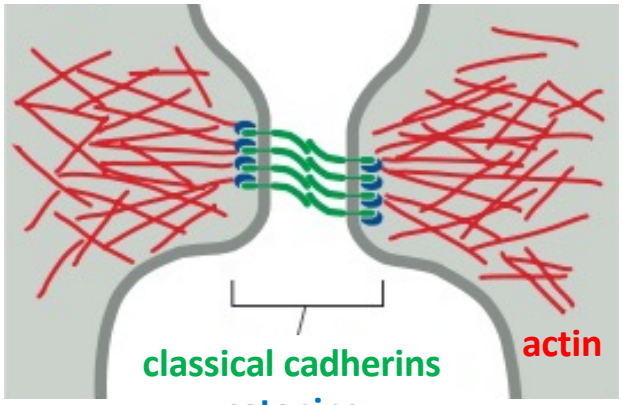
IgCAMs : immunoglobulin super family (fine tuning adhesion)
- NCAM neural (homophilic)
- EpCAM epithelial (homophilic)
- ICAMs intercellular, VCAMs vascular (heterophilic integrin)

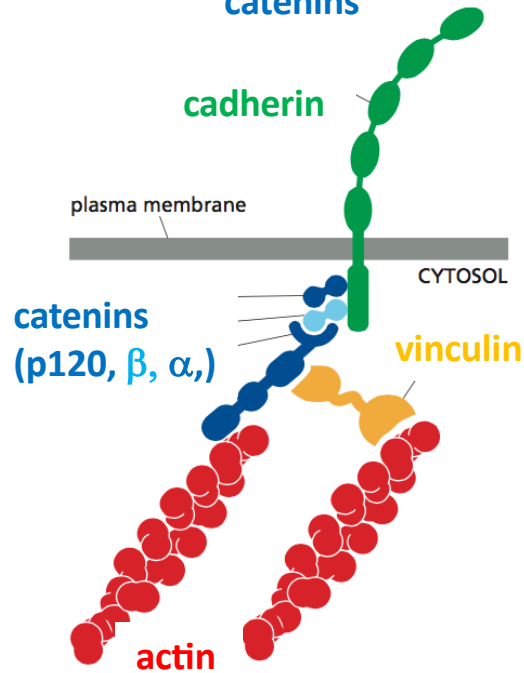
(cell / matrix junctions: Integrin / ECM binding (Ca2+ dpt))

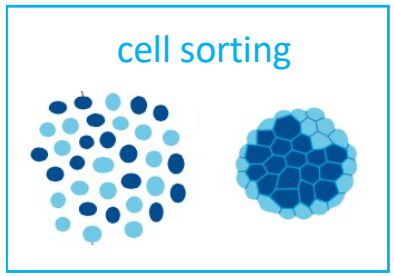
Pearson Education Inc, 2012

2. Adherens junctions and Desmosomes : cadherins

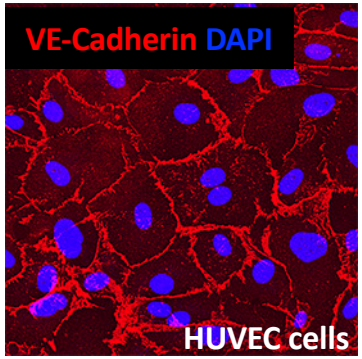
Adherens junctions /actin







E : epithelial
N : nerve
VE : vascular, endothelial
...



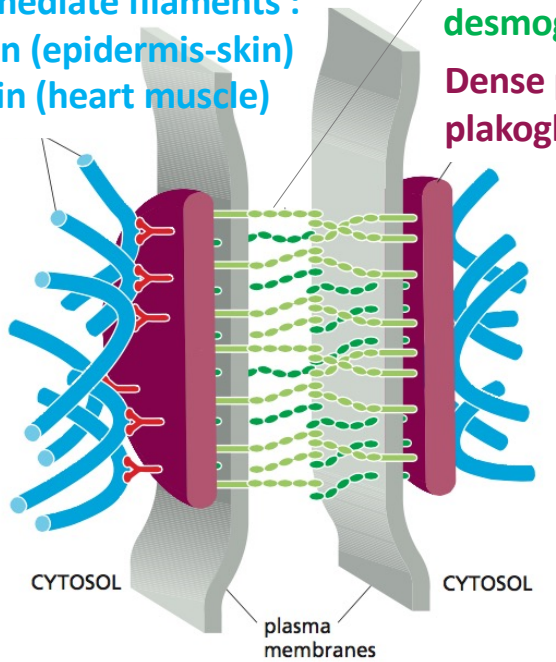
R&D Systems

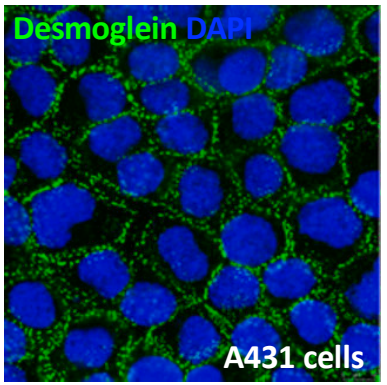
Anchoring desmosomes / intermediate filaments (mechanical strength)

Intermediate filaments :
keratin (epidermis-skin)
desmin (heart muscle)

Non classical cadherins :
desmoglein, desmocollin

Dense plaque of adaptor proteins :
plakoglobin, plakophilin, desmoplakin





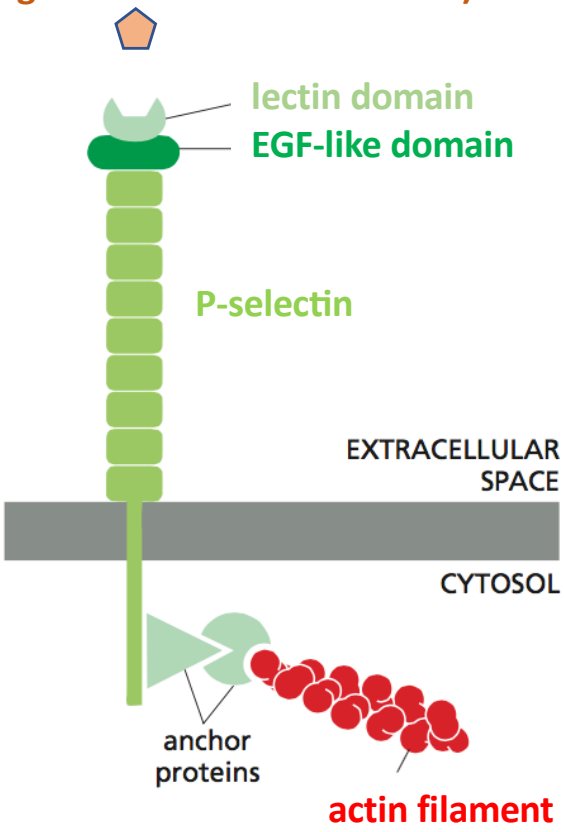
Merck

Figure 19-9-11 & 16, Molecular Biology of the Cell 6th

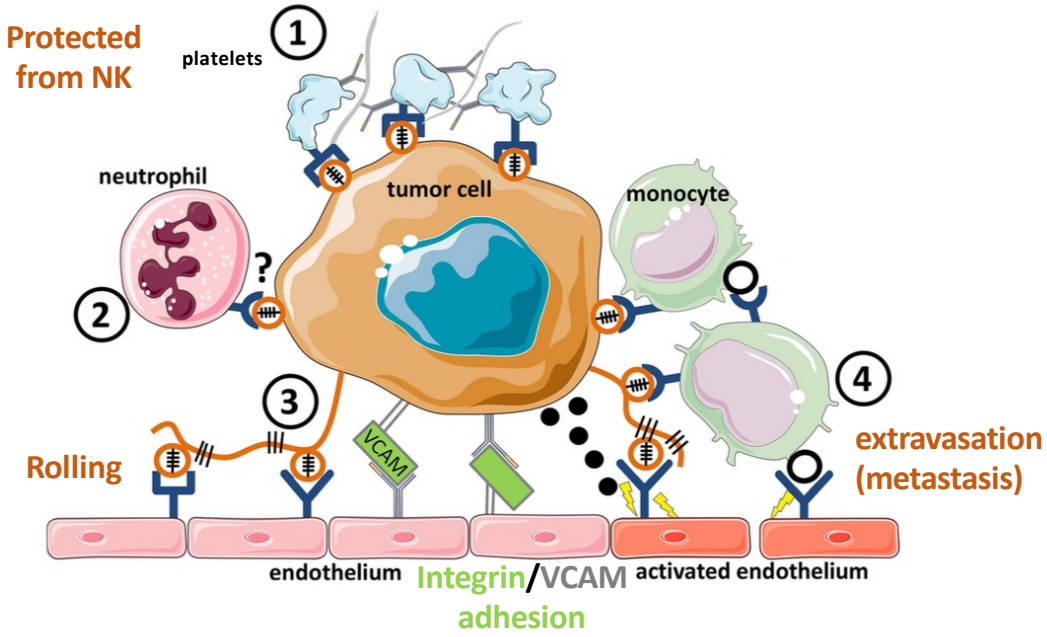
3. Transient cell-cell adhesion : selectins

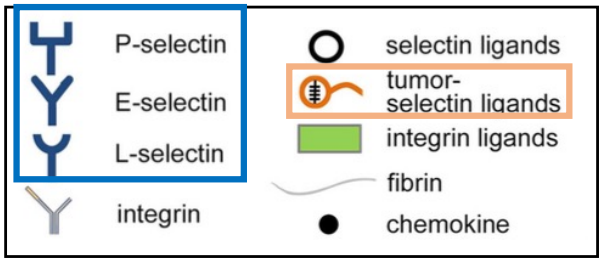
(not epithelial-epithelial contact)

Ligands = Glycoproteins, glycolipids (oligosaccharide at cell surface)



Tumor cells (or white blood cells) in blood vessels rolling in the bloodstream





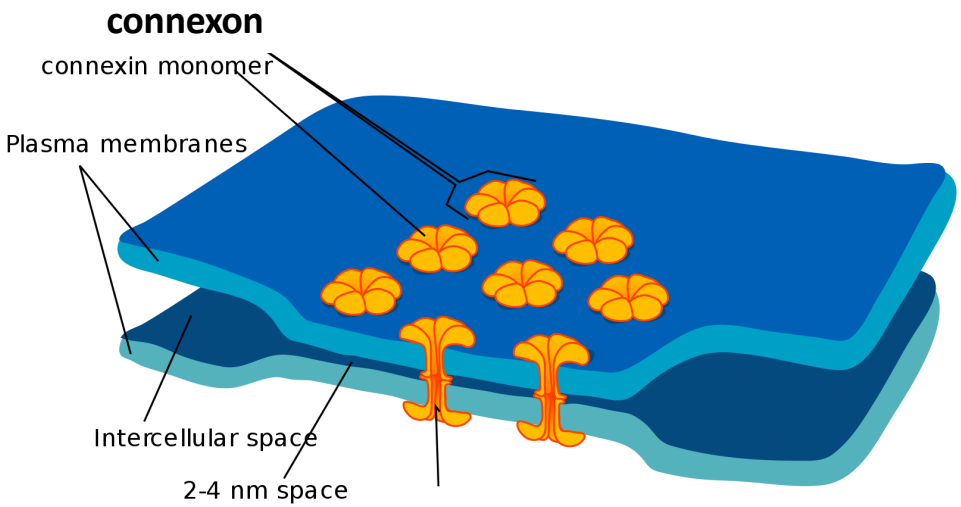
P-selectin : activated platelets, endothelial cells (1) (3)

L-selectin : leukocytes (white blood cells) (2) (4)

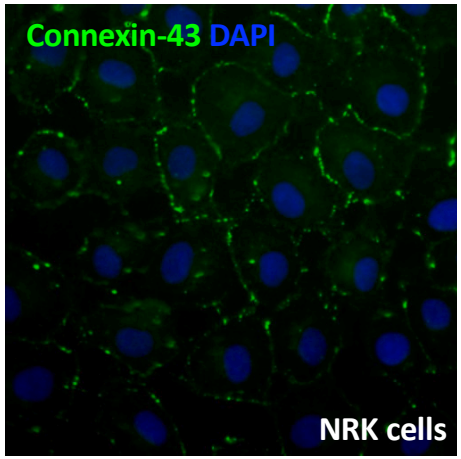
E-selectin : activated endothelial cells (3) (4)

Figure 19-28, Molecular Biology of the Cell 6th
Laübli & Borsig, Front Imm, 2019

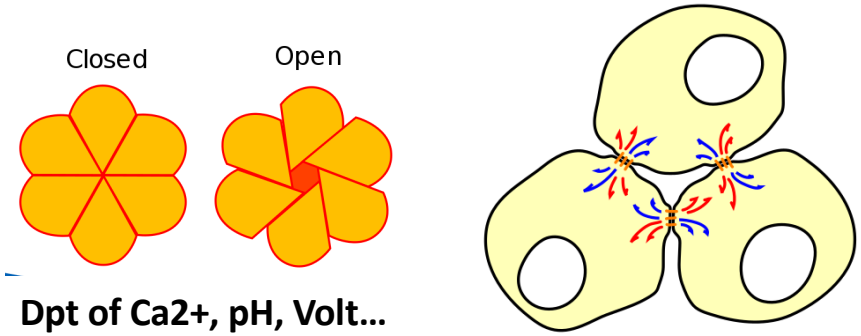
4. Channels / gap junctions : connexins



Hydrophilic channel



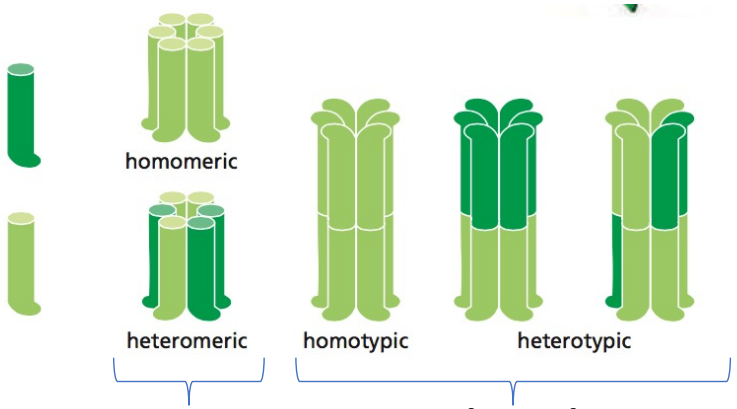
R&D Systems



Dpt of Ca2+, pH, Volt…

Pore size of 1.4 nm, exchange inorganic ions and small water-soluble molecules (1 kDa)

Chemical and electrical coupling



Adapted from wikipedia

Figures 19-23 & 25, Molecular Biology of the Cell 6th

Cell-cell junctions and diseases

Tight junctions : claudin

Leaky barrier : enteric disorder, asthma, neurodegeneration …

Sawada, Path. International, 2012, Greene et al., Fluids & Barriers of the CNS, 2019

Anchoring junctions : adherens junction - classical cadherins

Macular dystrophy (eye disease)

El-Amraoui & Petit, Pro. Mol. Biol. Trans. Sci., 2013

Anchoring junctions : desmosome - non classical cadherins

- Arrhythmogenic cardiomyopathy if plakophilin, desmoplakin, desmoglein or desmocolin mutations.

Akdis et al., Cardiovasc Med, 2017 , Stevens et al., J. Card. Dev & Disease, 2020

- Pemphigus = blistering skin disease if desmoglein autoantibodies

Schmidt et al., The Lancet, 2019

Gap junctions : connexin

- Atrial fibrillation (heart arrhythmia))
- Charcot-Marie-Tooth disease (PNS)

Hernández-Guerra et al., J. Hepato., 2019

Virus/bacteria infections

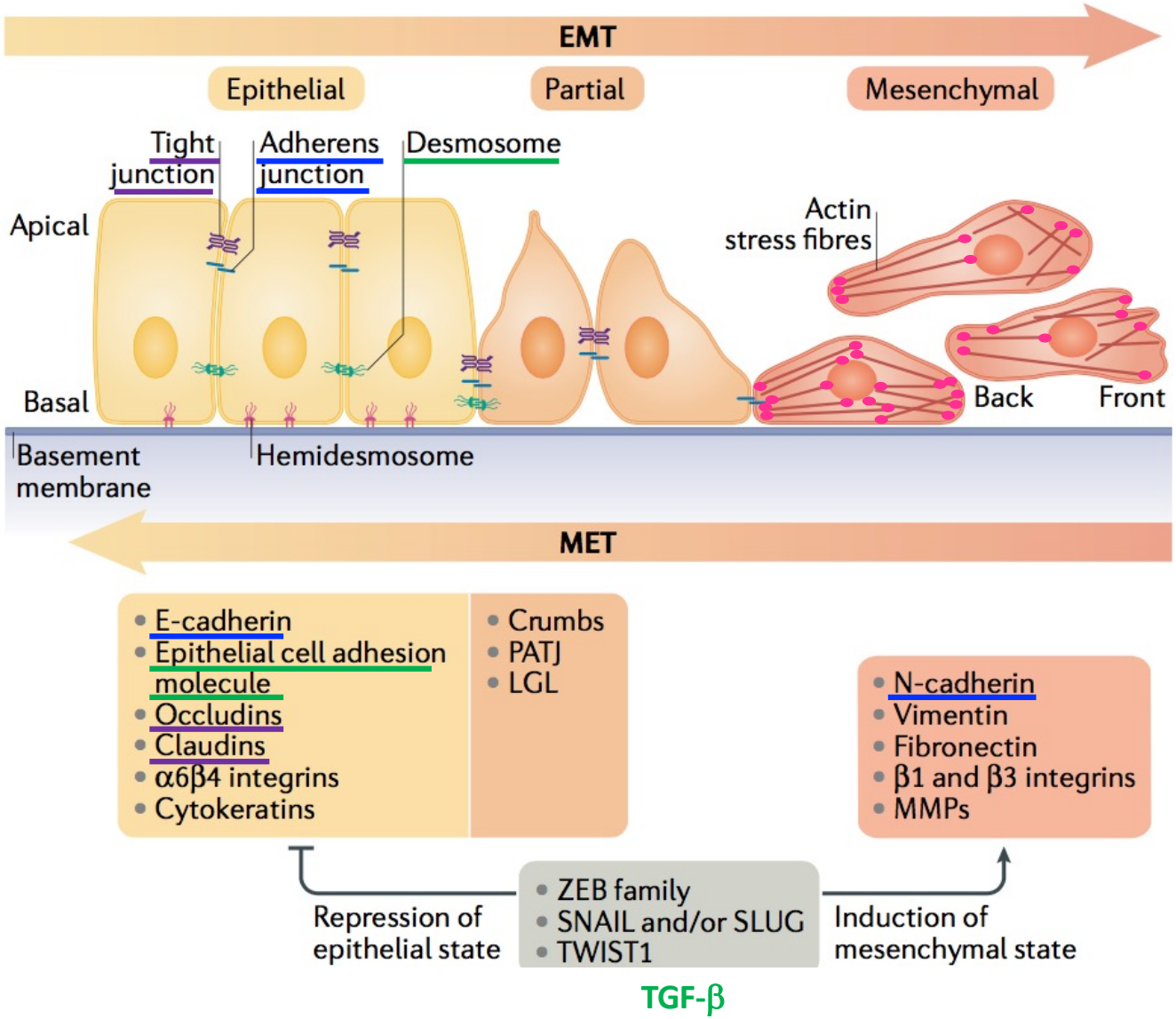
Dong et al., Thoracic cancer, 2020

Transient cell-cell adhesion : selectin

Inflammation disease (innate immune response)

Impellizzeri & Cuzzocrea, Expert Opi. Ther. Targets, 2014

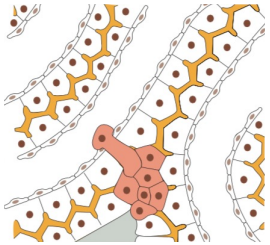
EMT = epithelial–mesenchymal transition
MET = mesenchymal-epithelial transition



Cell junction remodeling

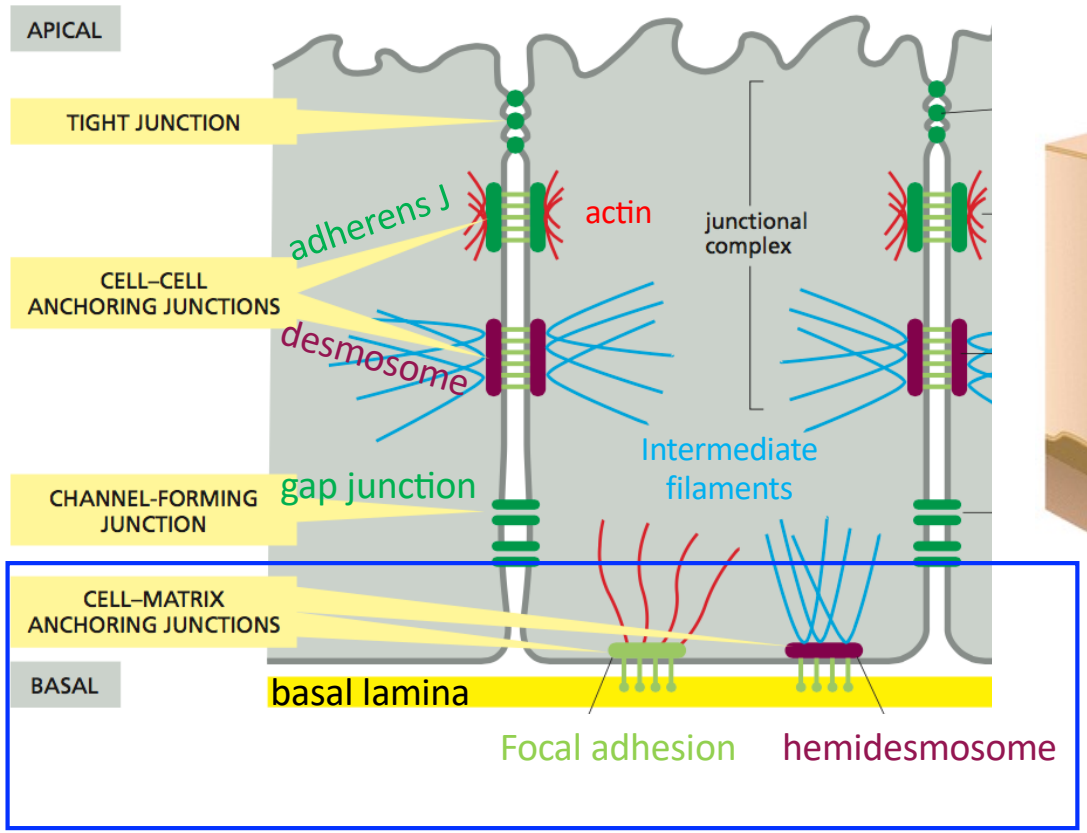
Claudin / tight junction
E-cadherins / adherens junction
Desmocollin, plakophilin / desmosome
Connexins / gap junction
Tumor suppressors but also prometastatics (collective migration, gap junctions with endothelium)

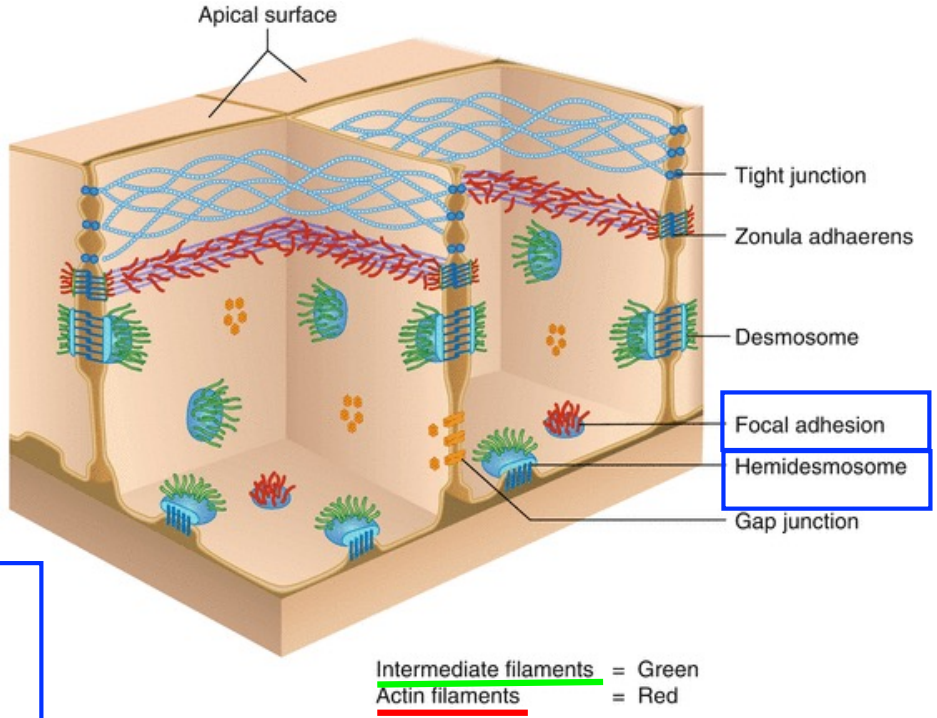
Selectins, VCAM/integrin :
extravasation MET (metastasis)



Adapted from Dongre & Weinberg, Nat. Rev. Mol. Cell Biol., 2019

6 types of junctions in epithelial cells : 2 are cell-matrix anchoring junctions

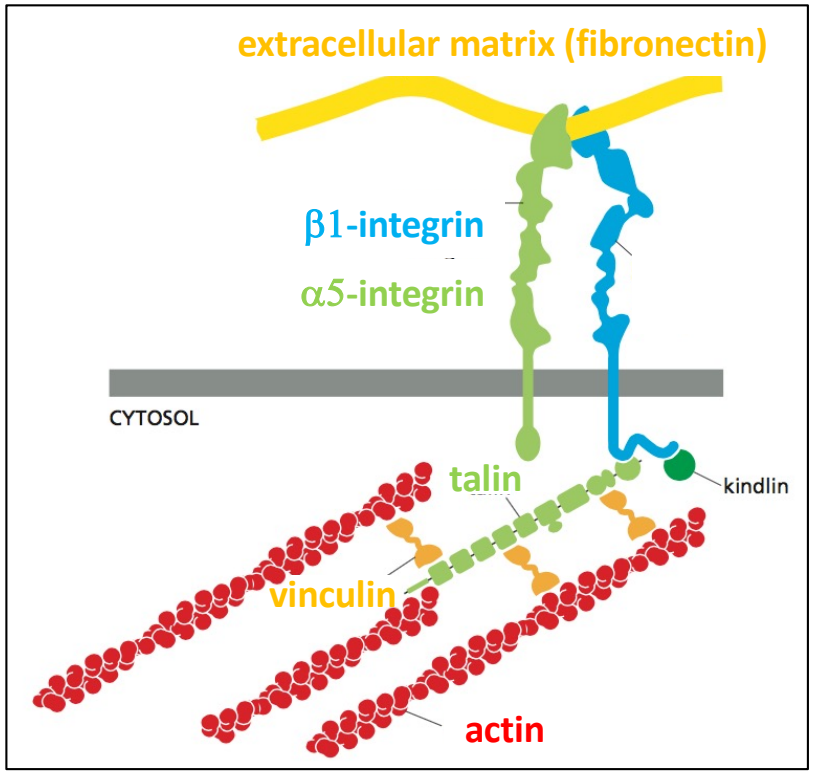




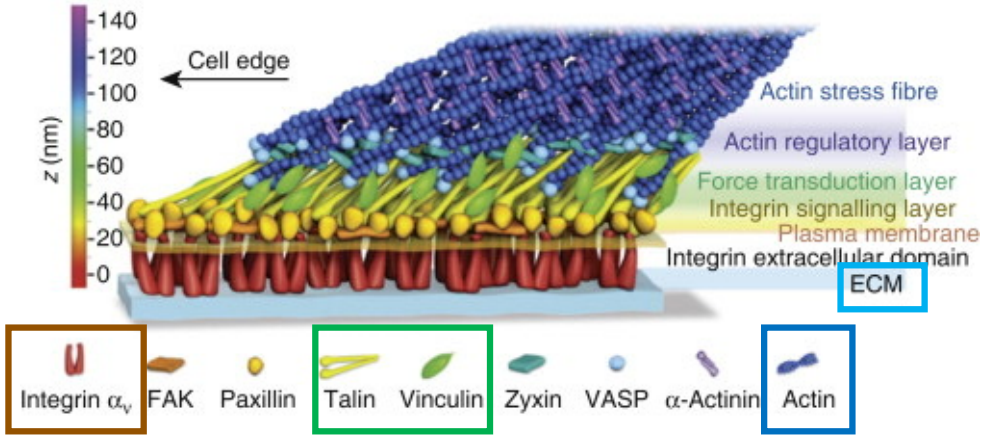
Adapted from figure 19-2, Molecular Biology of the Cell 6th

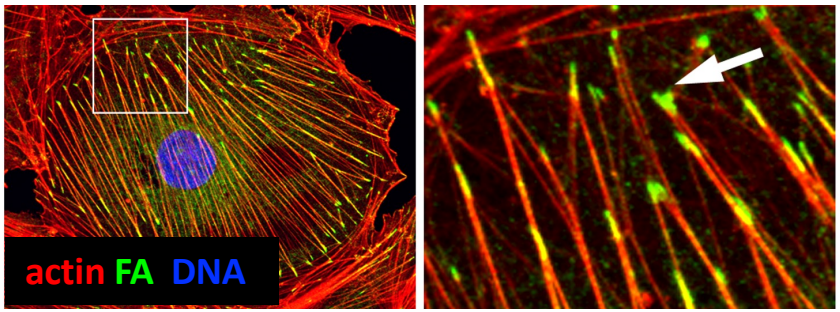
1. Cell-matrix anchoring junctions : integrins in focal adhesions (FAs)

Integrins : matrix receptors



focal adhesion

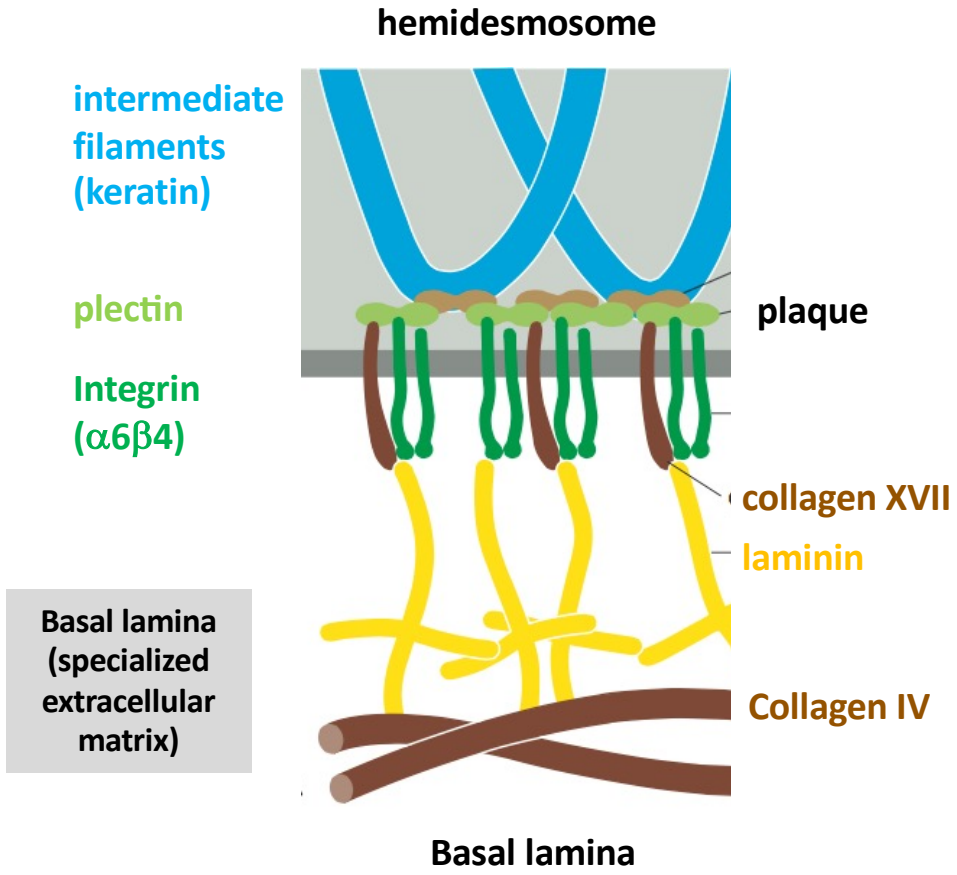


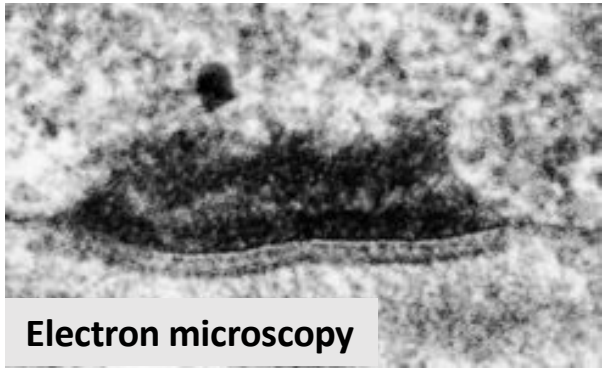


FA turnover important for cell migration

Figure 19-55, Molecular Biology of the Cell 6th
Schwartz, Curr Biol, 2011 ; Jeruschke et al., PLOS ONE, 2015

2. Cell-matrix anchoring junctions : integrins in hemidesmosomes





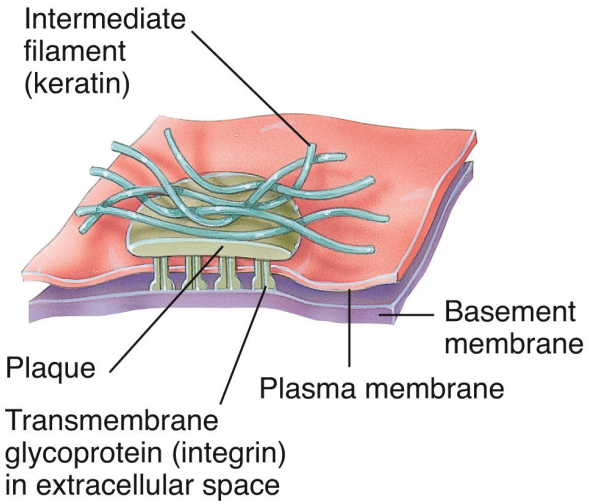
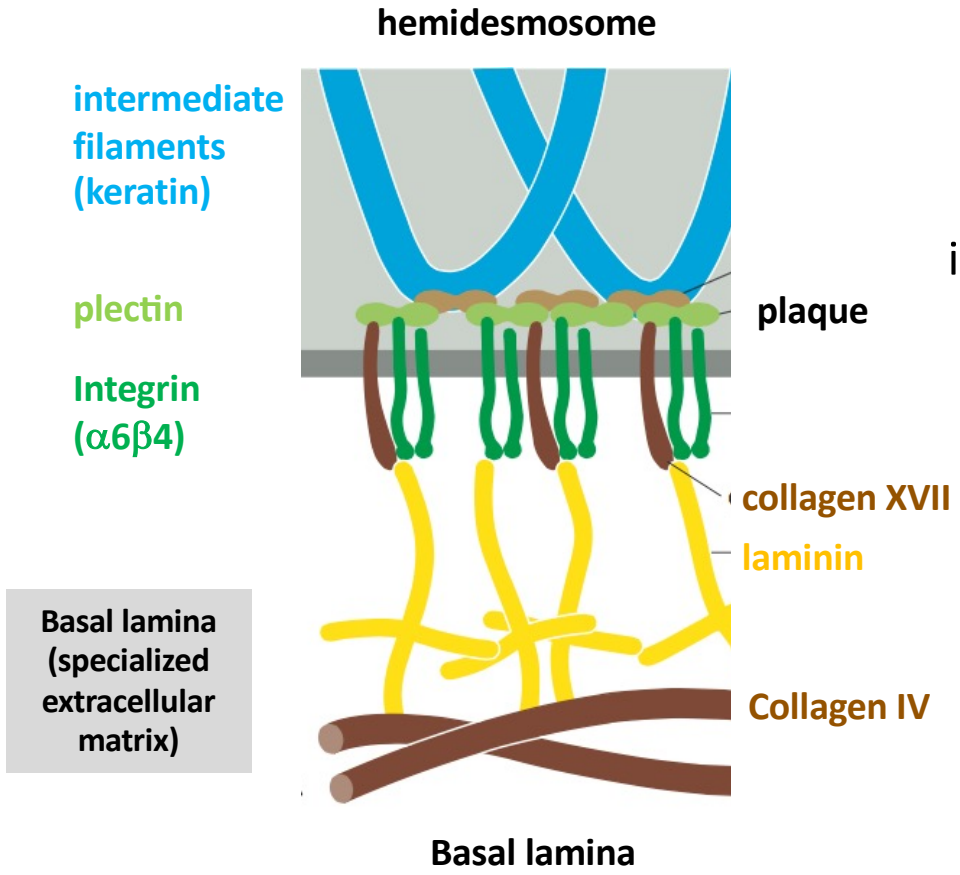


Figure 19-56, Molecular Biology of the Cell 6th
H. Jastrow ; Quizlet

Cell-matrix junctions and diseases



Skin blistering disorders :
junctional epidermolysis bullosa (JEB)
mutations in
integrin α6β4, collagen XVII, laminin or plectin

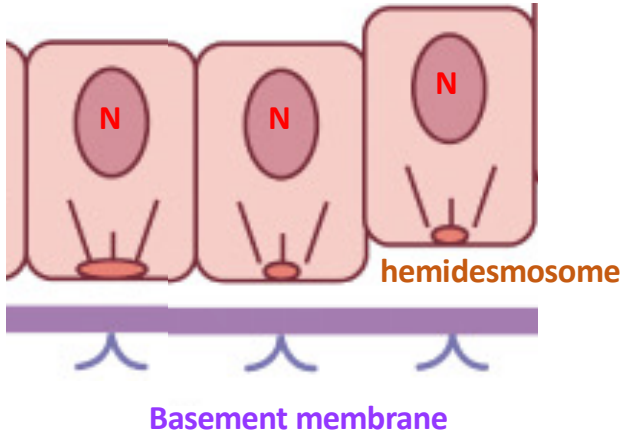
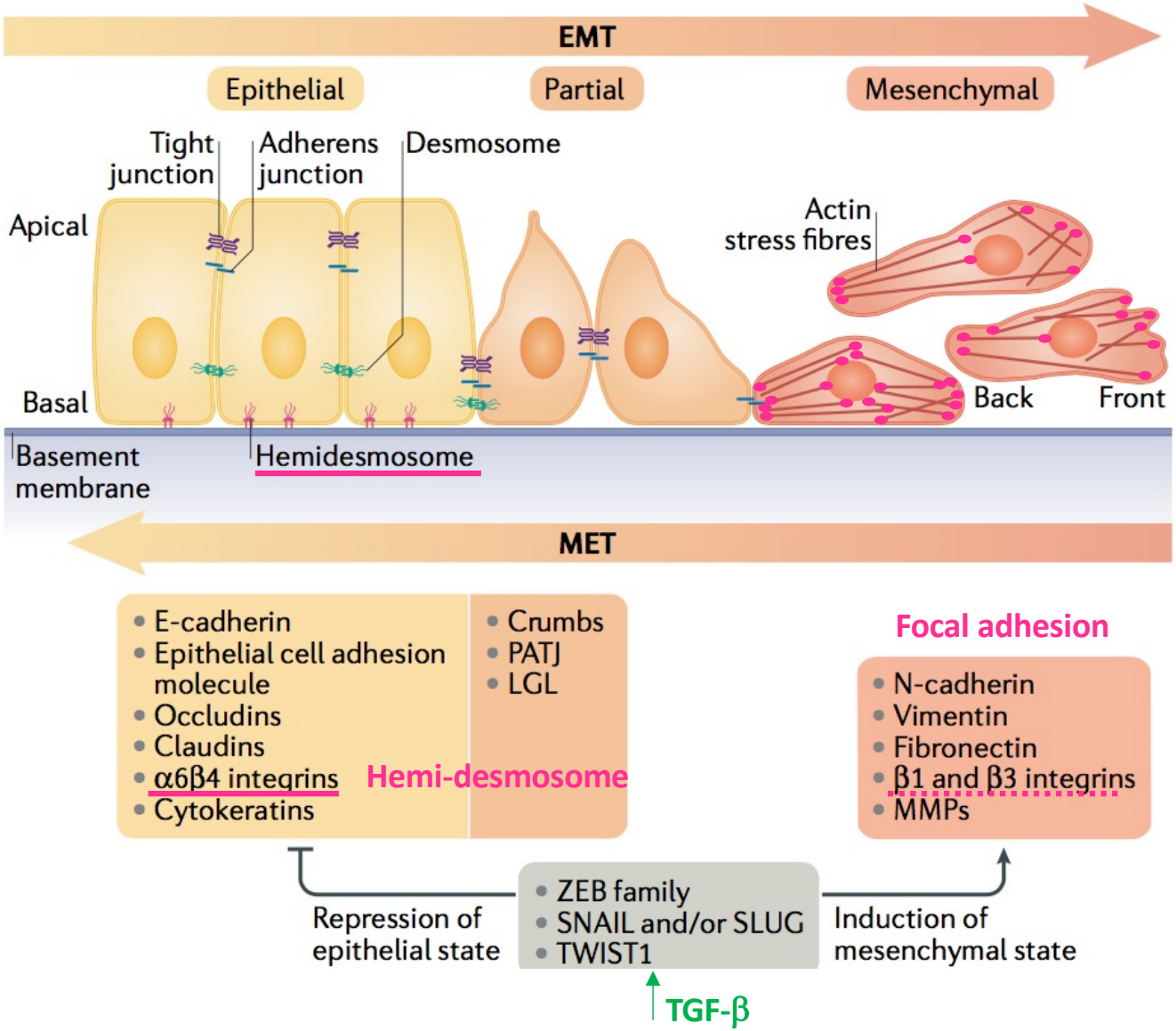


Figure 19-56, Molecular Biology of the Cell 6th
Plastic surgery key

EMT = epithelial–mesenchymal transition
MET = mesenchymal-epithelial transition



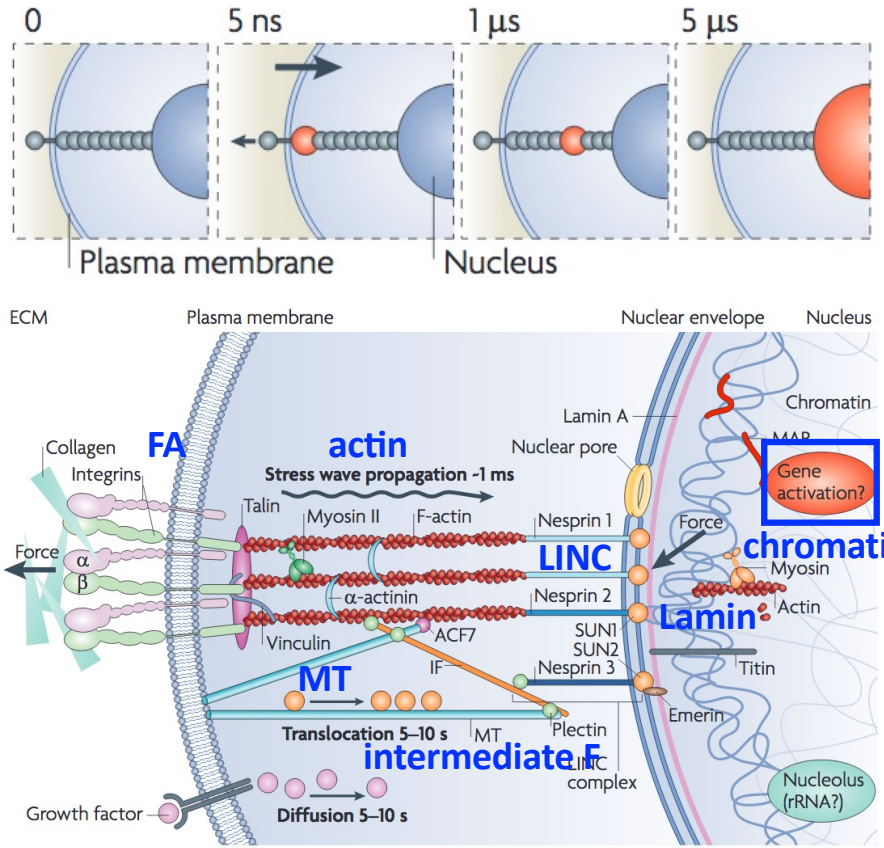
Cell-matrix junction remodeling

Hemi-desmosome
Tumor suppressor …
Focal adhesion
Pro-tumoral …

Adapted from Dongre & Weinberg, Nat. Rev. Mol. Cell Biol., 2019

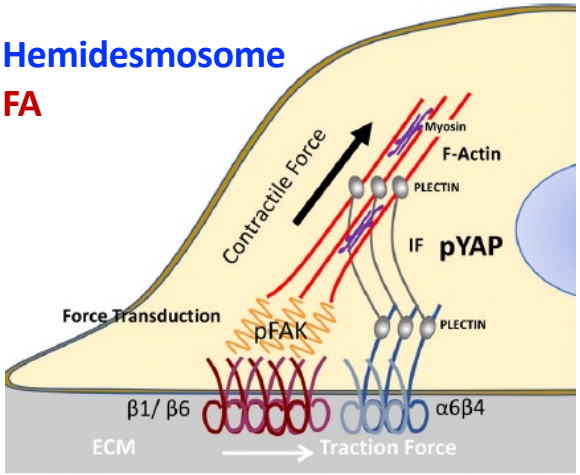
FA and hemidesmosome : mechanotransduction

FA : mechanical force propagation to the nucleus



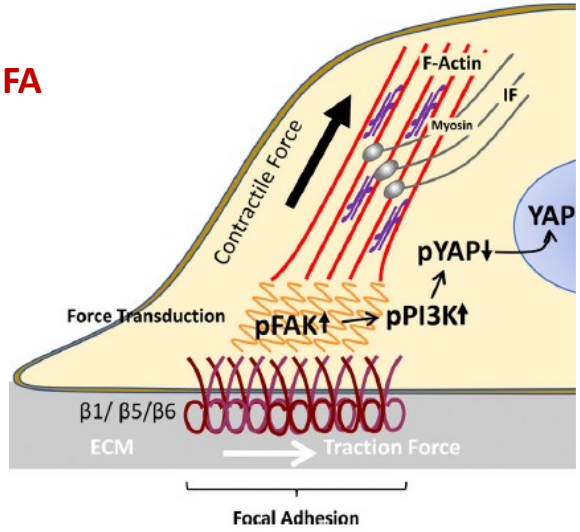
Hemidesmosome

FA



keratinocyte

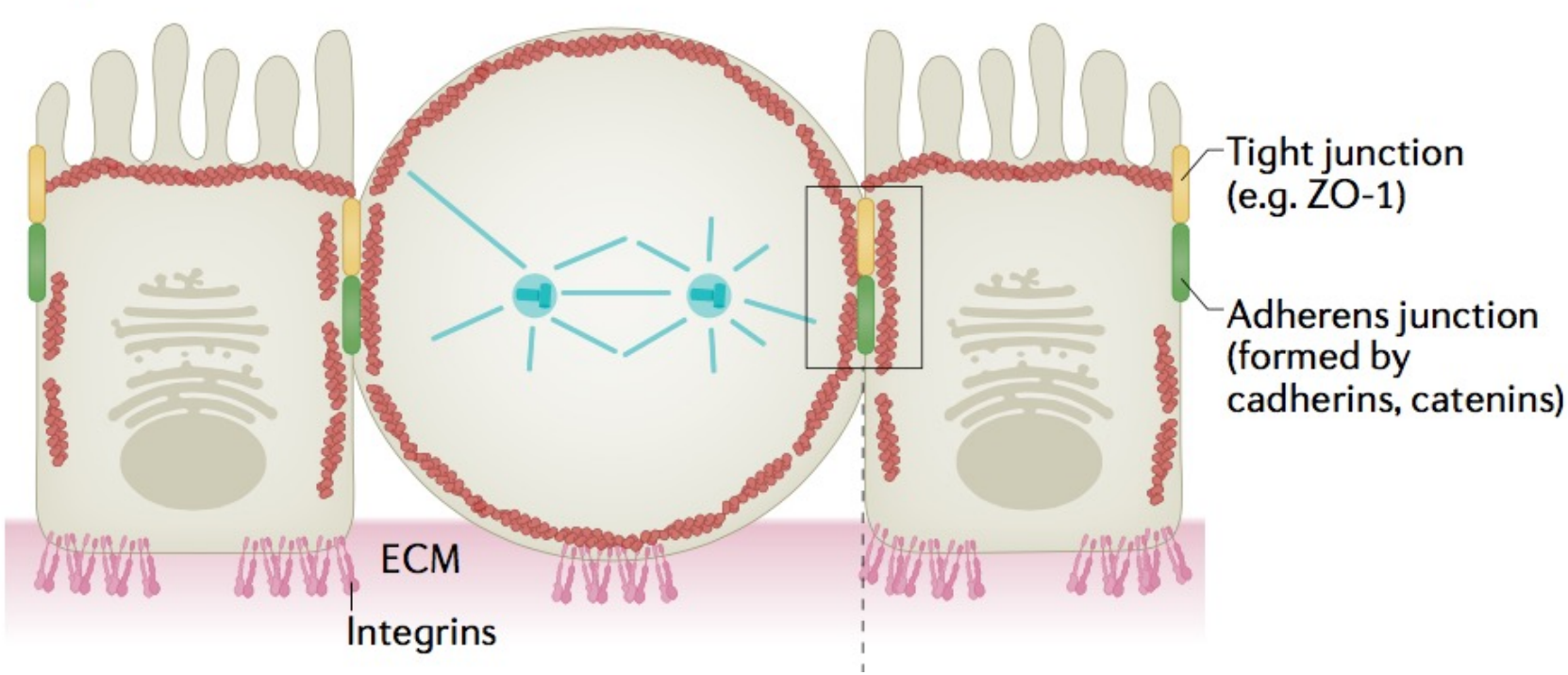
FA



Proliferation invasion

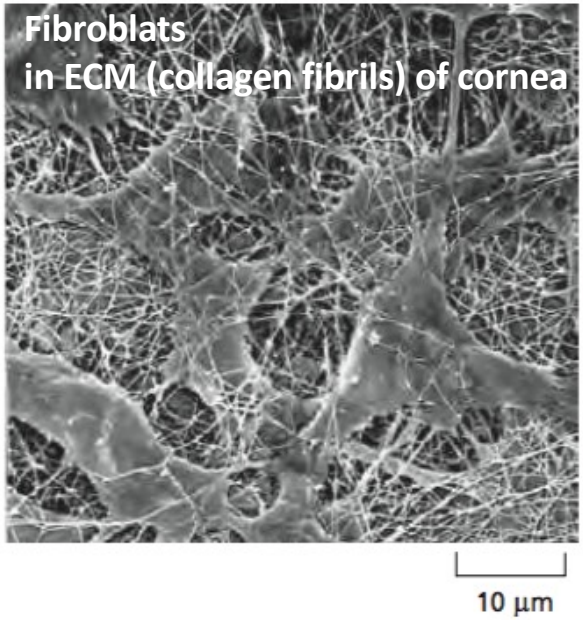
Wang et al., Mol. Cell Biol., 2009 ; Wang et al., JCB, 2020

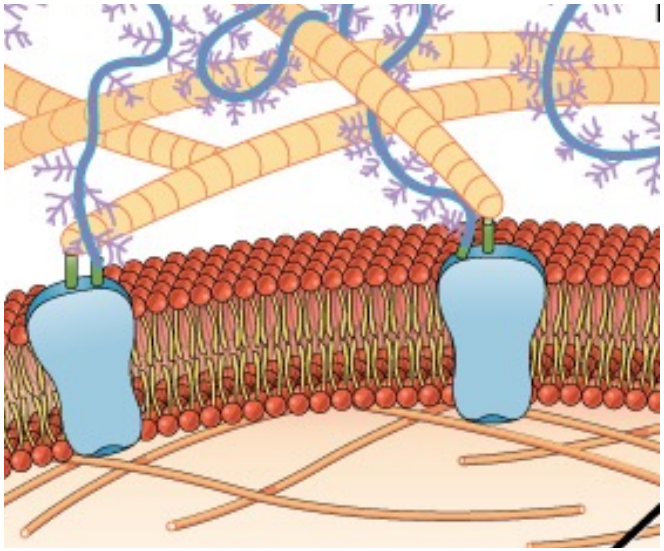
Junctions and mitosis



Lechler & Mapelli, Mol. Cell Biol., 2021

The extracellular matrix (ECM)



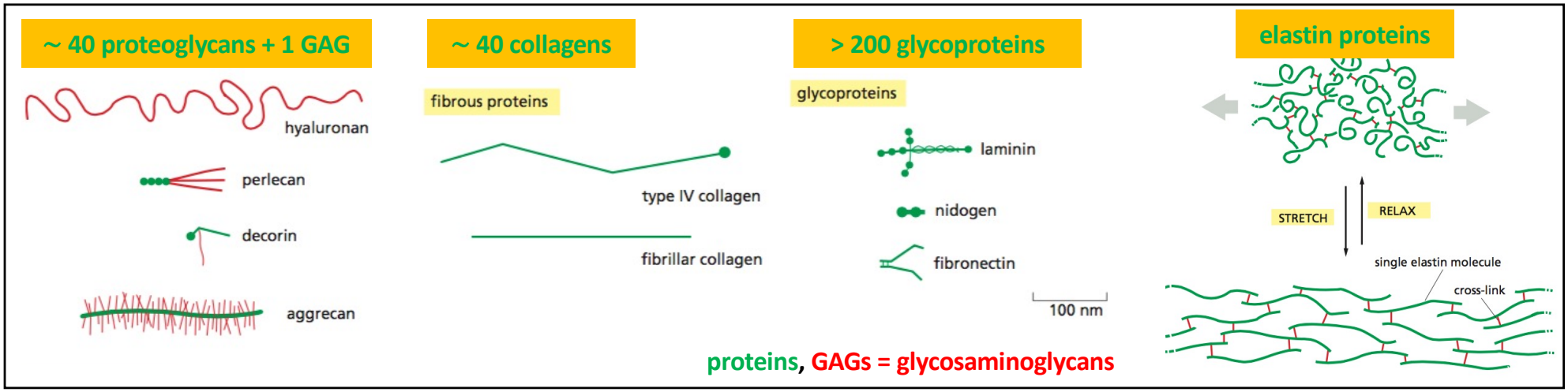


Proteoglycan
collagen fibrils
fibronectin
integrin
cytoskeleton

almost 300 ECM proteins

bone/teeth : calcified
cornea : transparent
tendon : rope-like

secreted from sparse fibroblast cells or related (osteoblasts)

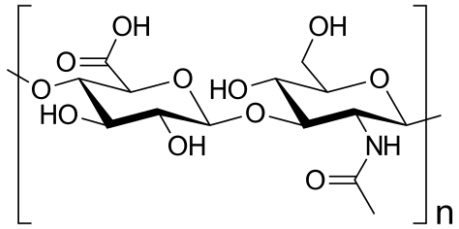


OpenStax Biology
Figure 19-30 & 32, Molecular Biology of the Cell 6th

1. Glycosaminoglycans (GAGs), proteoglycans

GAG = disaccharide repeats

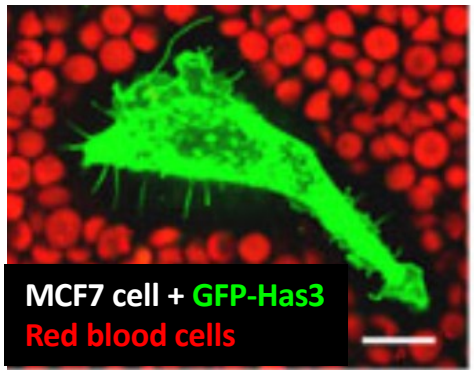
negatively charged, stiff and bulky : attract Na+ and H2O creating a turgor against compressive forces



Ex : hyaluronan

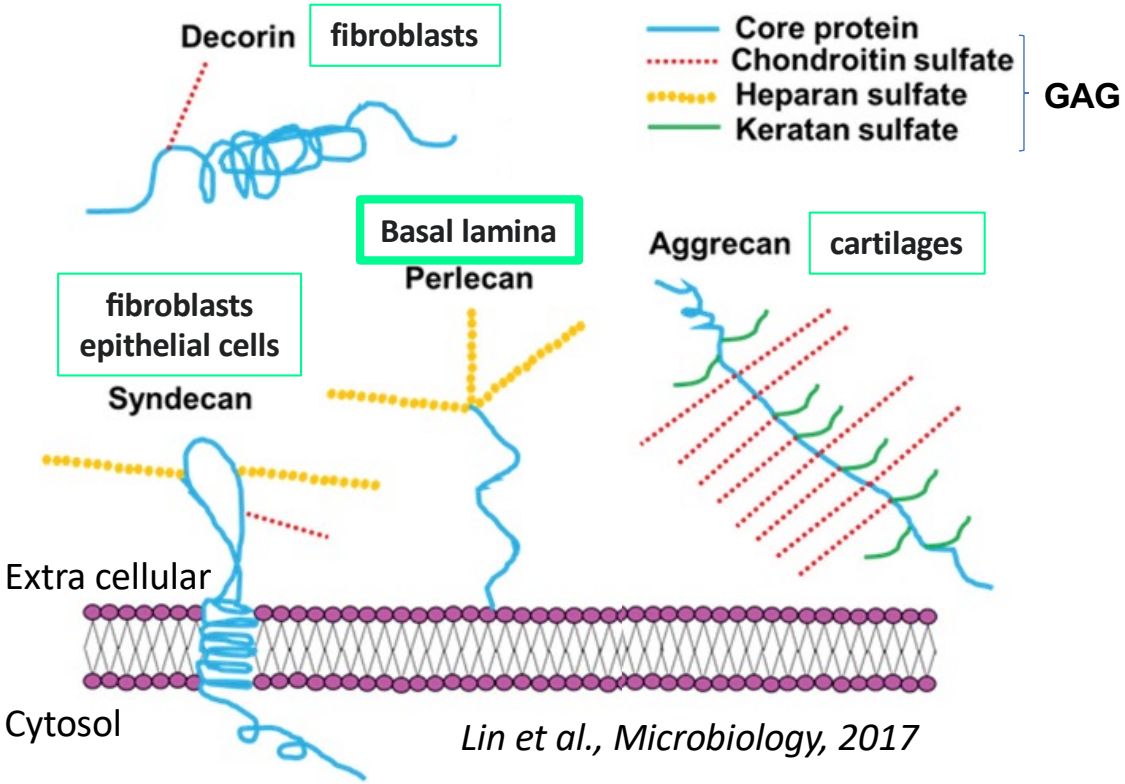
(-4GlcUAβ1-3GlcNAcβ1-)$_n$

Migration, wound healing



Kultti et al., JBC, 2006

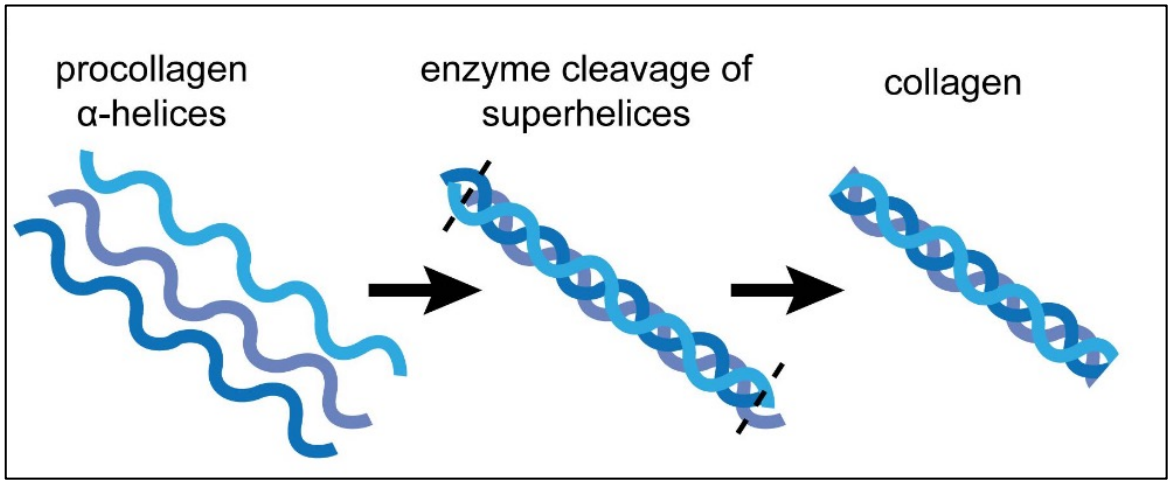
proteoglycans



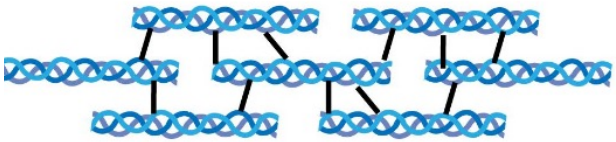
Lin et al., Microbiology, 2017

- Resist compressive forces
- Diffusion of nutrients, metabolites, hormones (blood / tissues)

2. Collagens



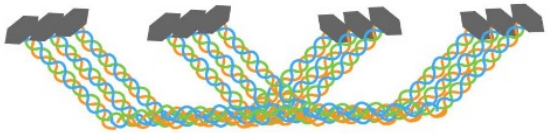
fibrillar collagen (i.e. type I, III, V)



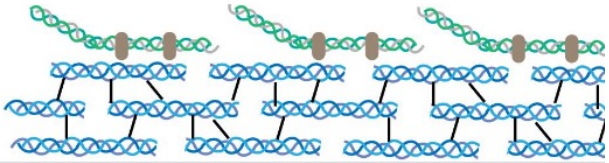
- **hydrophobic, non elastic**
- **type I : skin, bone …**
- **resist tensile forces**
- **organized by cell tension**

beaded (i.e. type VI)

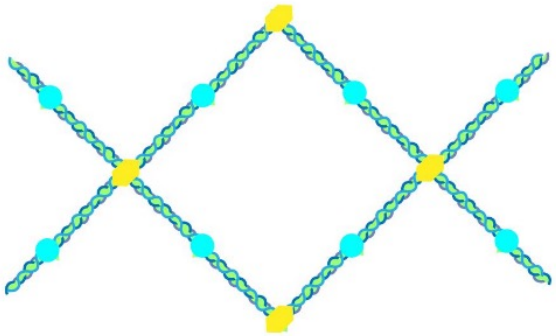
anchoring (i.e. VII)



FACIT (i.e. type XII, XIV)



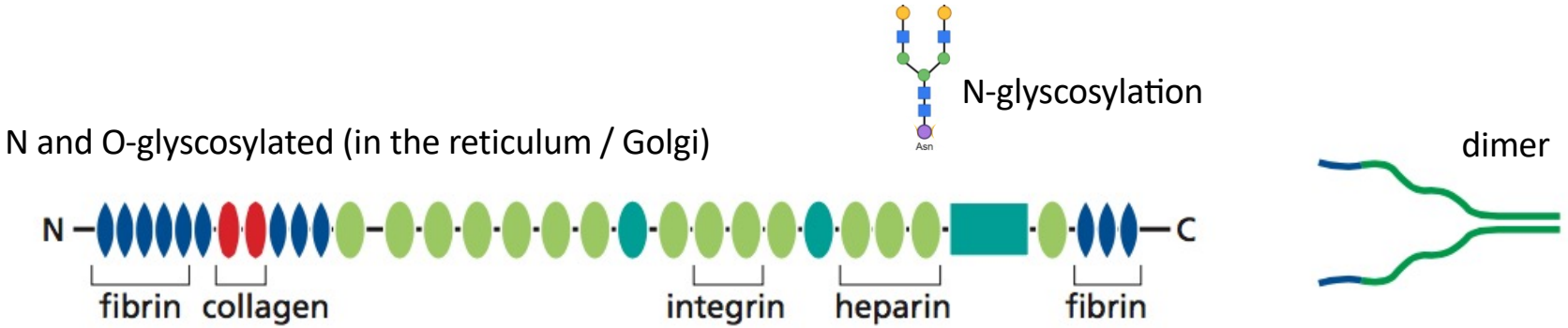
netforming collagen (i.e. type IV)

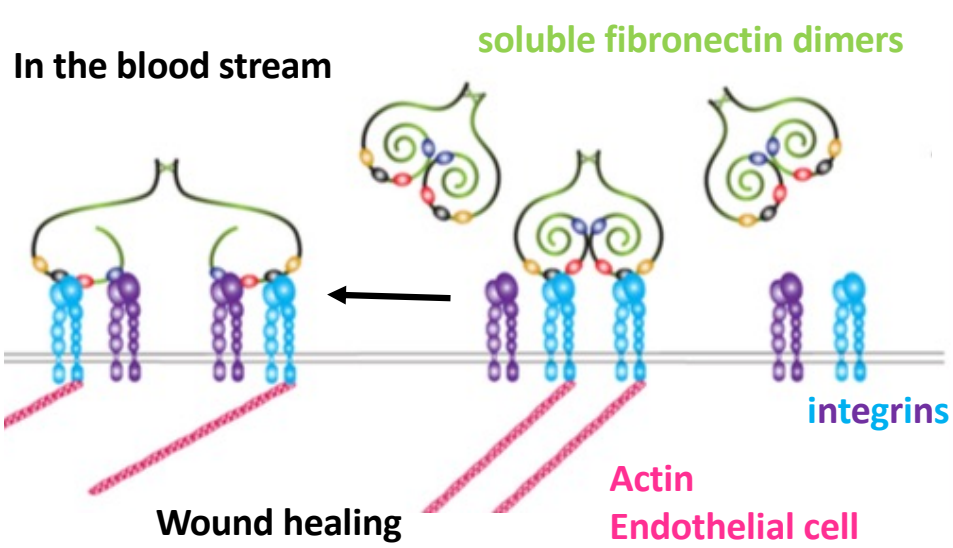


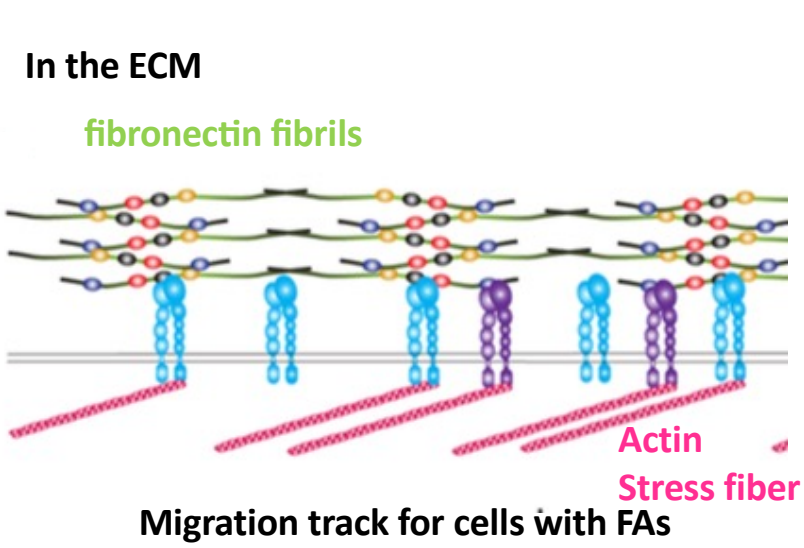
Basal lamina
(specialized extracellular matrix)

Pfisterer et al, Front Cell Dev Biol, 2021

3. Glycoproteins : fibronectin

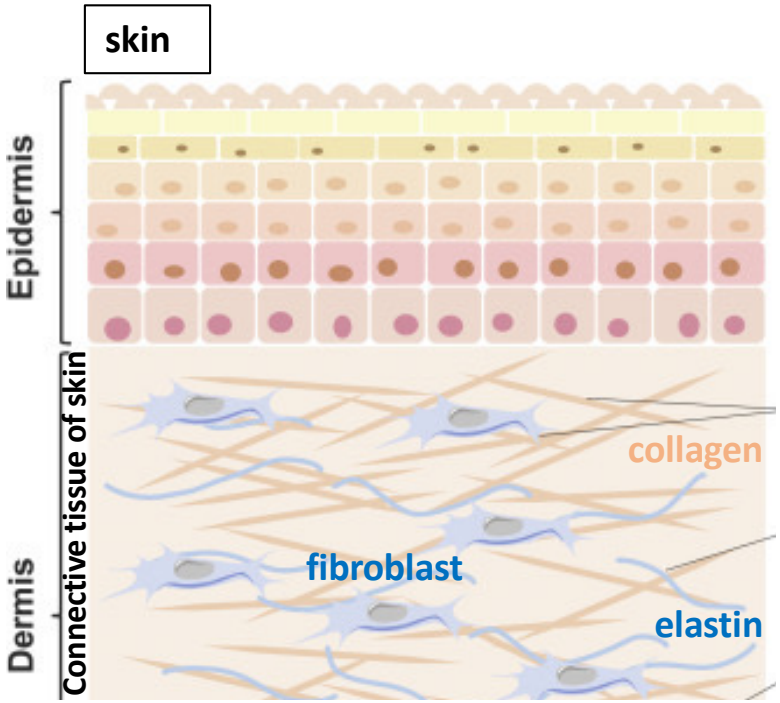




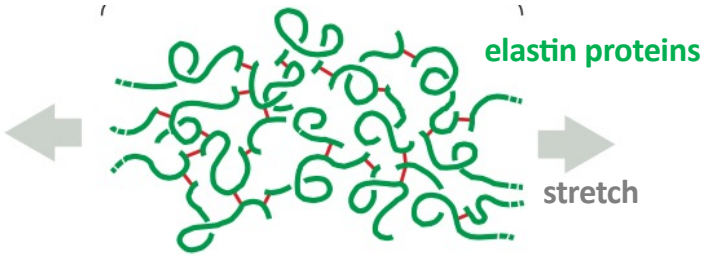


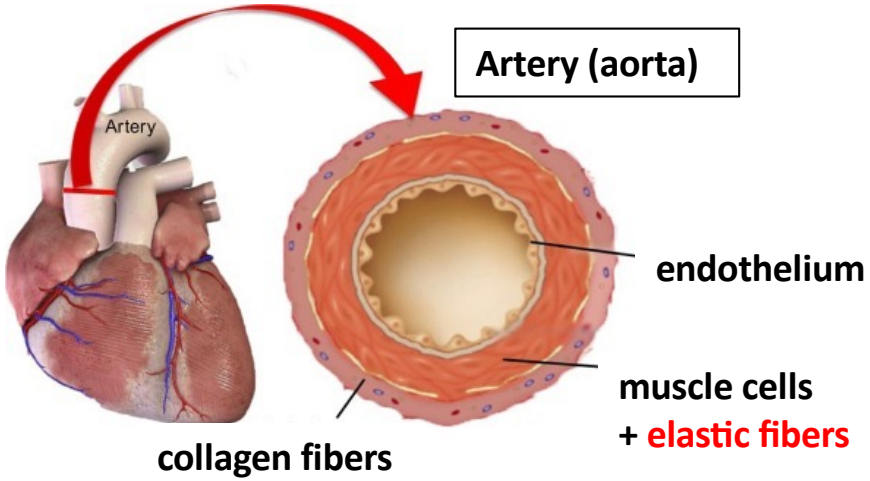
Werkman et al., Scientific Reports, 2020
Figures 19-46 & 48, Molecular Biology of the Cell 6th

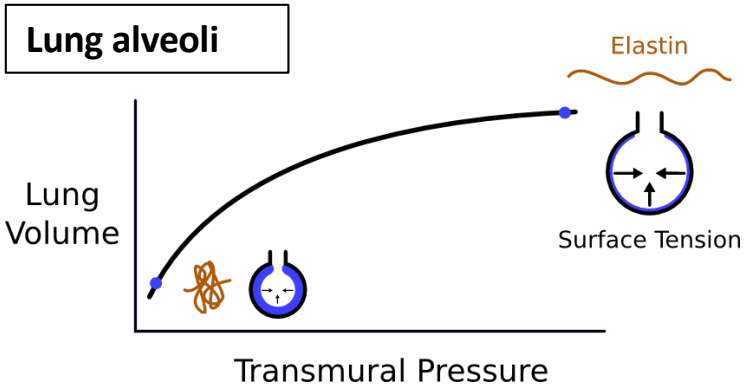
4. Elastin



- hydrophobic, elastic (stretch and relax)
- resilience of the matrix after stretch

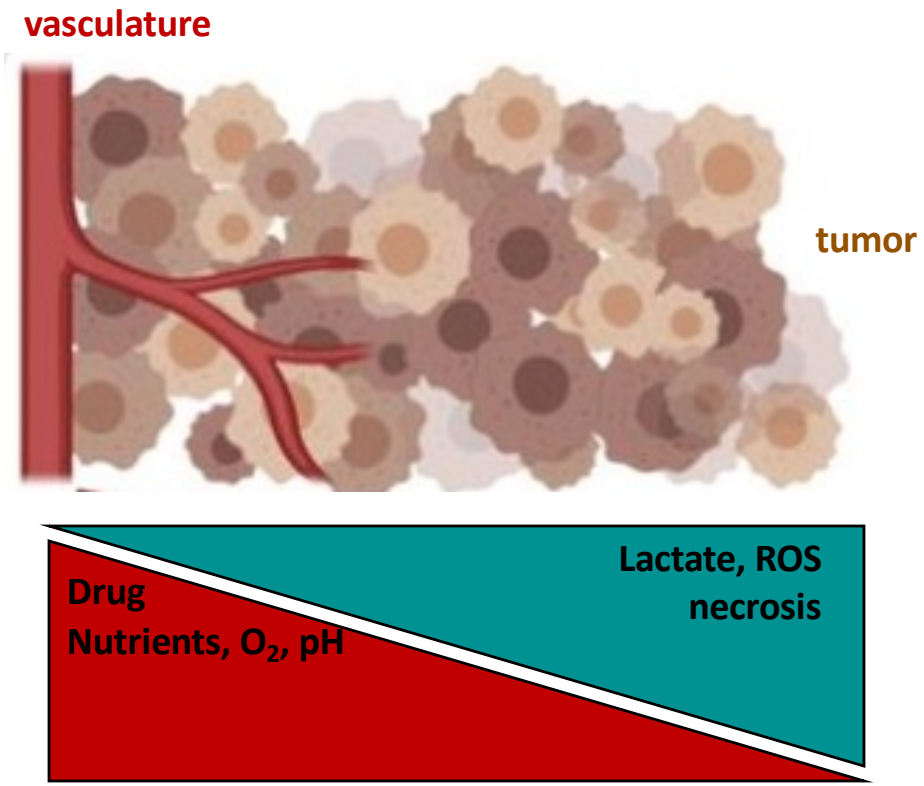




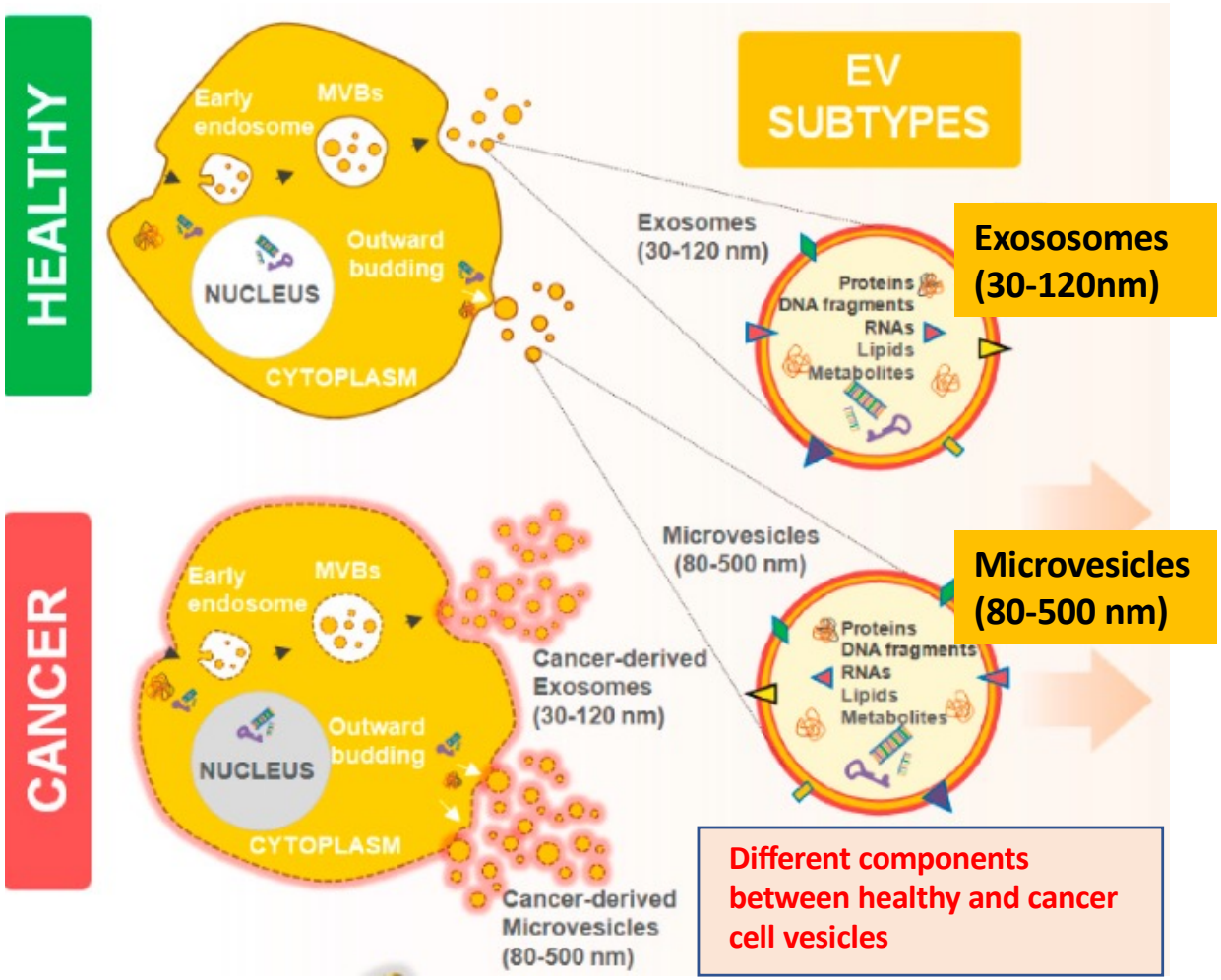


Freitas-Rodriguez et al., BBA, 2017
Figure 32, Molecular Biology of the Cell 6th
Taki et al., Comput. & Visualiz. for Intravascular Imaging & Comp.-Assisted Stenting, 2017
Pathway medecine

ECM contains nutrients, GFs, cytokines, hormones



ECM contains nutrients, GFs, cytokines, hormones but also extracellular vesicles (EVs)



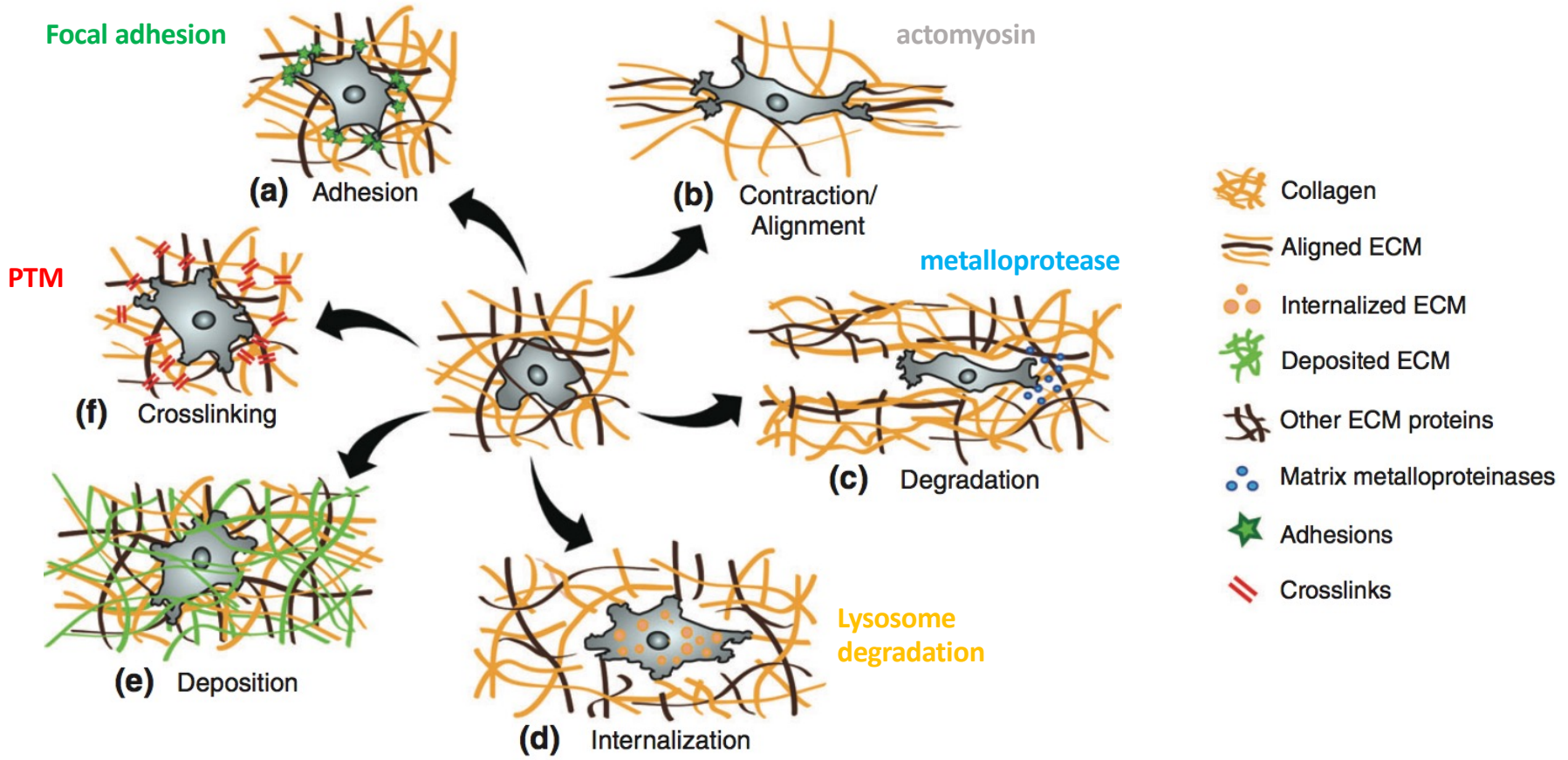
- Can act on neighboring or far away cells.

- Role in tumor initiation, progression, metastasis and chemotherapy failure.

- Found in blood, urine, saliva (can help diagnosis/prognosis).

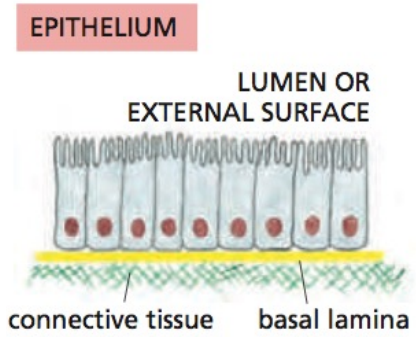
Xavier et al., Cells, 2020

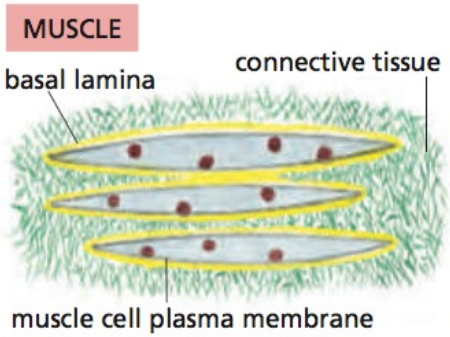
Extracellular matrix remodeling by cells : stiffness



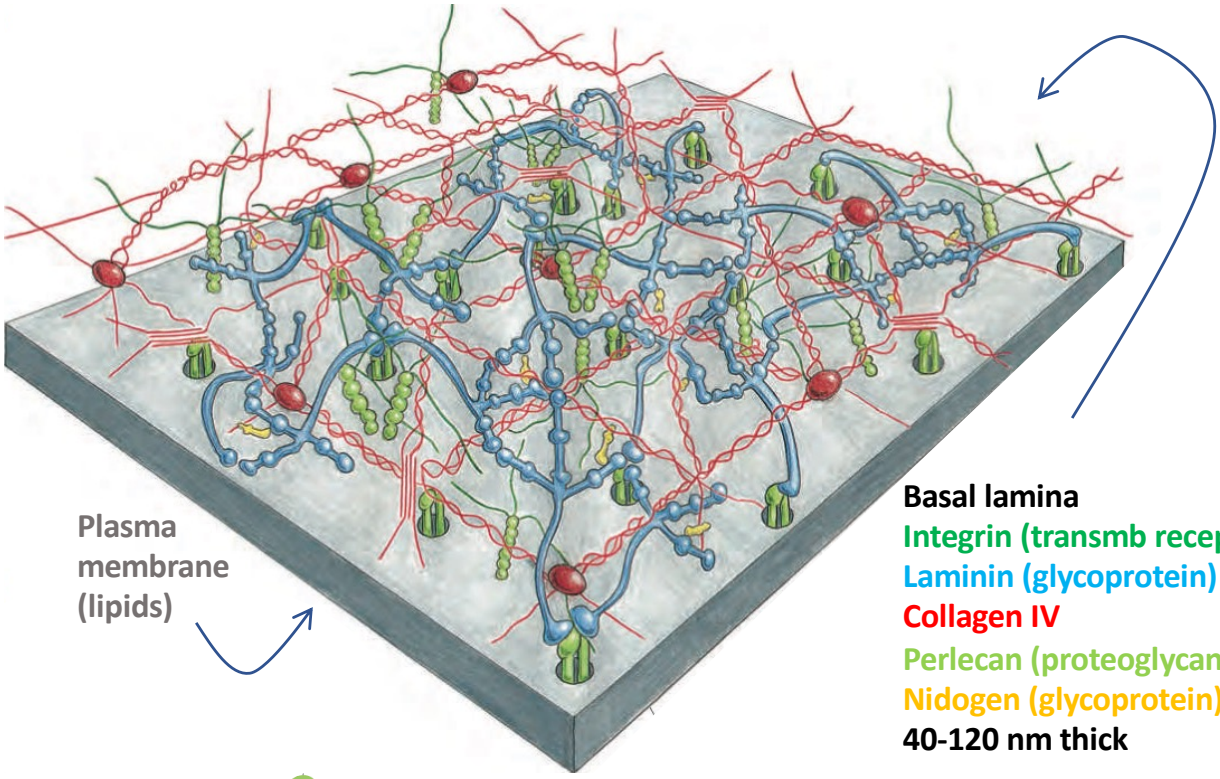
Ford & Rajagopalan, WIREs NanoMed & NanoBiotec, 2018

A thin specialized matrix sheet : the basal lamina (or basement membrane)

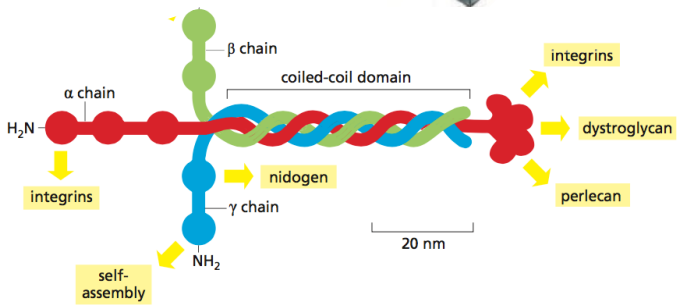




- Mechanic connection
- Filter, cell barrier
- Tissue regeneration
- Polarity, survival, proliferation, differentiation, migration



Basal lamina
Integrin (transmb receptor)
Laminin (glycoprotein)
Collagen IV
Perlecan (proteoglycan)
Nidogen (glycoprotein)
40-120 nm thick

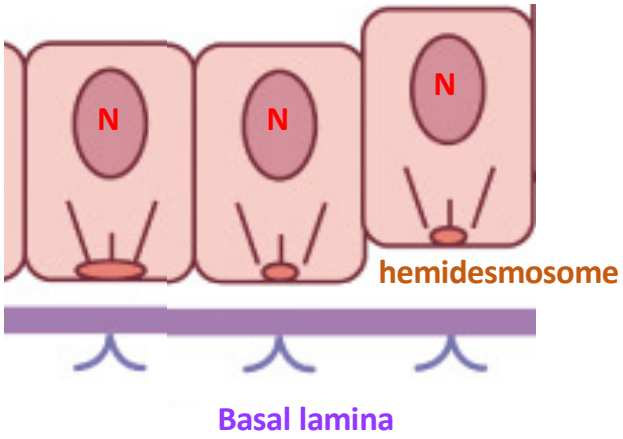


Laminin α, β, γ

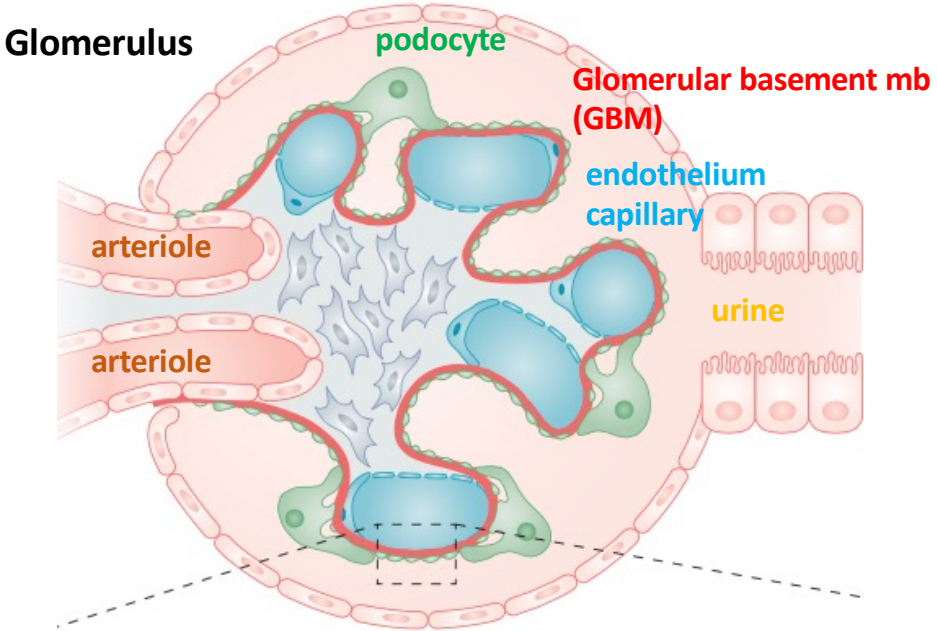
Figure 19-50, 52, 53, Molecular Biology of the Cell 6th

Basal lamina and diseases

Junctional epidermolysis bullosa (JEB)
(Laminin)

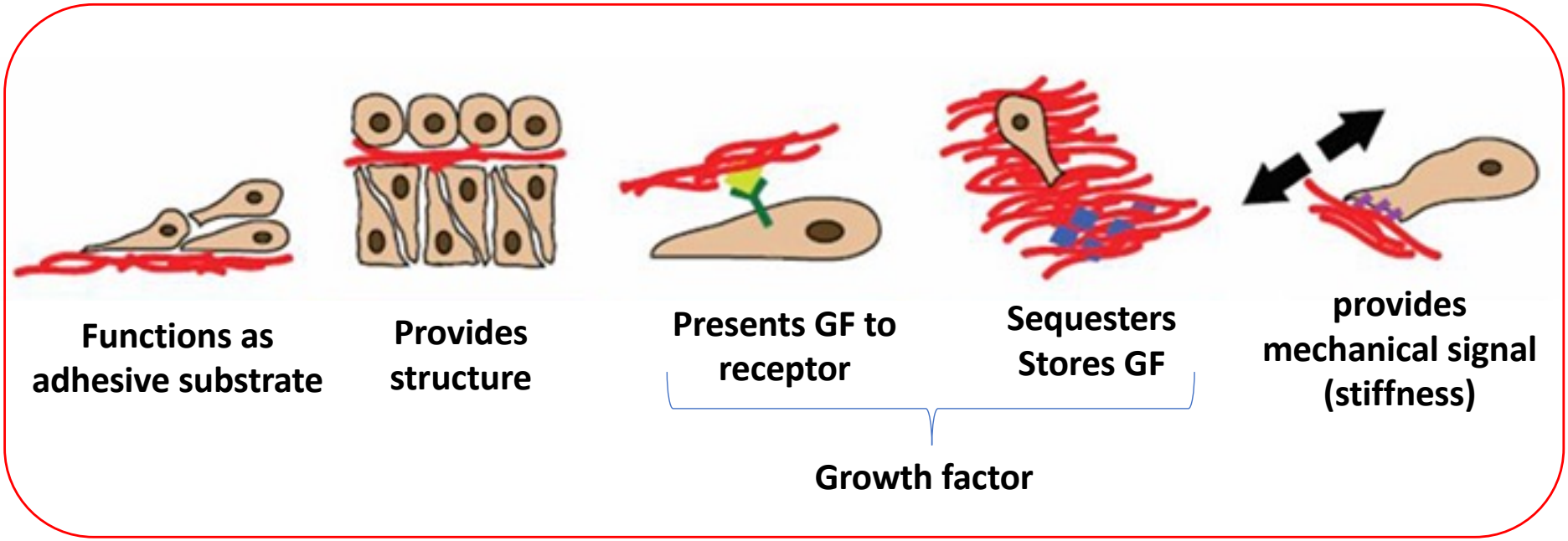


Kidney disorders
(Collagen IV, laminin :
basal lamina thickening or disruption)



Plastic surgery key
Figure 19-56, Molecular Biology of the Cell 6th
Naylor et al, Nephrology, 2020

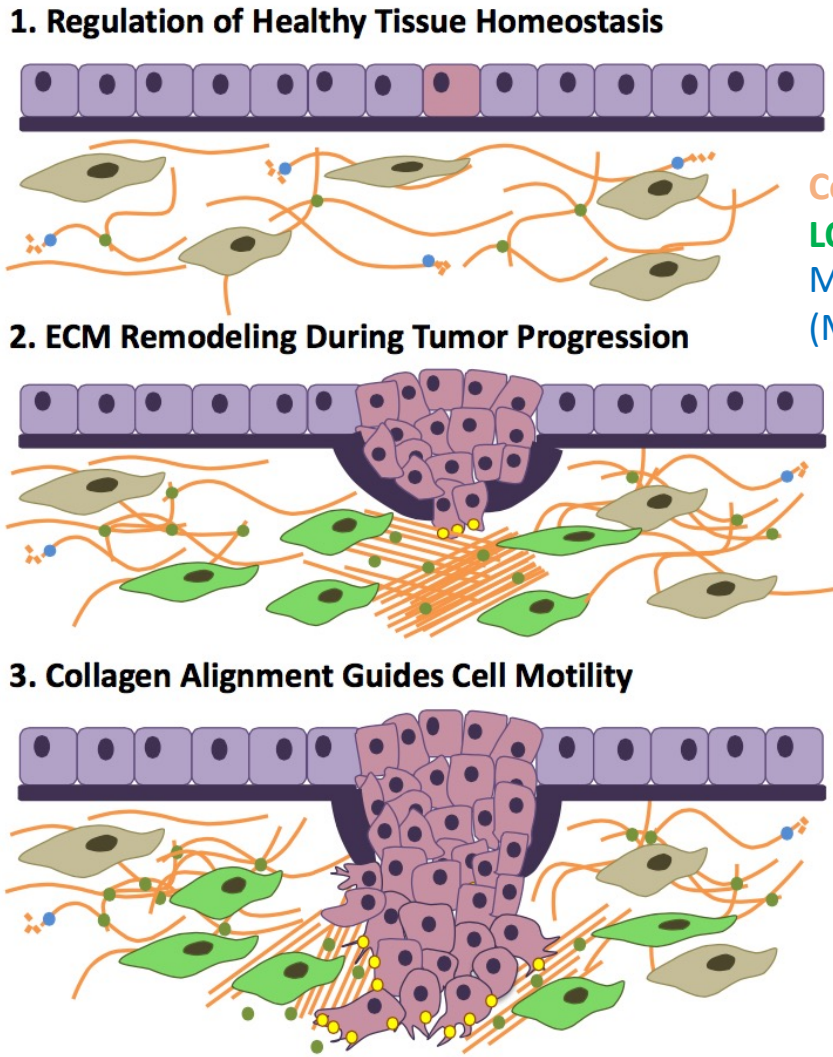
Functions of the extracellular matrix (ECM)



Misregulation in cancer

Adapted from Tumor metastasis, Edited by Ke Xu

Invasive tumor : ECM remodeling for migration



Fibroblasts (connective tissues)

CAFs : cancer associated fibroblasts

epithelium

Basement membrane/basal lamina

Collagen

LOX crosslinker

Matrix metalloproteinases (MMPs)

Basement membrane tension and rupture

Aligned collagen

Tumor LOX

(Elastin fragmentation = stiff ECM)

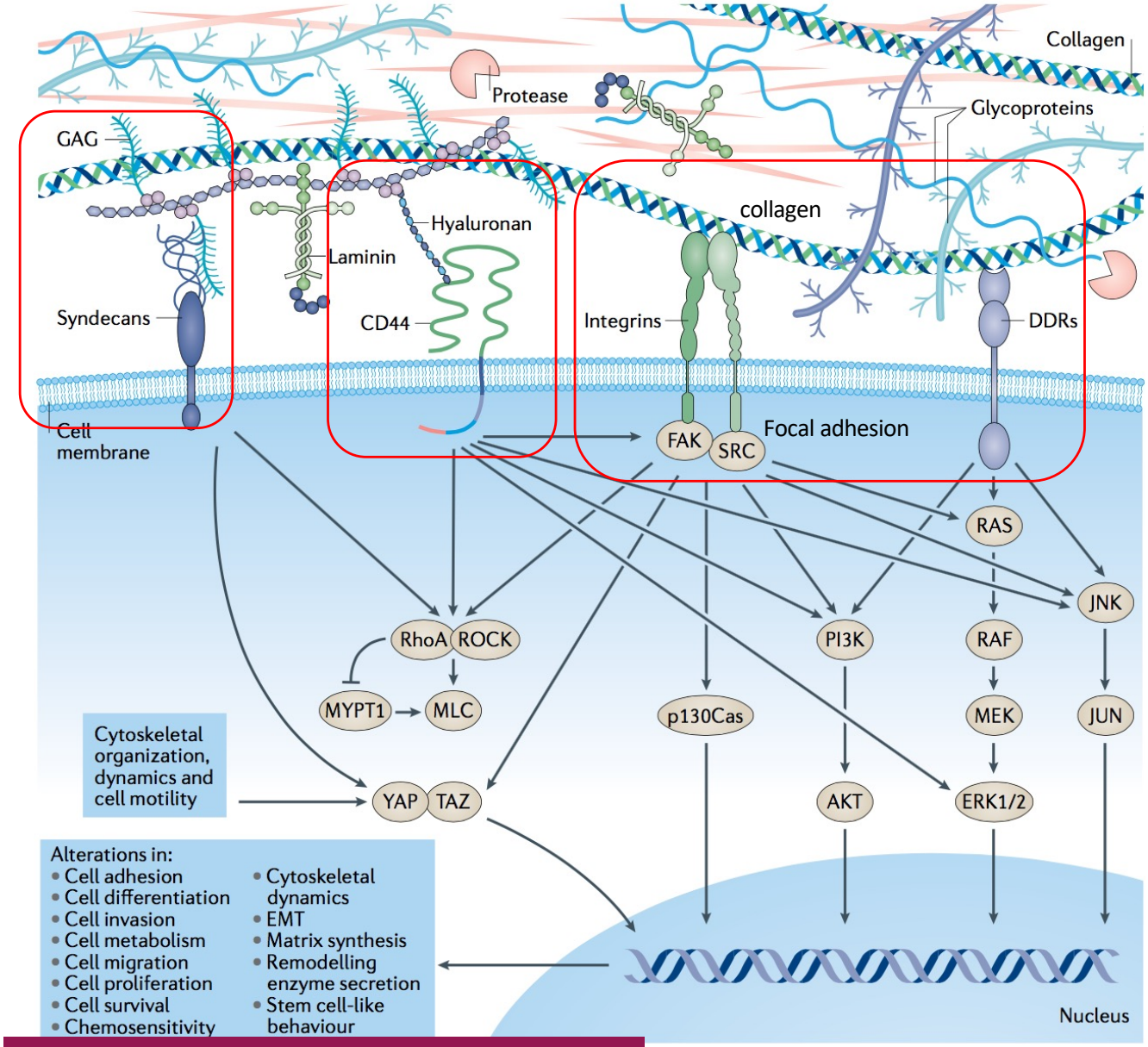
ECM alteration

- Disruption of basement membrane
- ↑ Tissue stiffness
- ↑ Fibrillar collagens
- ↑ Remodeling enzymes

Desmoplasia
growth of fibrous connective tissue (fibrosis) around the tumor

Walker et al., In J Mol Sci, 2018

ECM : cell signaling in cancer



Receptor / signaling / transcription
Cell proliferation : Pi3K, Ras, MAPK
Cell survival
Cell adhesion /migration : FA, actin
Cell invasion
Cell differentiation

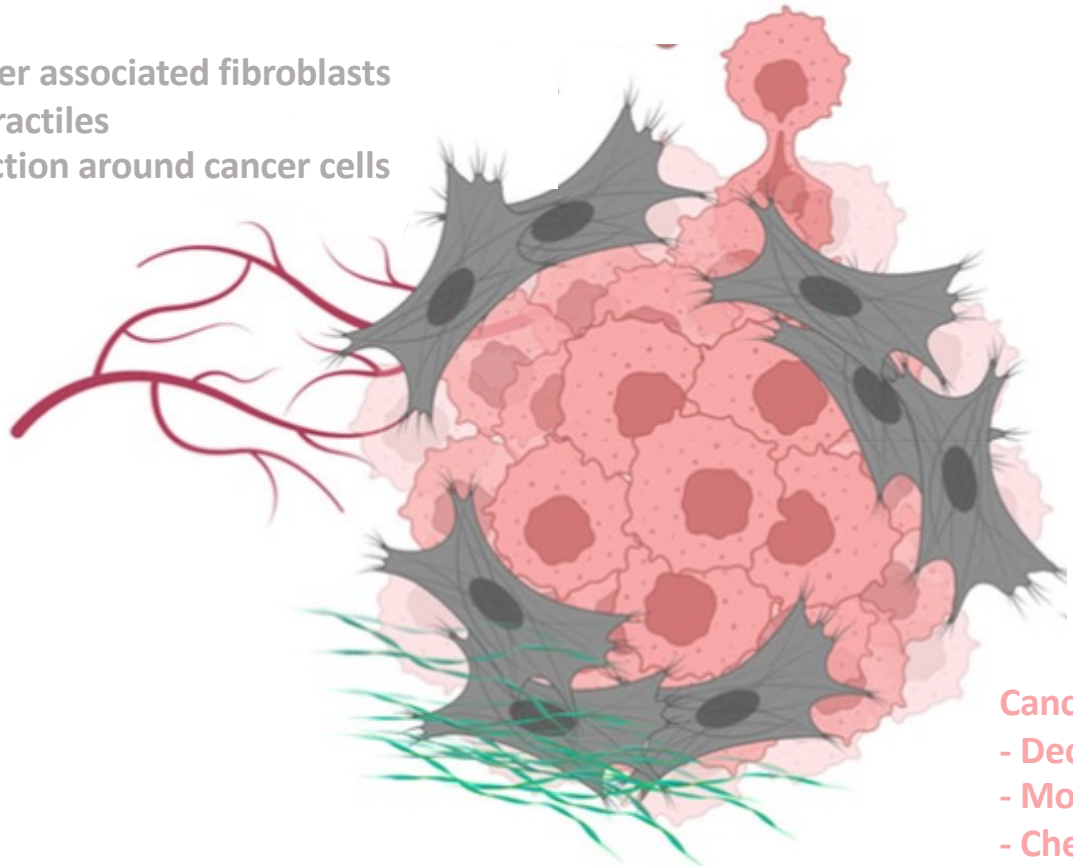
Matricryptins
- Generated by ECM proteolysis
- Chemokines, cytokines-like

. Anti-tumoral :
collagen XVIII : endostatin
. Pro-tumoral :
Laminin 111 fragments

Cox et al., Cancer, 2021

A capsule of cancer-associated fibroblasts (CAFs) that enwraps primary cancer cells

CAFs : cancer associated fibroblasts
Highly contractiles
Rigid protection around cancer cells



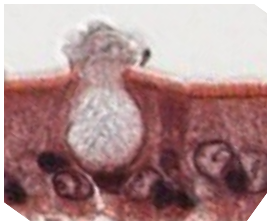
Cancer cells
- Decreased internal cell tension
- Modified YAP-mediated transcription
- Chemotherapy resistance

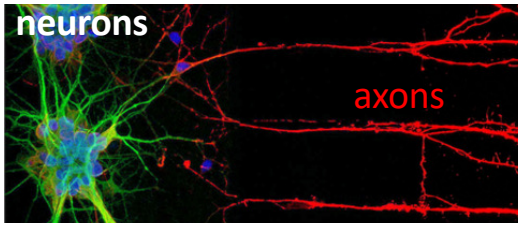
Proliferation, stemness, immunosuppression, angiogenesis, metastasis

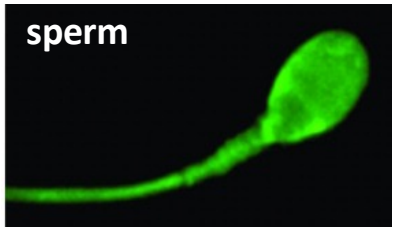
Barbazan et al., Nat Comm., 2023

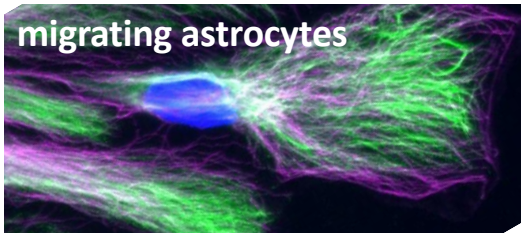
Cell polarity

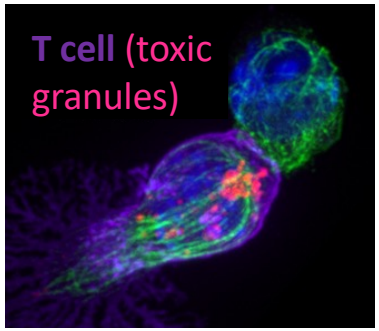
Intestinal epithelium







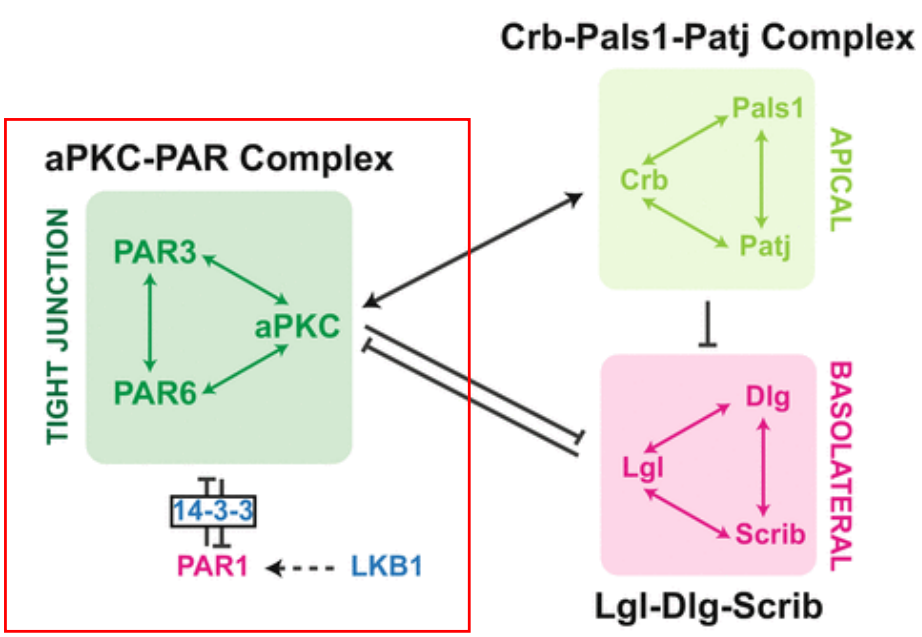


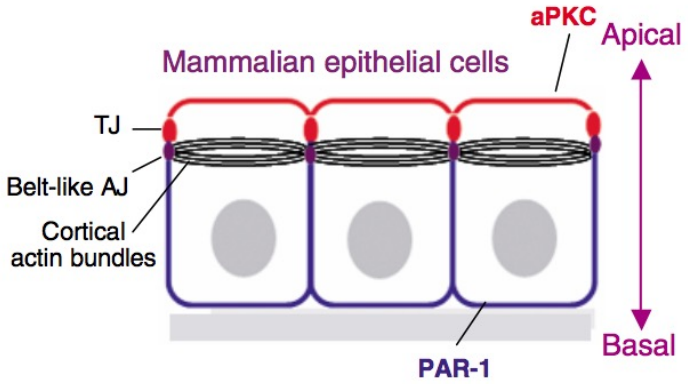


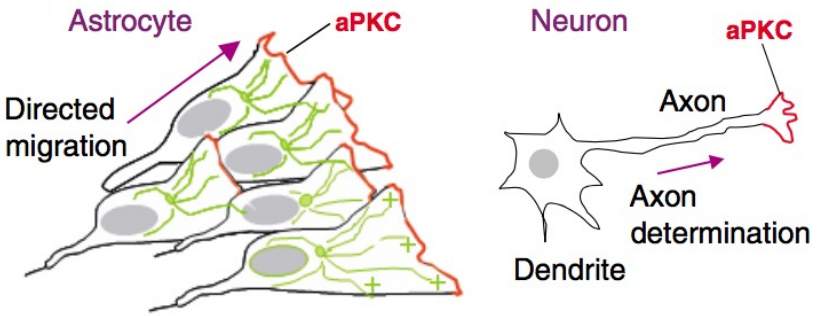
- asymmetric cellular shape
- asymmetric distribution of molecules / organelles
- asymmetric functions

Need :
- to break symmetry and then to maintain asymmetry
- establish subcellular domains
- cytoskeleton

Three polarity complexes : initiation and maintenance



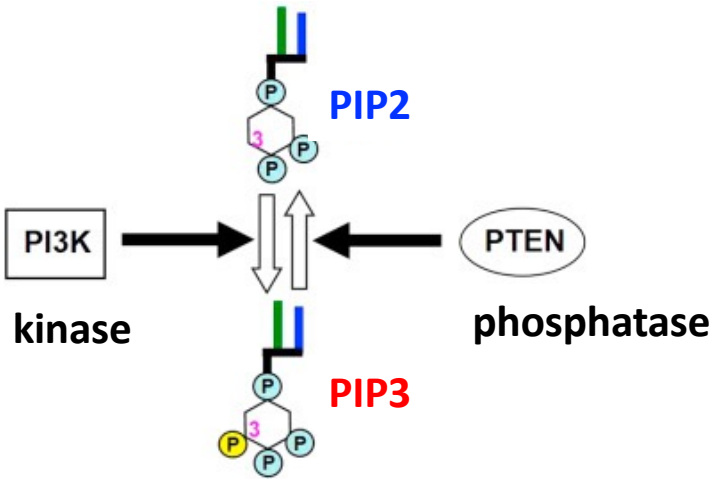


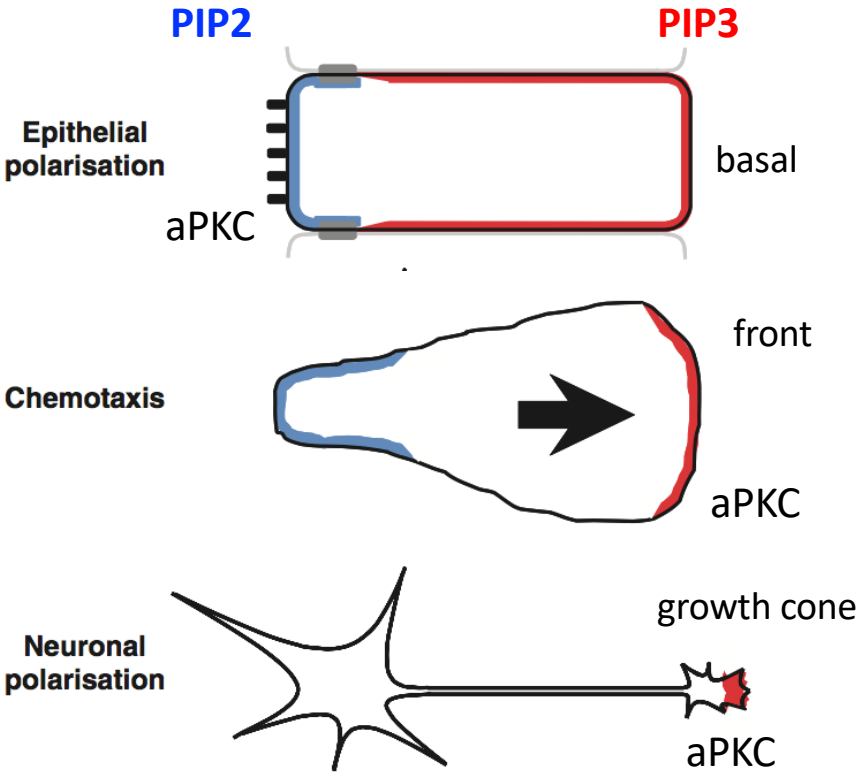


Ohno et al., Cell Polarity, 2015
Suzuki & Ohno, J Cell Sci, 2006

Two phospholipids : initiation and maintenance

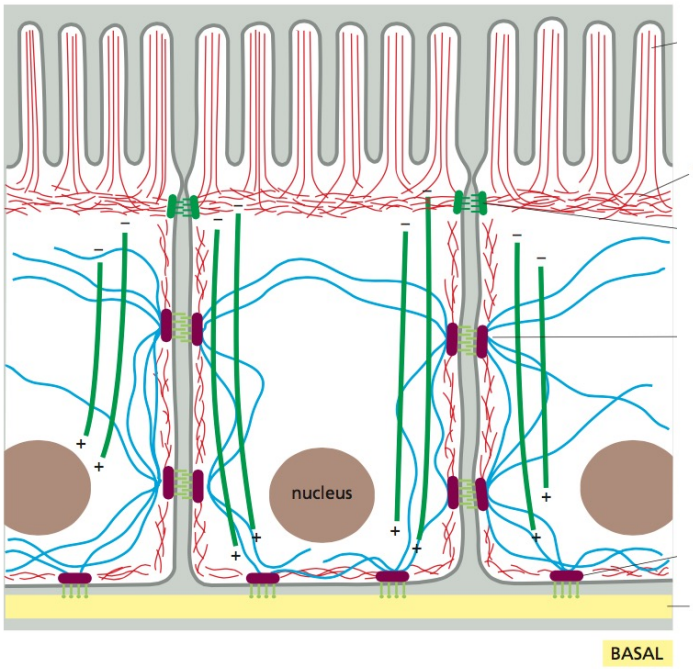
Phosphatdylinositol lipids



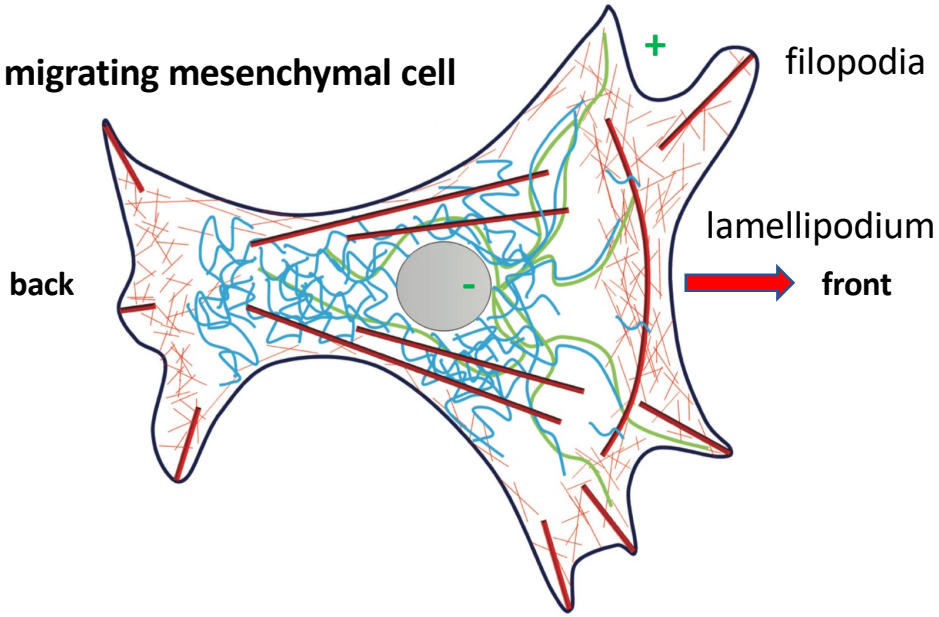


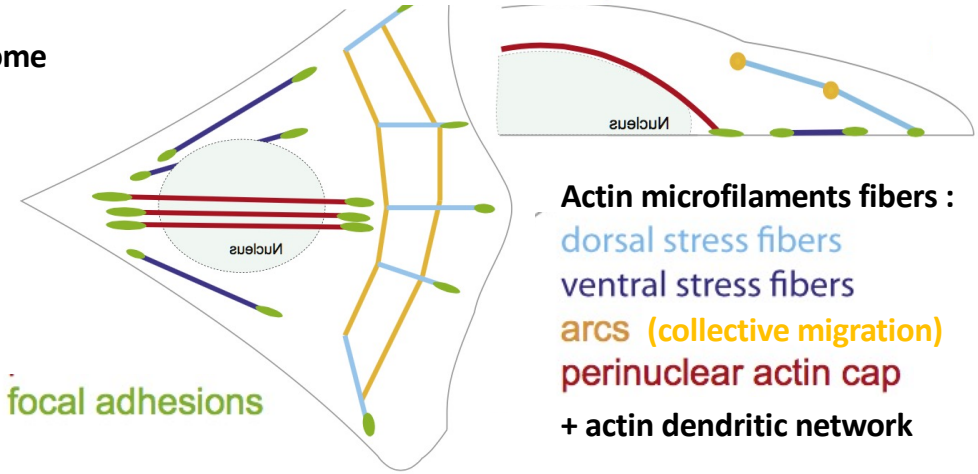
Lesli et al., Oncogene, 2008

Cytoskeleton and polarity



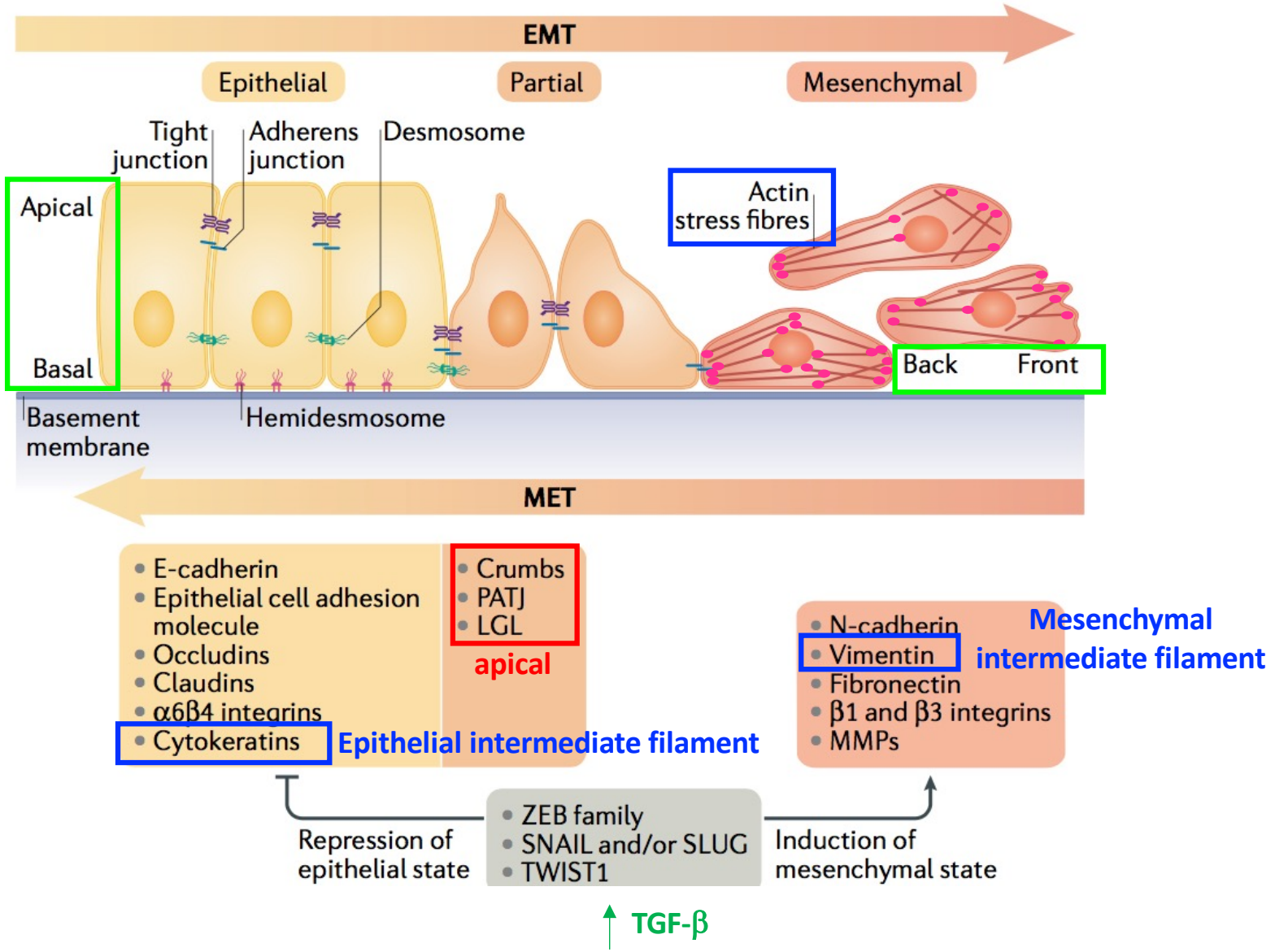
Actin microfilament / septin
Microtubules Intermediate filaments





Adapted from figure 16-4, Molecular Biology of the Cell 6th
Battaglia et al., F1000 Res., 2018
Burridge & Guilluy, Exp Cell Res, 2015

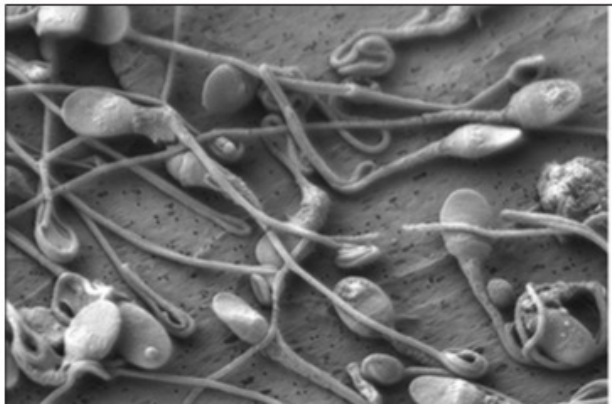
EMT = epithelial–mesenchymal transition
MET = mesenchymal-epithelial transition



Adapted from Dongre & Weinberg, Nat. Rev. Mol. Cell Biol., 2019

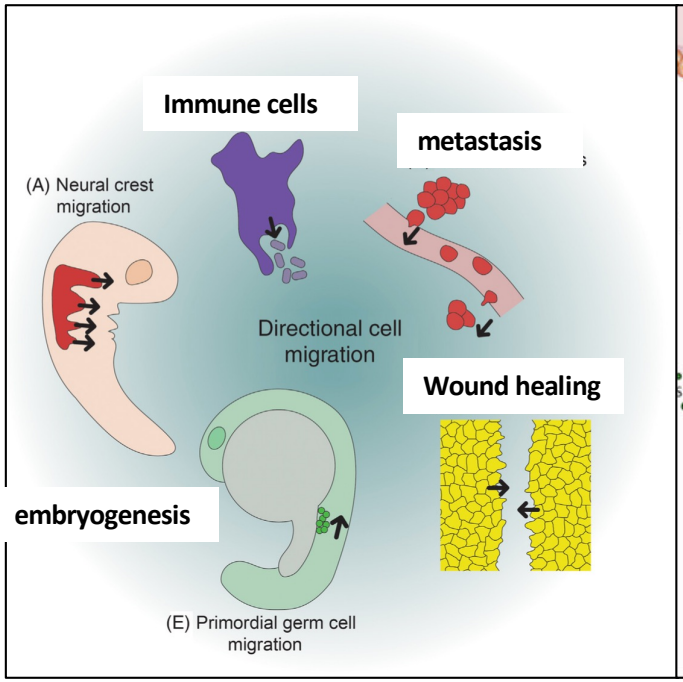
Cellular migration in human

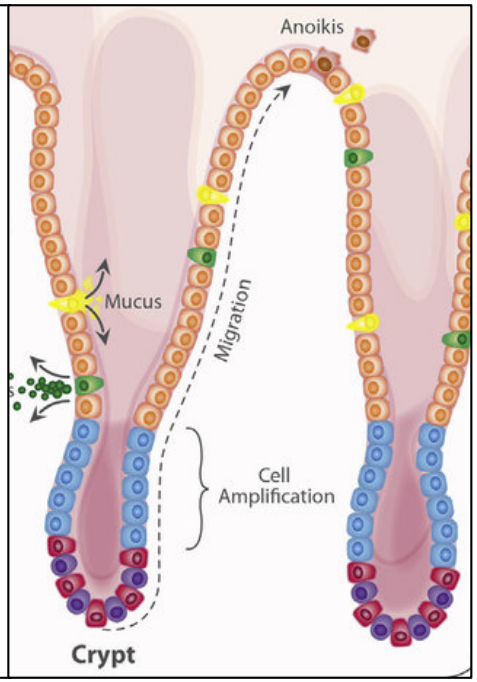
sperm : swimming not migration …



Nussdorfer et al., Bosnian J Basic Med Sci, 2019

crawling cells : in embryos or adults

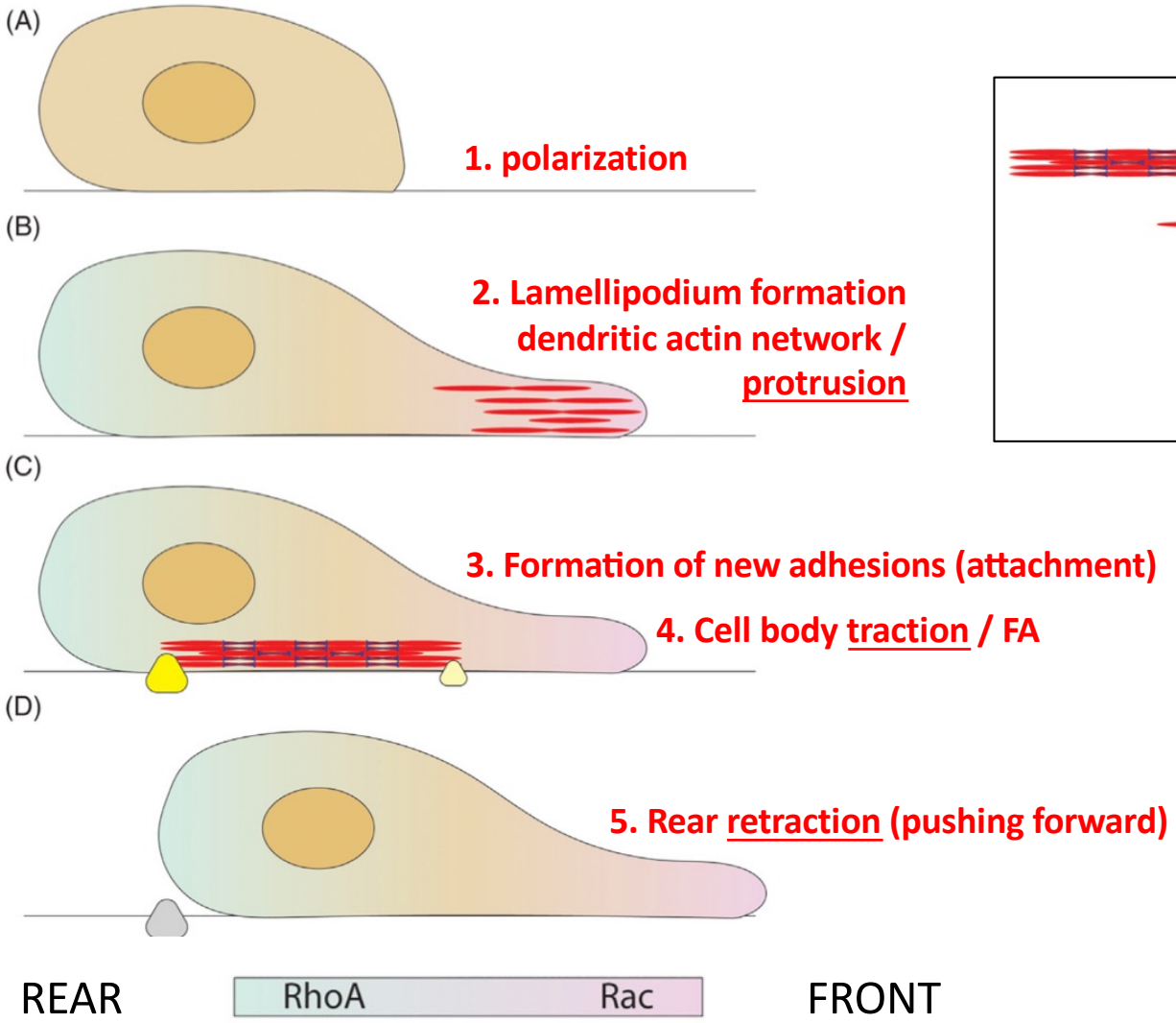


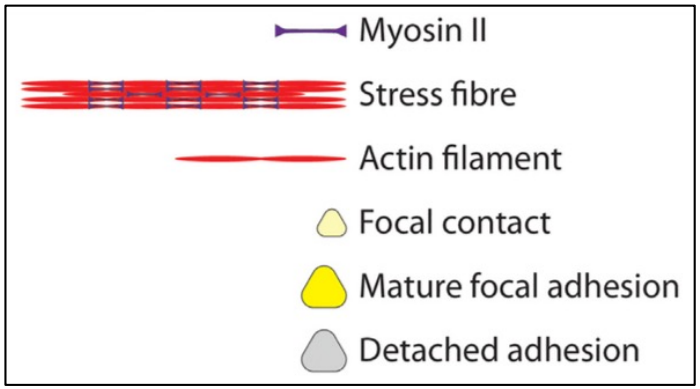


Shellard & Mayor, Trends Cell Biol, 2020

N. Bradbury

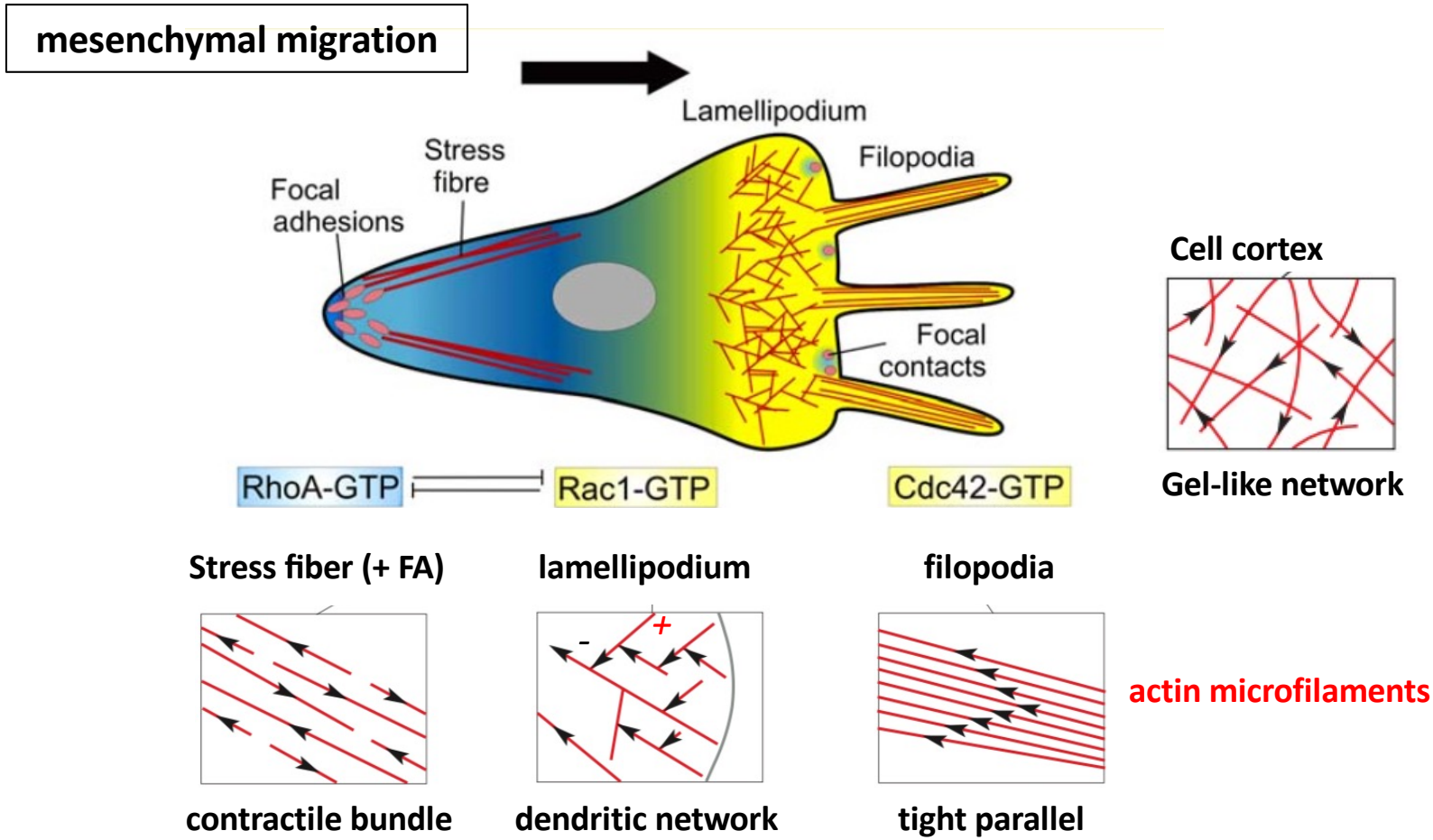
Five steps for mesenchymal cellular migration in 2D





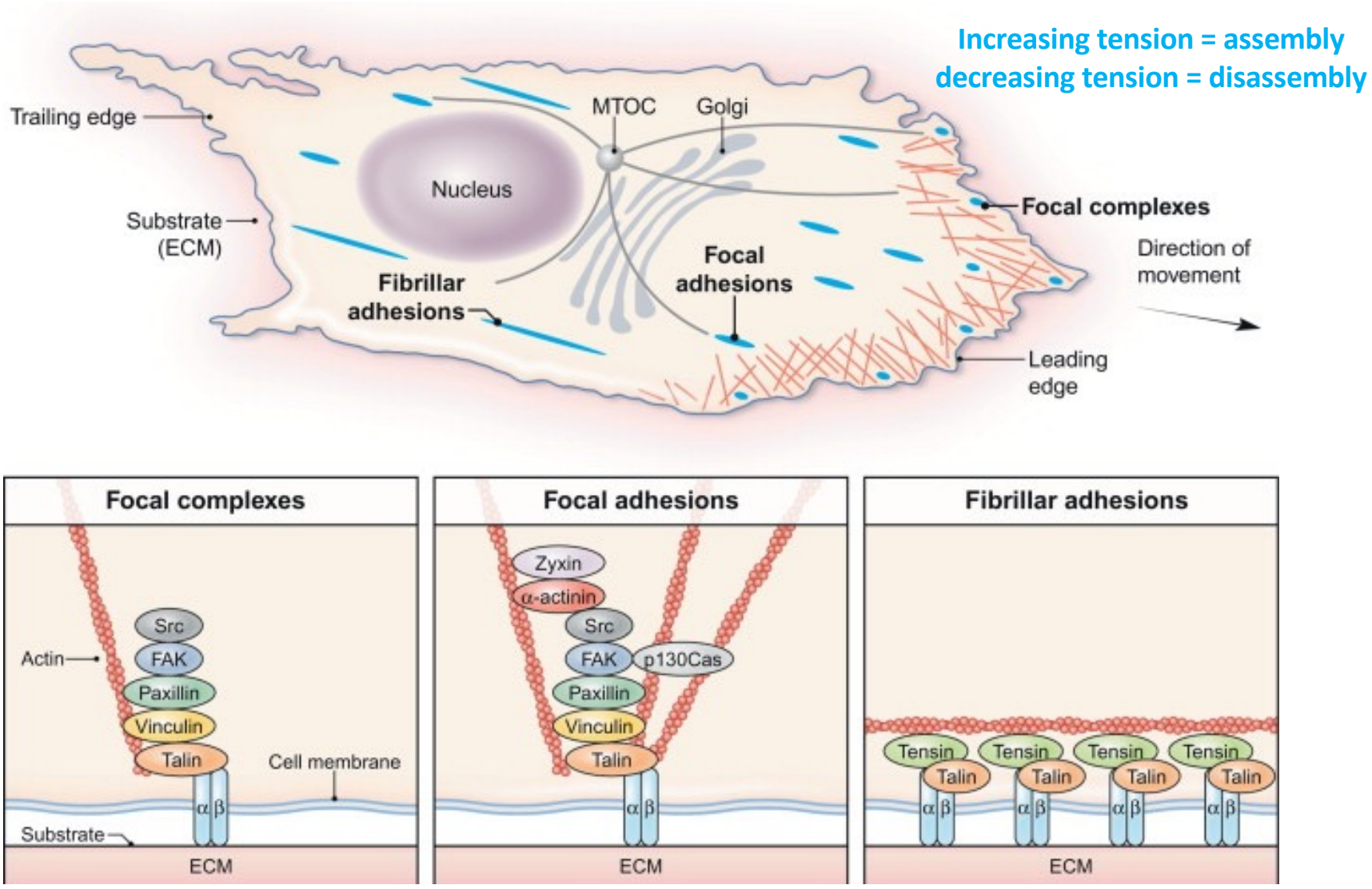
Shellard & Mayor, Trends Cell Biol, 2020

Rho, Rac, Cdc42 GTPases and actin cytoskeleton



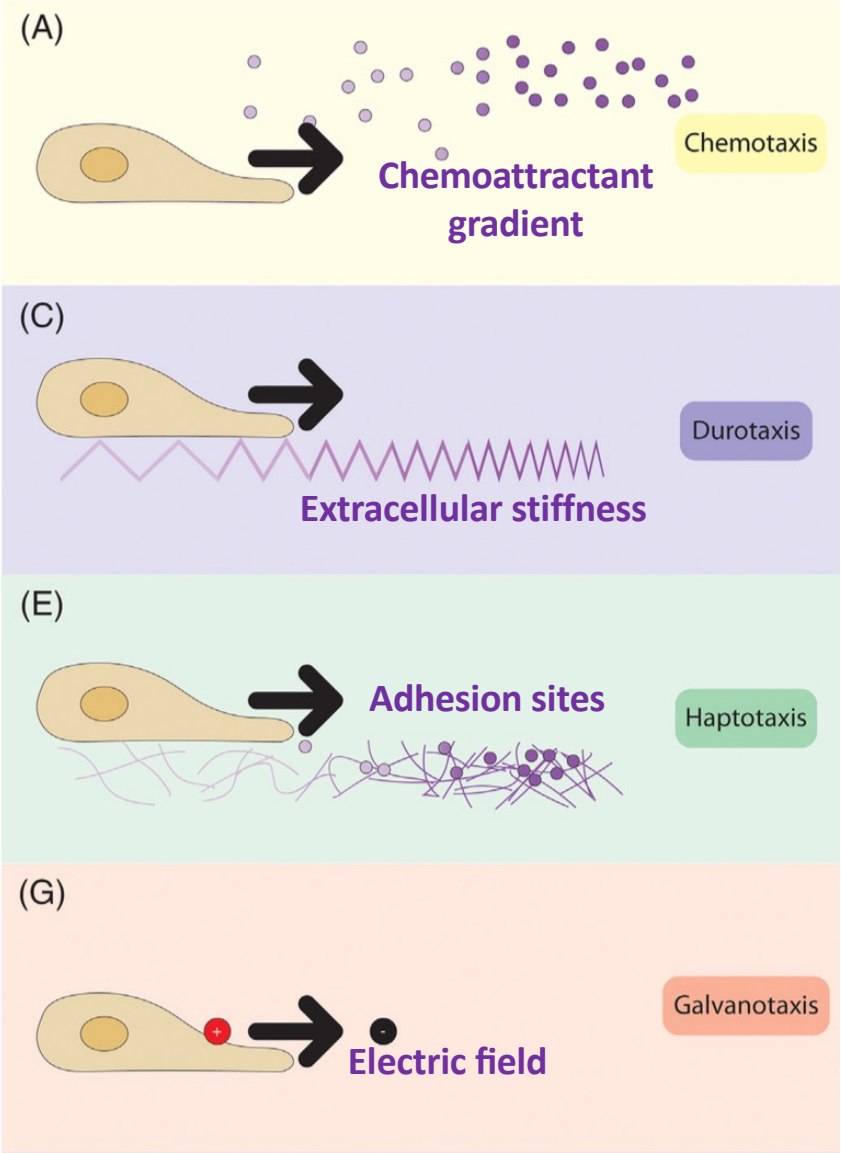
Mayor & Carmona-Fontaine, Trends Cell Biol , 2010
Figure 16-21, Molecular Biology of the Cell 6th

Focal adhesions maturation and disassembly

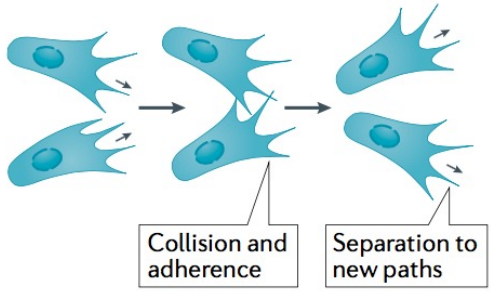


Joo & Yamada 2015, Chapter 5, Cell Adhesion and Movement

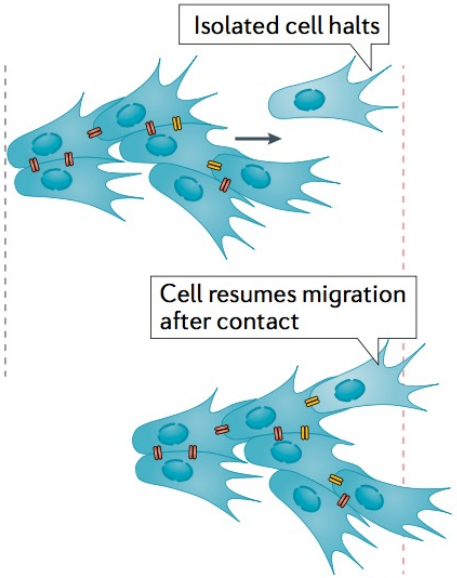
Determinants of migration direction



Contact inhibition of migration

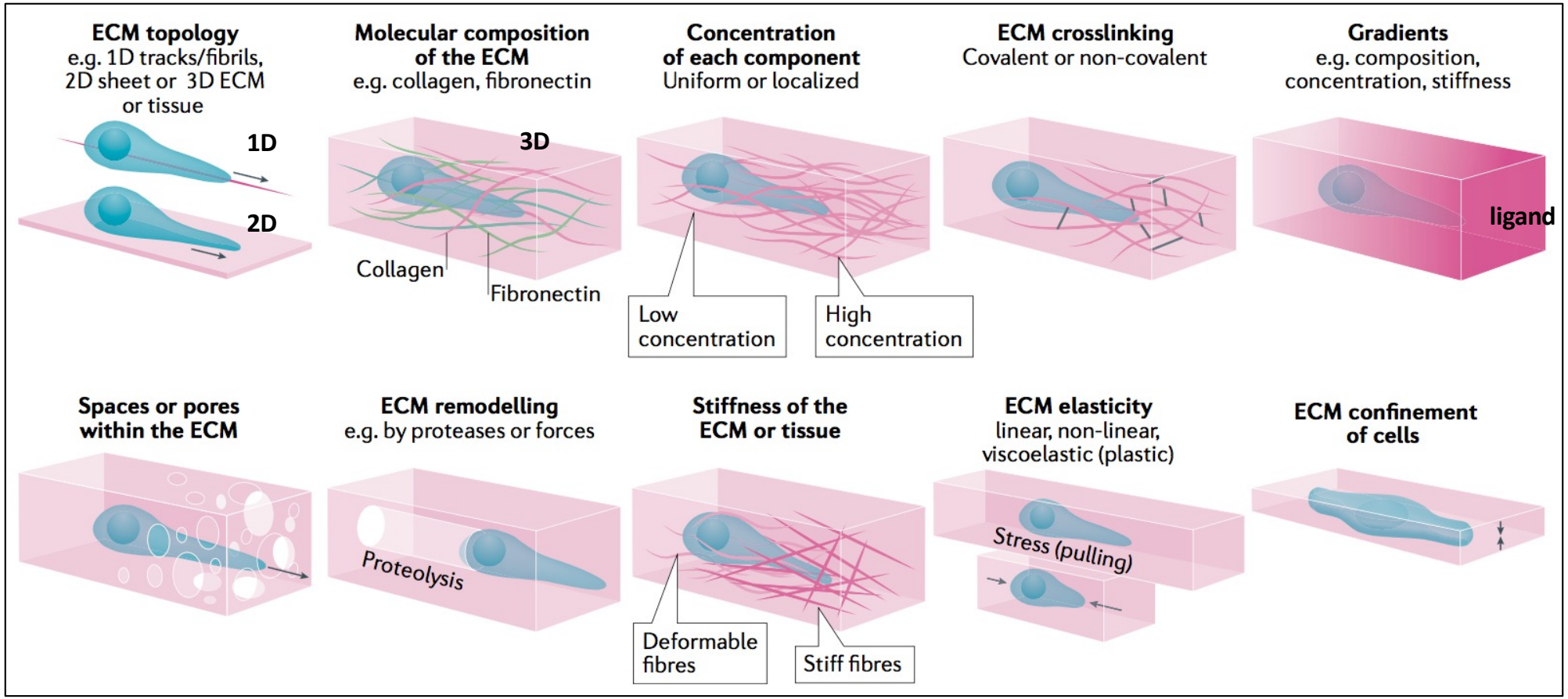


Contact stimulation of migration



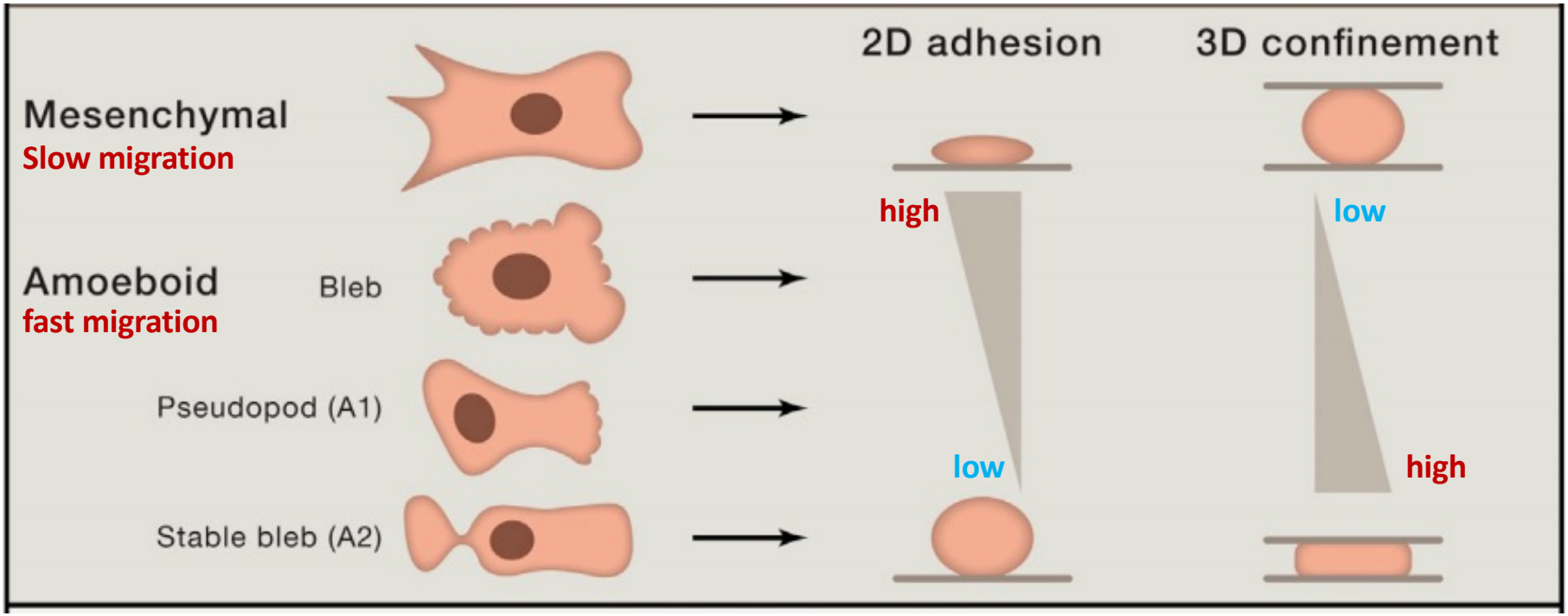
Shellard & Mayor, Trends Cell Biol, 2020
Yamada & Sixt,Mol Cell Biol, 2019

ECM feature modulating migration in 3D



Yamada & Sixt,Mol Cell Biol, 2019

Modes of migration adopted by cells in 2D/3D

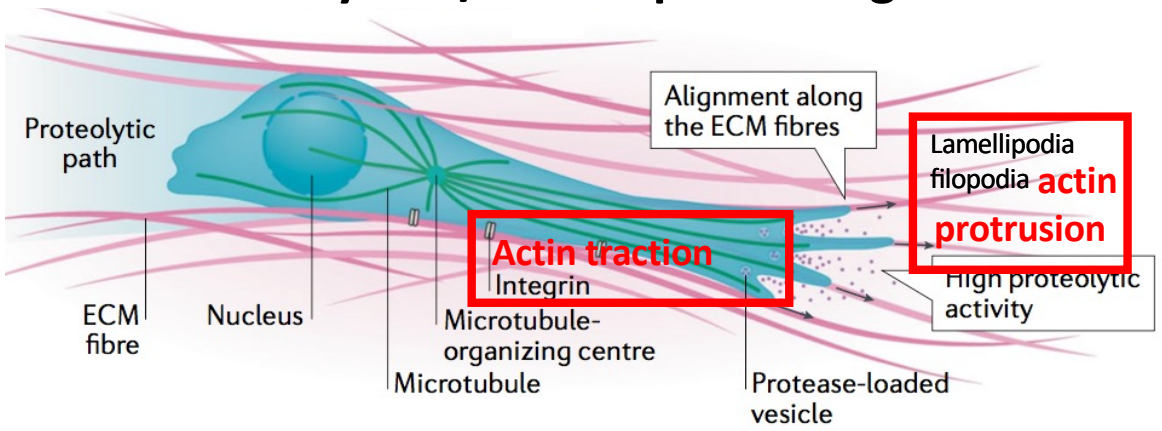


Influenced by strength of :
- **Adhesion to the substrate**
- **Physical confinement**
- **Contractility**

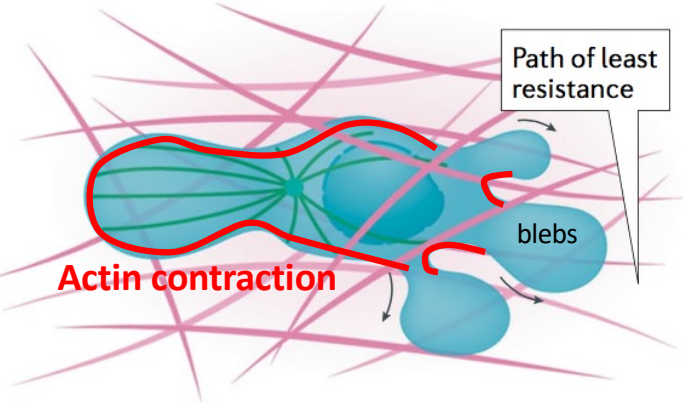
Welch, Cell, 2015

Modes of migration adopted by cells in 3D

Mesenchymal / lamellipodial migration



Amoeboid migration



Traction

Cell break the wall

Propulsion

Cell go through holes in the wall

Strong adhesion ECM

Front : Rac1 branched actin protrusion

ECM proteolysis

Nucleus in the back / MTs in the front

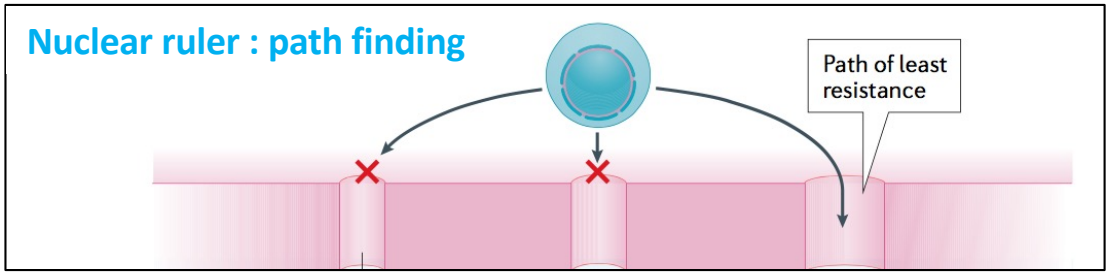
Low adhesion ECM

Back : RhoA Myosin contraction

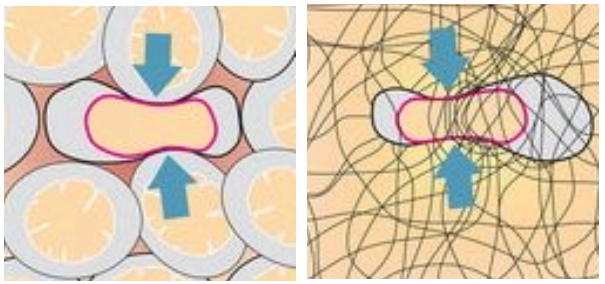
Nucleus in the front / MTs in the back

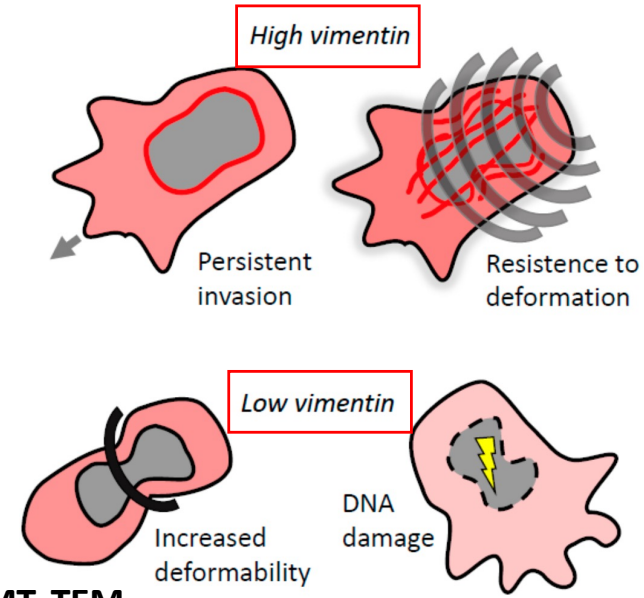
Yamada & Sixt, Mol Cell Biol, 2019

Nucleus and cell migration



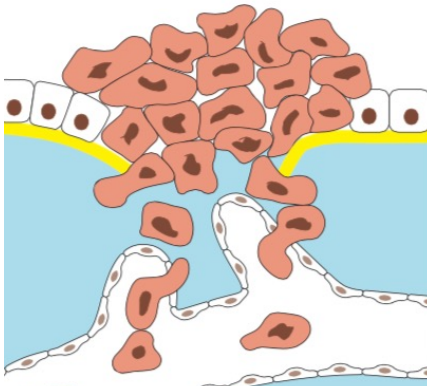
Nucleus = stress sensor



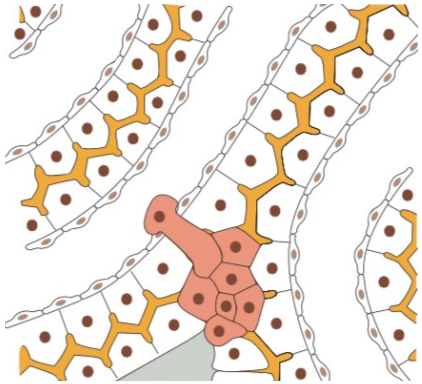


EMT, TEM
Soft cell

intravasation (EMT)



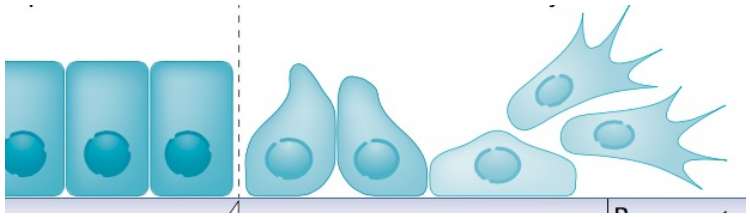
extravasation (MET)



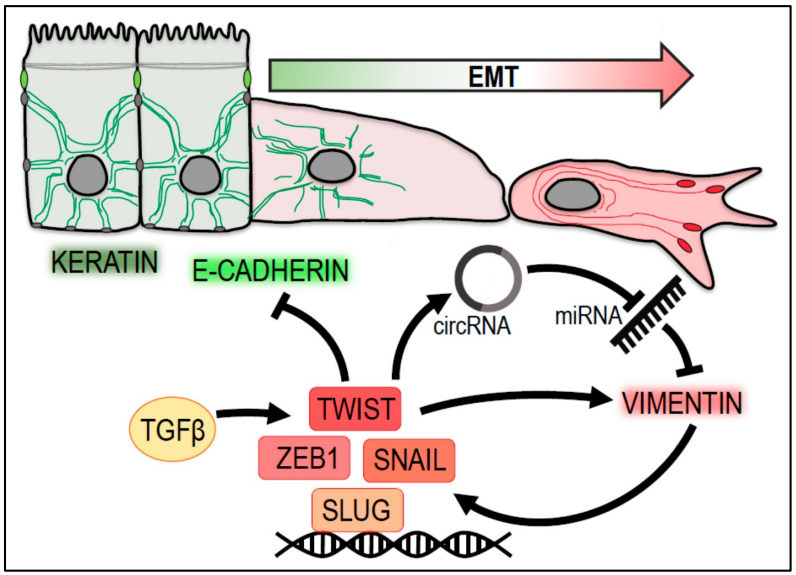
CTCs (circulating tumor cells in the blood stream) : round and stiff cells

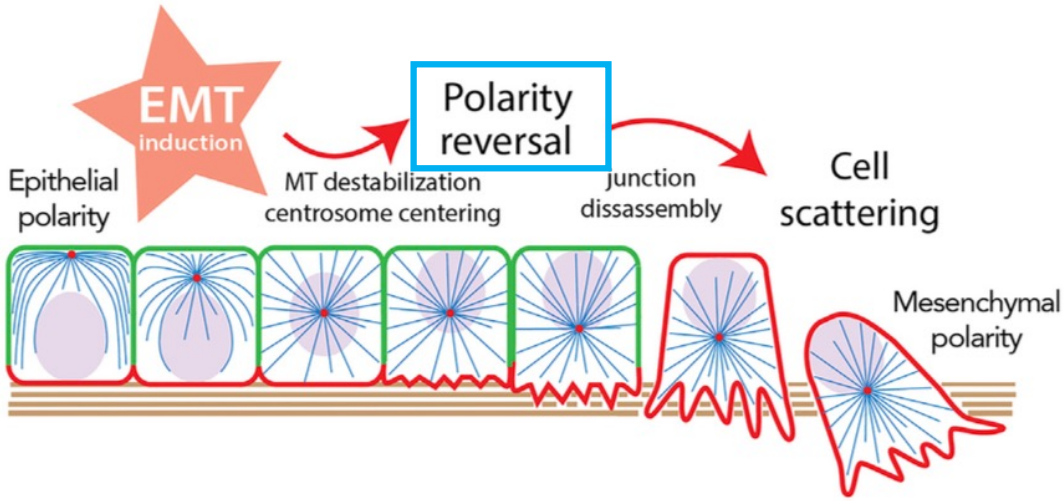
Venturini et al., Science, 2020
Yamada & Sixt, Mol Cell Biol, 2019
Strouhalova et al., Cancers, 2020
20-16, Molecular Biology of the Cell 6th

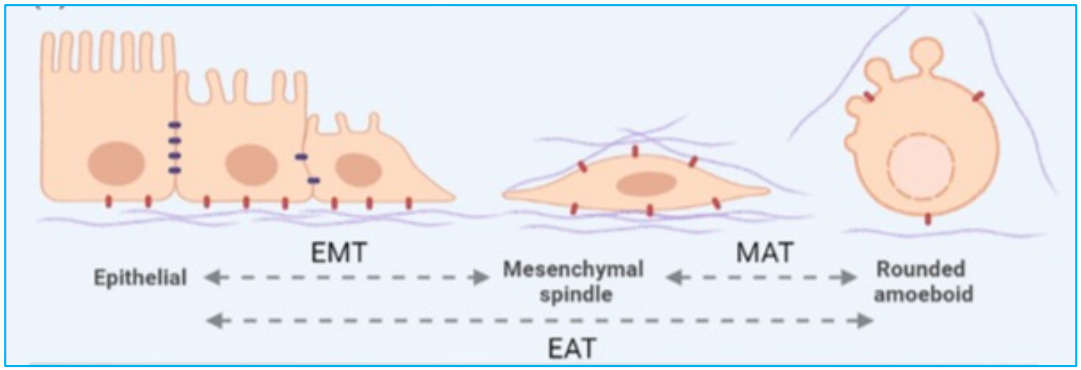
EMT = epithelial–mesenchymal transition



EMT & MET =
abnormally reactivated during metastasis



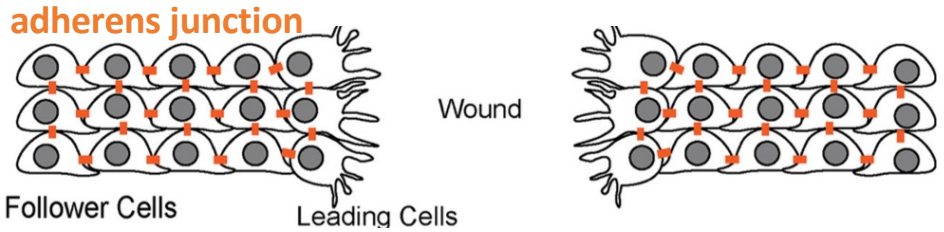




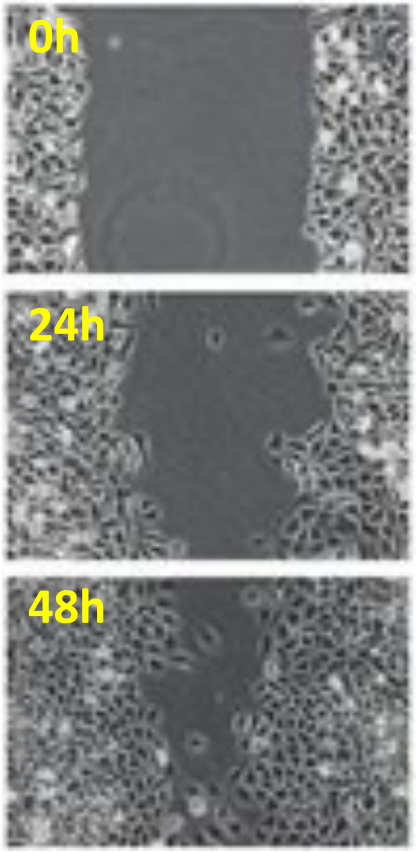
intermediate filaments : keratin / vimentin switch
Cadherin : E-Cad / N-Cad switch
Hemidesmosome / focal adhesion

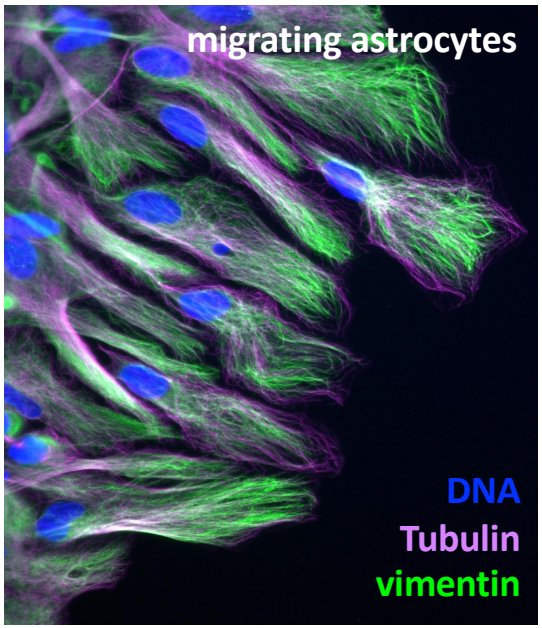
Yamada & Sixt, Mol Cell Biol, 2019 ; Strouhalova et al., Cancers, 2020
Burute et al., Dev Cell, 2017 ; Graziani et al, Trends in Cell Biology, 2022

Partial EMT : collective cell migration



wound healing

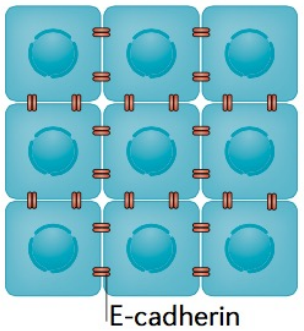




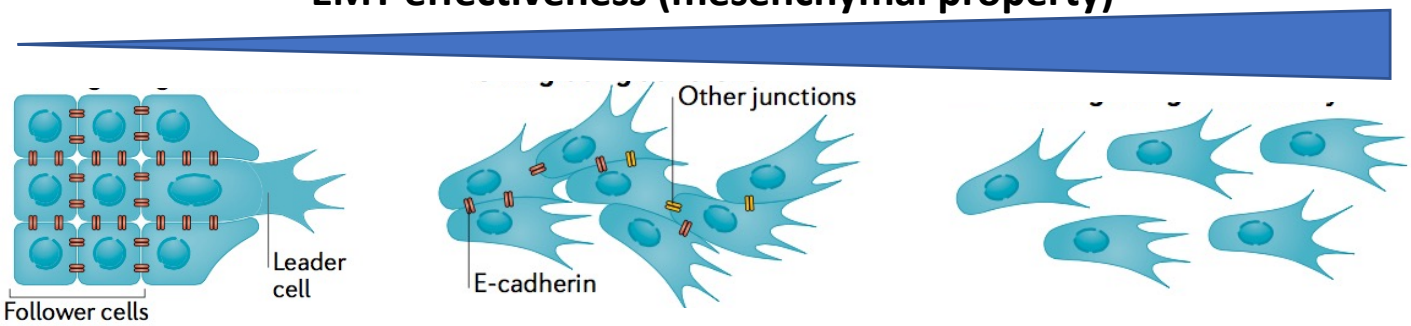
Olson & Nechiporuk, Front Cell Dev Biol, 2018
Wu et al., Int J Oncology, 2019
Pasteur

EMT in cancer : individual or collective migration

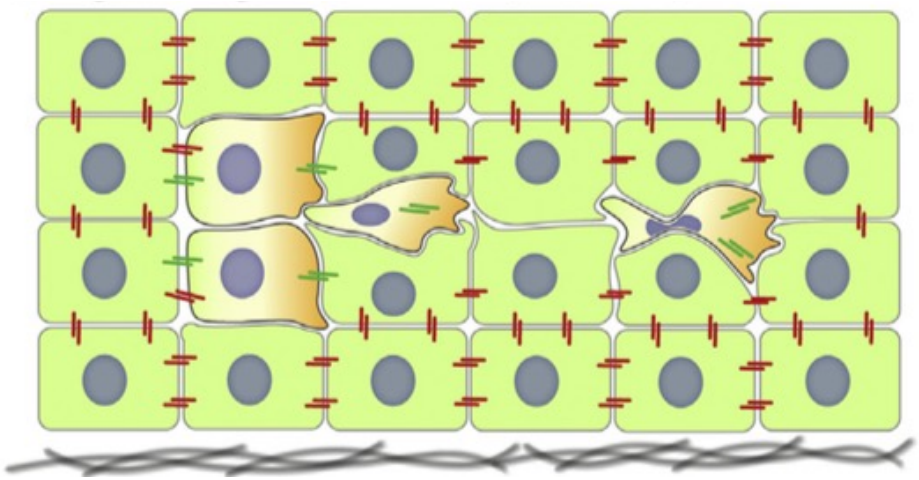
epithelium



EMT effectiveness (mesenchymal property)

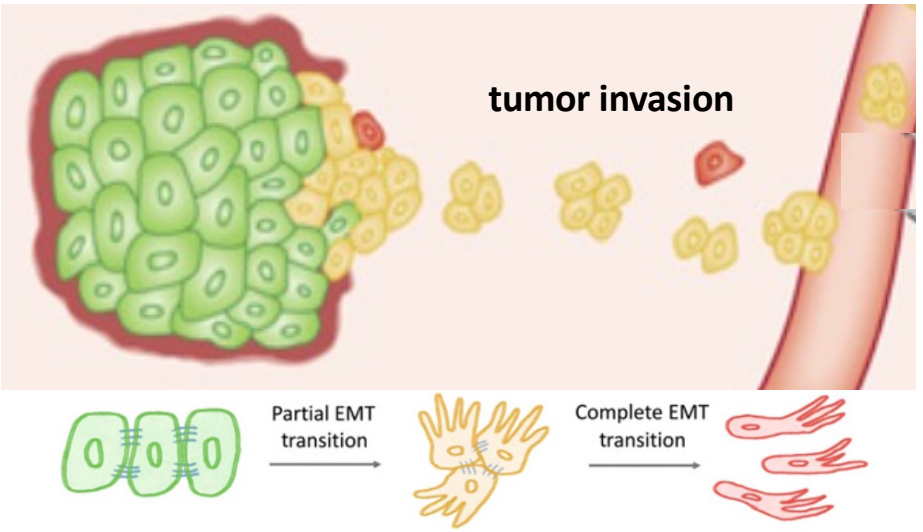


Complete EMT : confinement of the single migrating cell in the epithelium



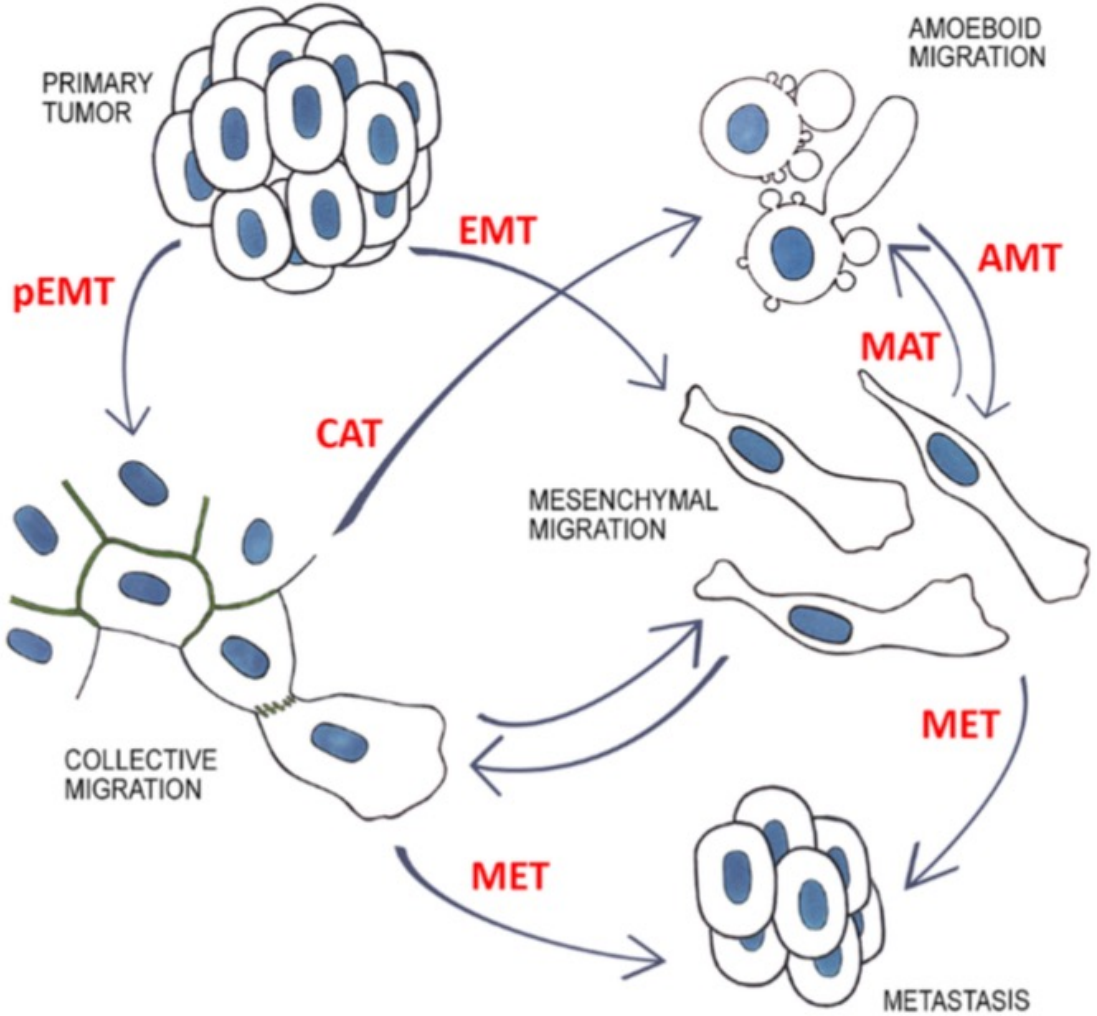
E-Cad / N-Cad switch

Partial EMT : collective cell migration



Yamada & Sixt,Mol Cell Biol, 2019
Barriga & Mayor, Sem Cell Dev Biol, 2018
Bocci et al., Cancer Research, 2019

Plasticity of cancer cell migration



Migrastatics :
anti-invasion / anti-metastatic drugs ?

Rubtsova et al, Int. J. Mol. Sci., 2021

Therapeutic strategies related to metastasis ?

cells

Preventing EMT (TEM) ?

. How

. When ? (early/late events of dissemination)

Targeting circulating tumor cells ?

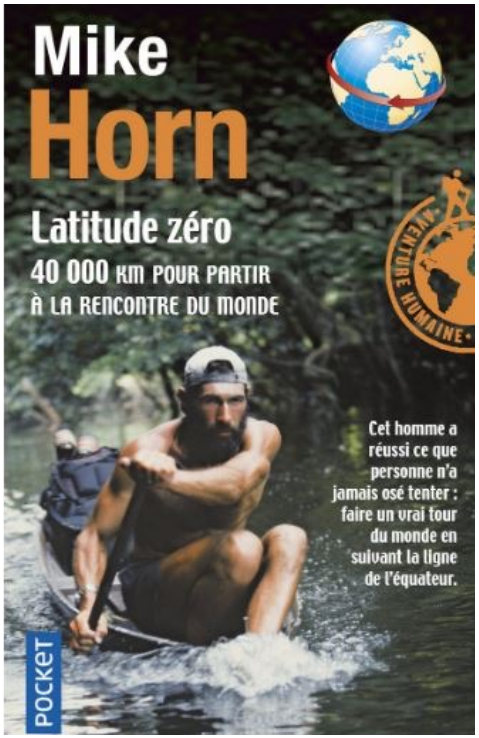
Probably not in the blood stream for a long time …

Best chance : targeting DTCs / their niches ?

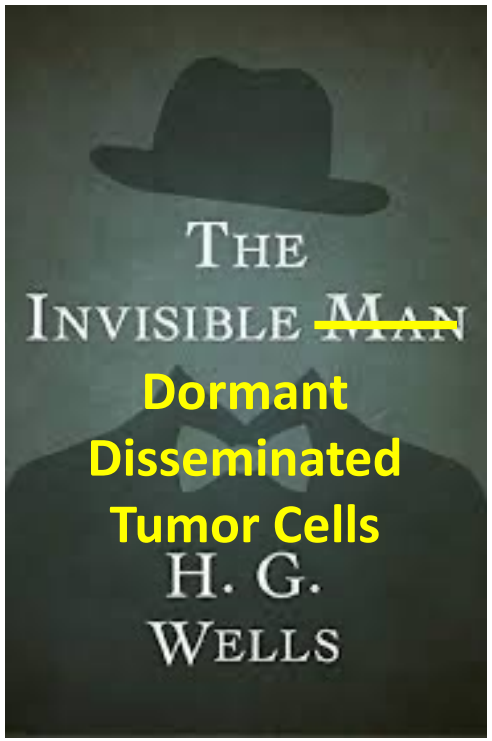
Modulating quiescence - senescence ?

See cell cycle slides

Migrating cells



DTC : dormant, resistant and killers if they wake-up



Ways to reduce your cancer risk

World Health Organization

TOGETHER LET'S BEAT CANCER
#beatNCDs

Do not smoke or use any form of tobacco

Make your home **smoke-free**

Enjoy a **healthy diet**

Breastfeeding reduces the mother's cancer risk

Vaccinate your children against Hepatitis B and HPV

Avoid too much sun, use **sun protection**

Reduce indoor and outdoor **air pollution**

Be **physically active**

Limit alcohol intake

Take part in organized **cancer screening programmes**

Credit: WHO