

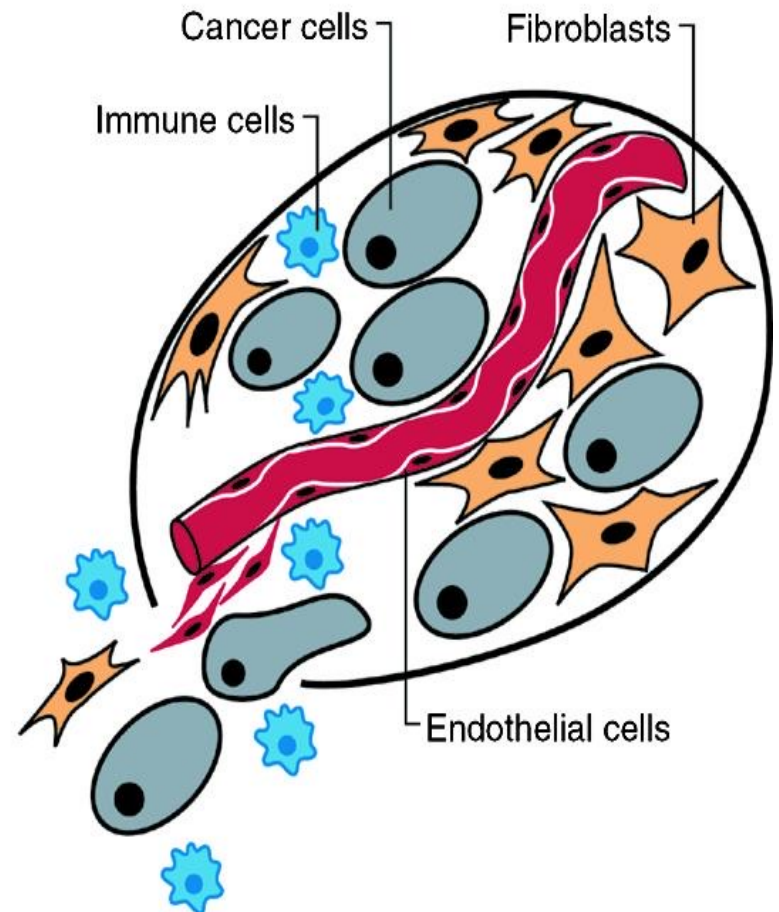
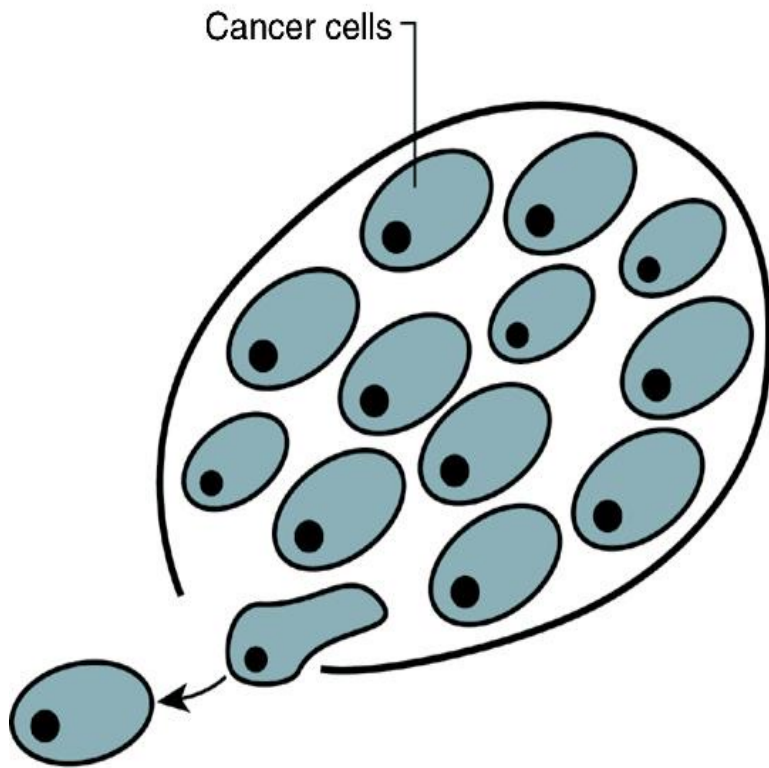
Corso di Biologia Cellulare del Cancro

AA 2020-2021

IL MICROAMBIENTE TUMORALE

I tumori sono organi

Visione riduzionista



La componente stromale dei tumori

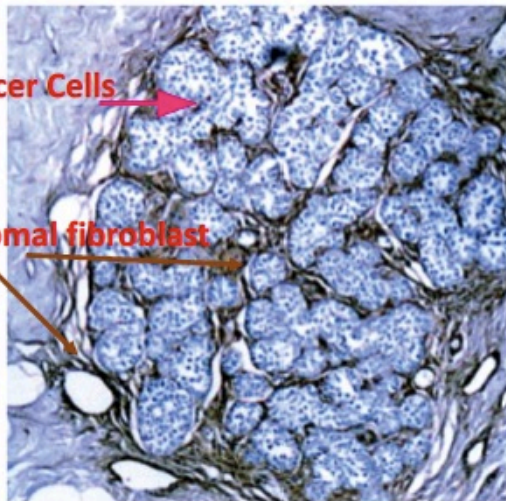


Figure 11.3c The Biology of Cancer (© Garland Science 2014)

Lobular CA in situ of the Breast

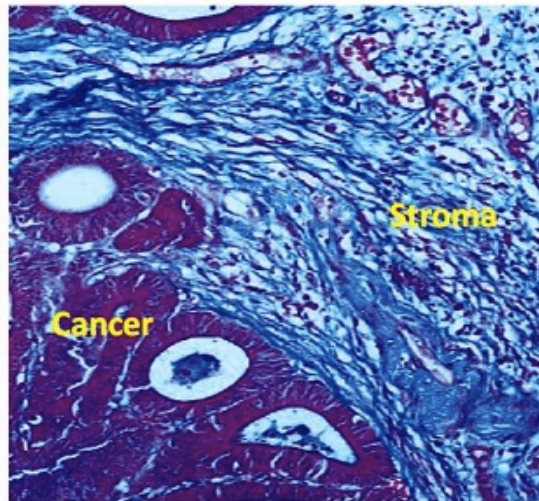


Figure 13.1d The Biology of Cancer (© Garland Science 2014)

Adenocarcinoma of the stomach

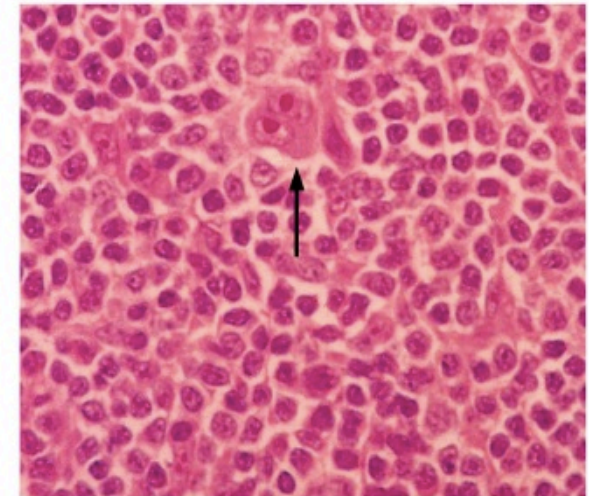


Figure 13.1a The Biology of Cancer (© Garland Science 2014)

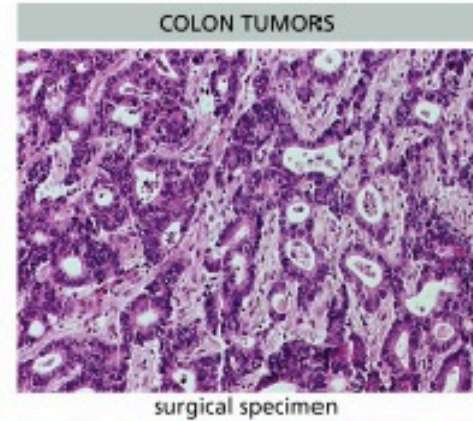
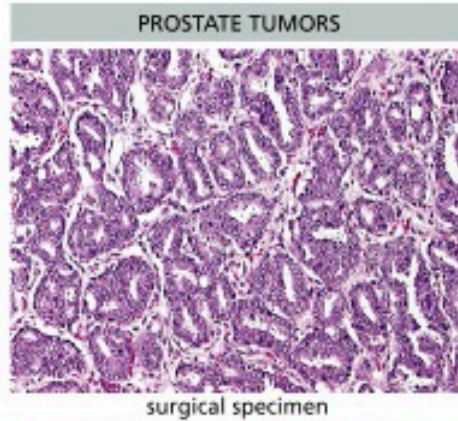
In Hodgkin disease rare cancer cells
Surrounded by normal lymphocytes

I classici modelli tumorali in vitro/ in vivo non ricapitolano la complessità dei tessuti tumorali

Tumore primario

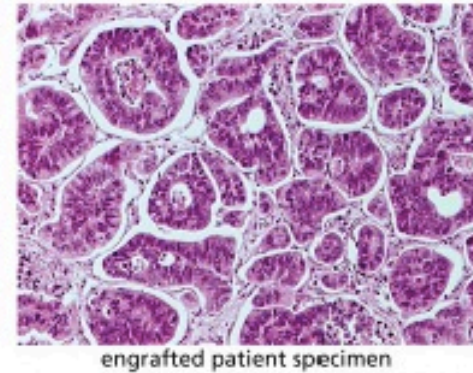
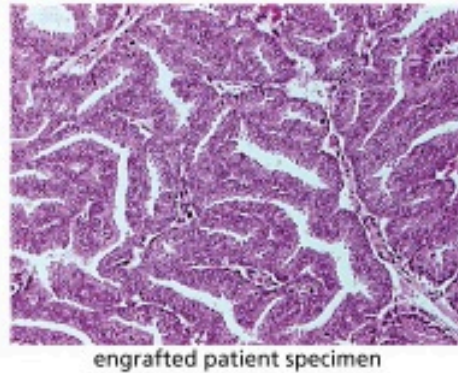
A

or

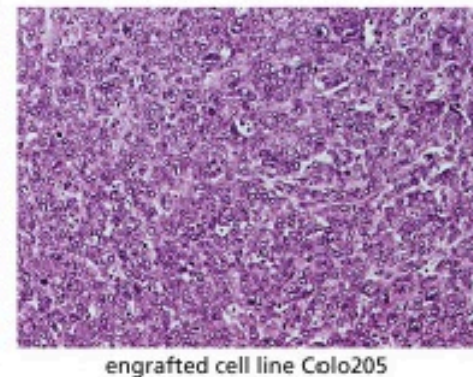
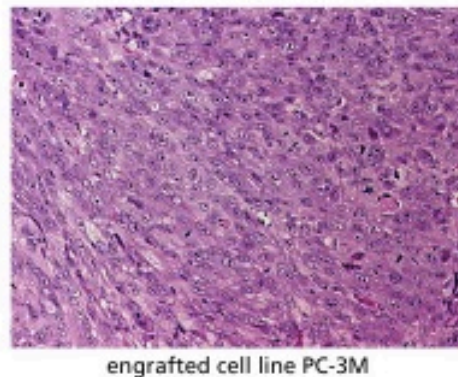


PDX: tumore trapiantato in animale immunocopromesso

B

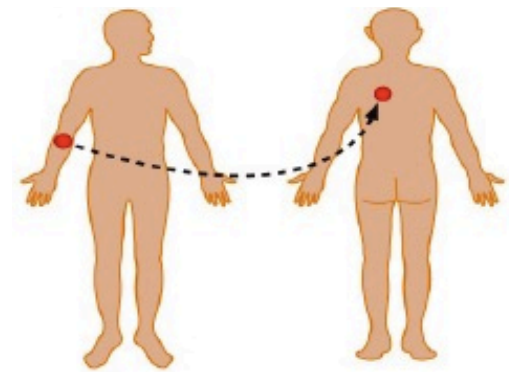


Trapianto di una linea cellulare tumorale in animale immunocopromesso

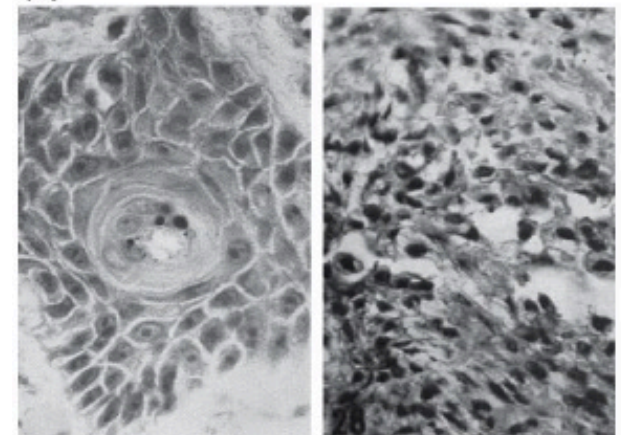


Un microambiente permissivo supporta la progressione tumorale

Trapianto autologo di carcinomi cutanei:
Solo le cellule tumorali trapiantate
assieme al proprio stroma
colonizzano il nuovo sito



(B)



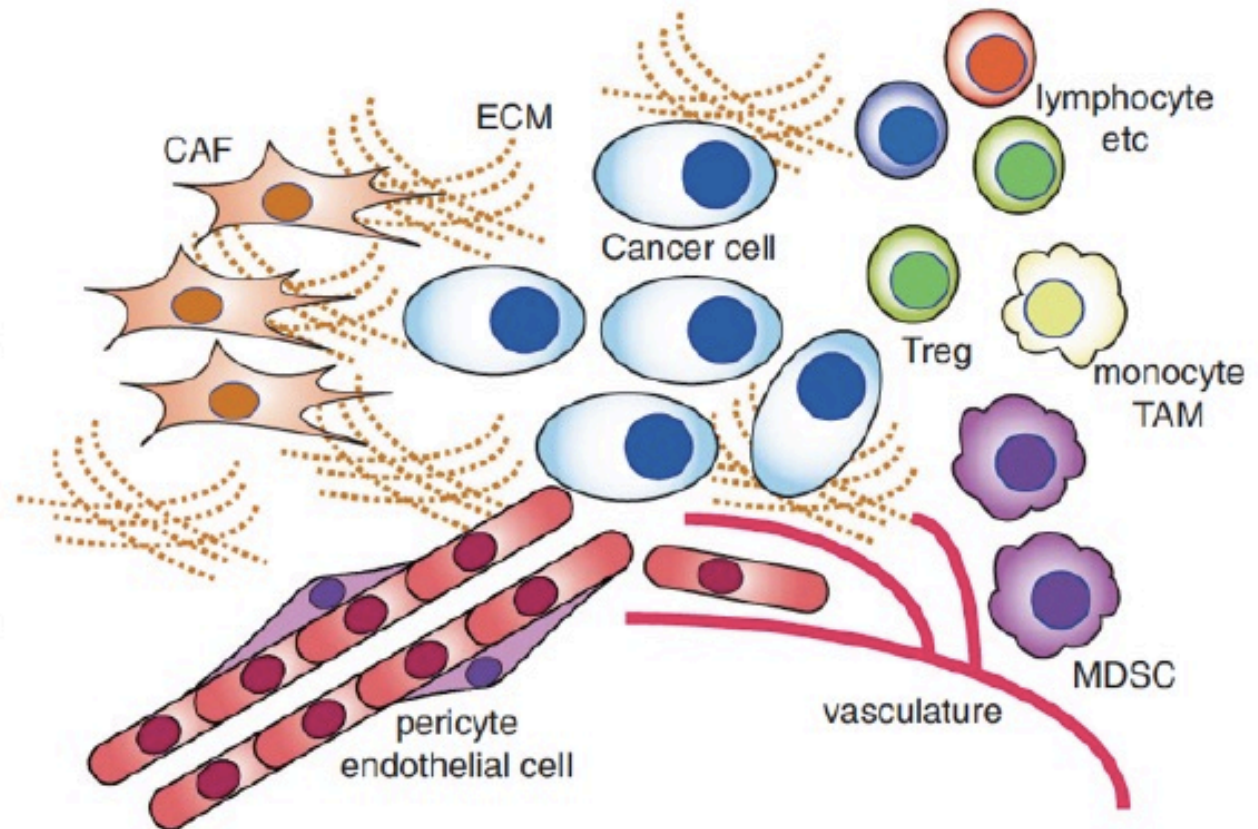
with stroma

without stroma

Figure 13.5 The Biology of Cancer (© Garland Science 2014)

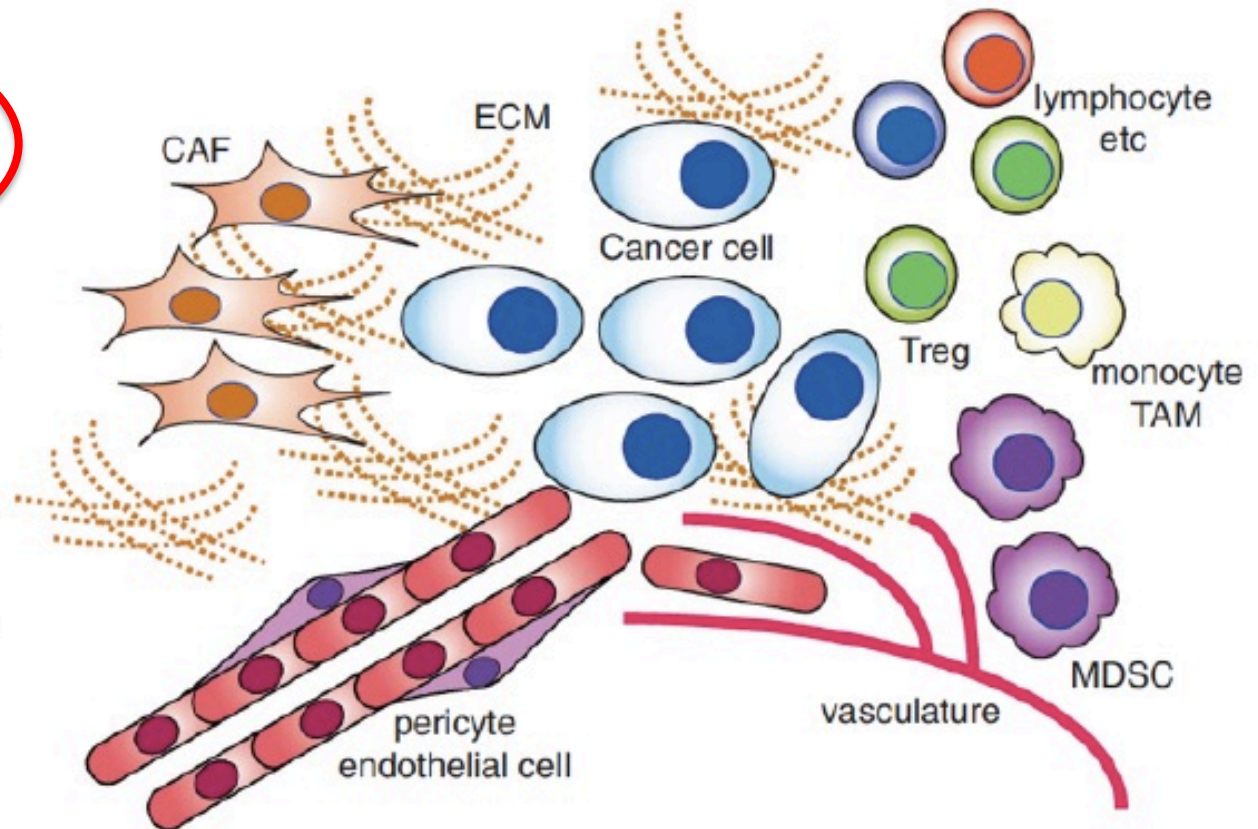
Il crosstalk tra le cellule tumorali e lo stroma

- Extracellular Matrix deposition and stiffening;
- Fibroblast activation (CAF);
- Neo-angiogenesis;
- Recruitment of cells from bone marrow.



Il crosstalk tra le cellule tumorali e lo stroma

- Extracellular Matrix deposition and stiffening;
- Fibroblast activation (CAF);
- Neo-angiogenesis;
- Recruitment of cells from bone marrow.

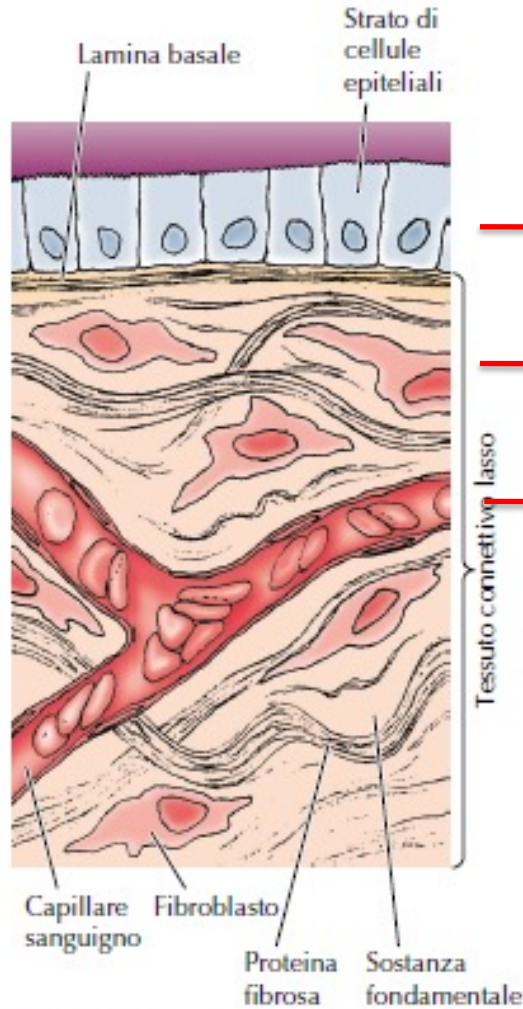


**IL MICROAMBIENTE TUMORALE:
LA MATRICE EXTRACELLULARE
E LA MECCANOTRASDUZIONE**

La matrice extracellulare: ECM

Lamina basale

Matrice interstiziale



cellule epiteliali

fibroblasti

vasi sanguigni

Tessuto connettivo lasso

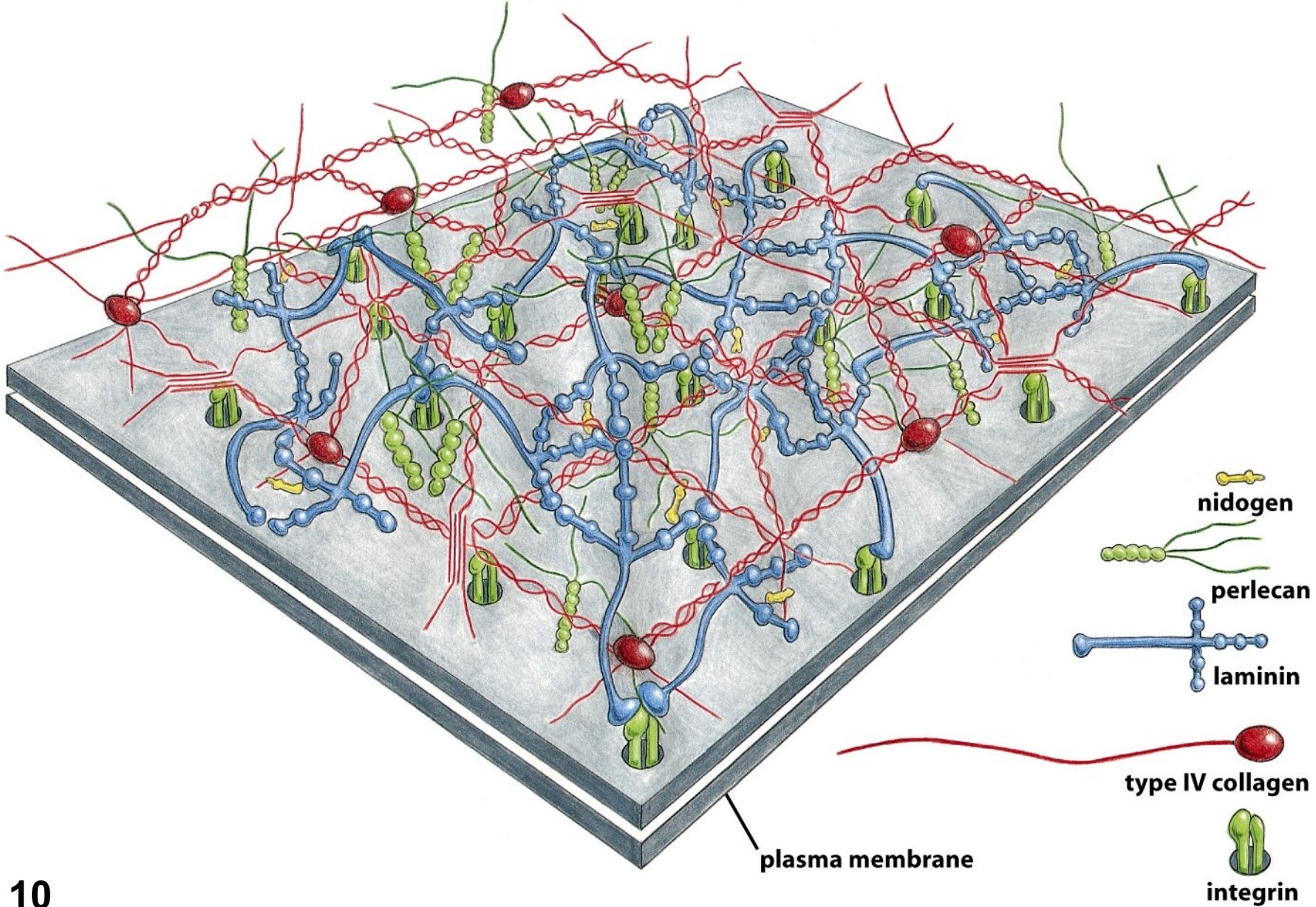
Capillare sanguigno

Fibroblasto

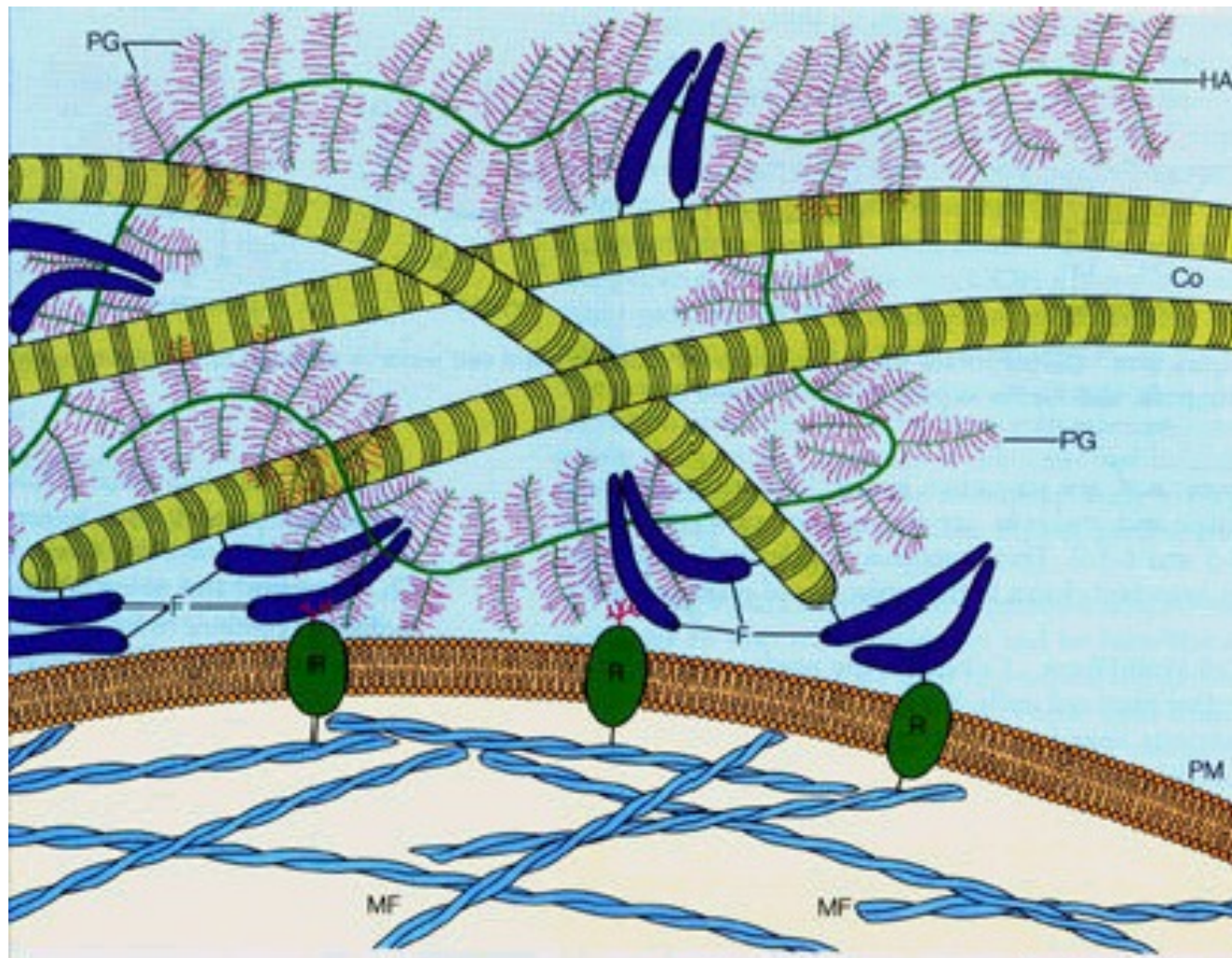
Proteina fibrosa

Sostanza fondamentale

La lamina basale:

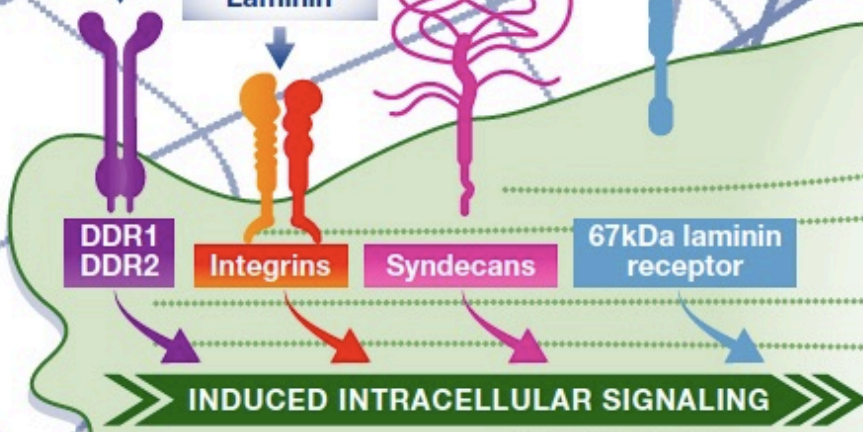


La matrice interstiziale



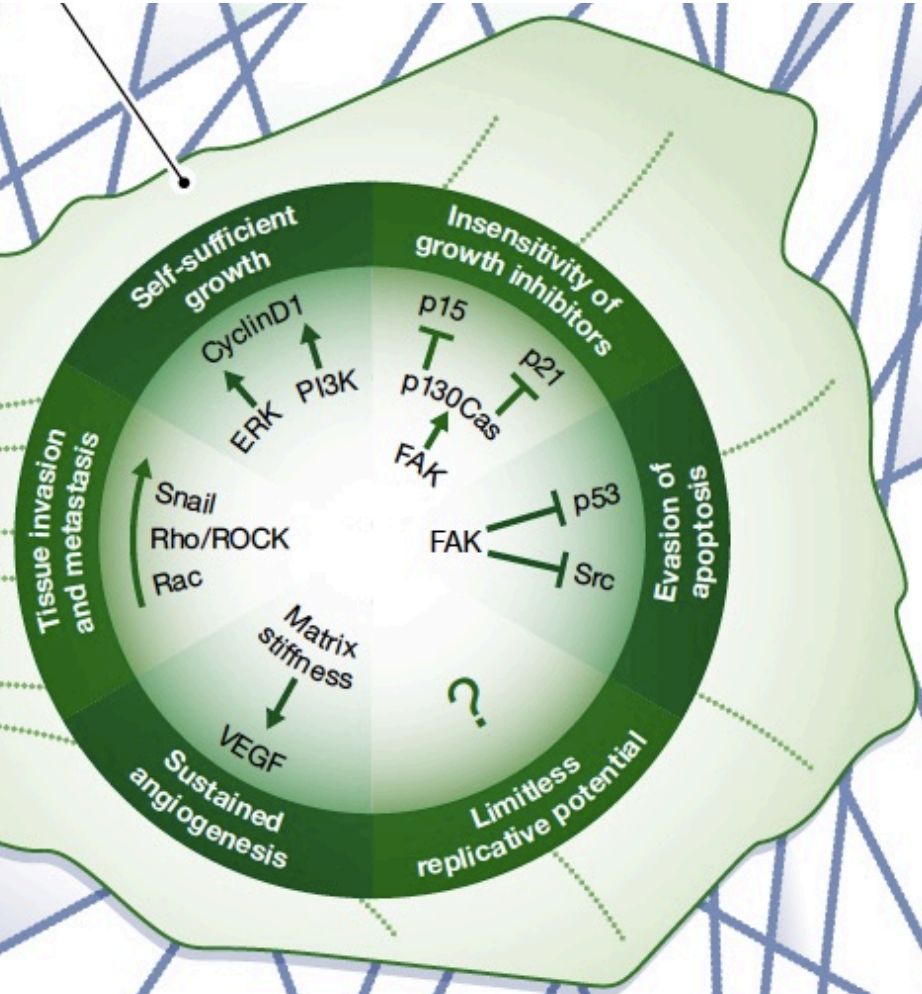
La progressione tumorale avviene in una matrice che evolve in modo dinamico

Ligandi per recettori di membrana

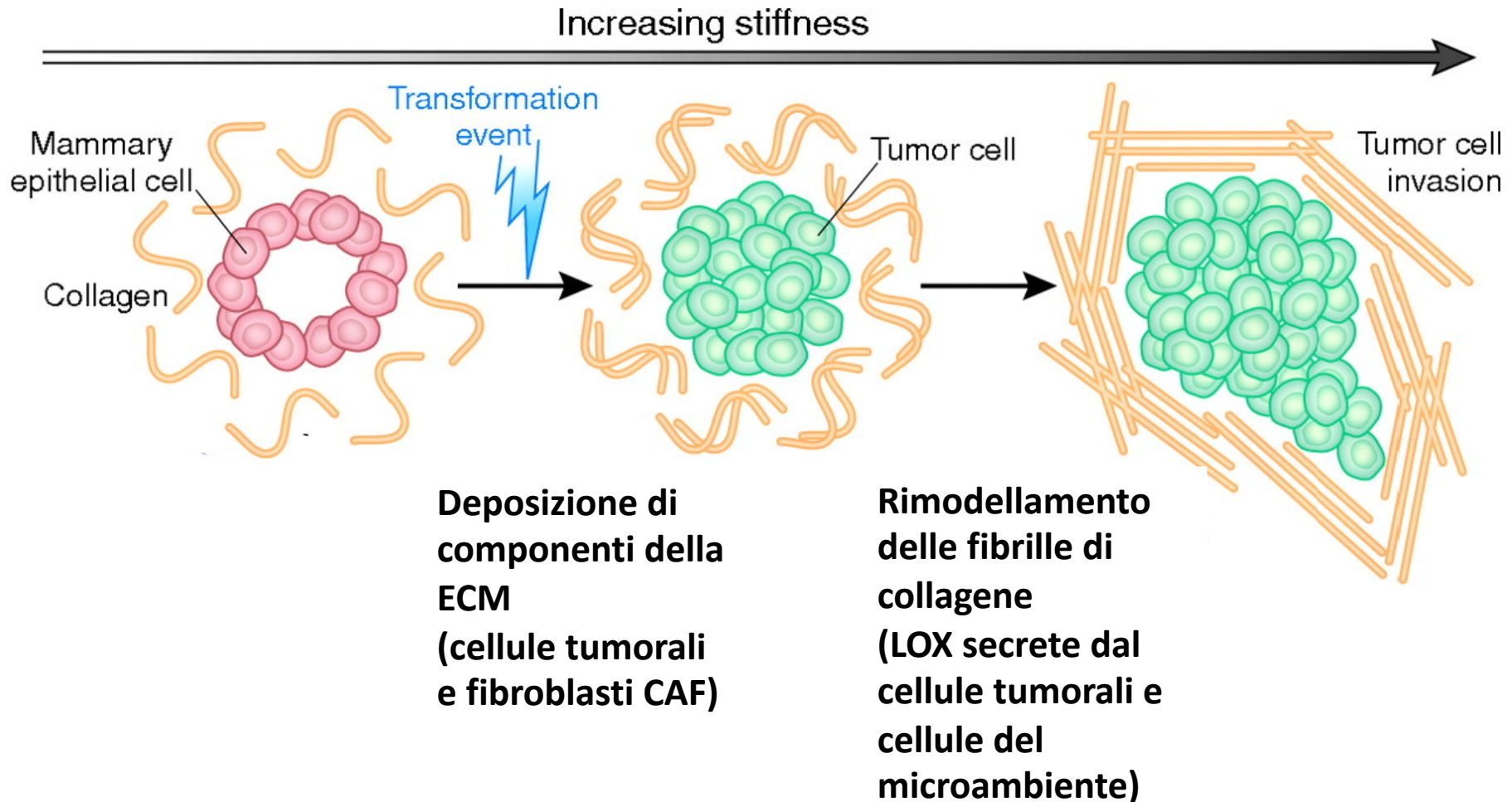


pH
struttura
idratazione

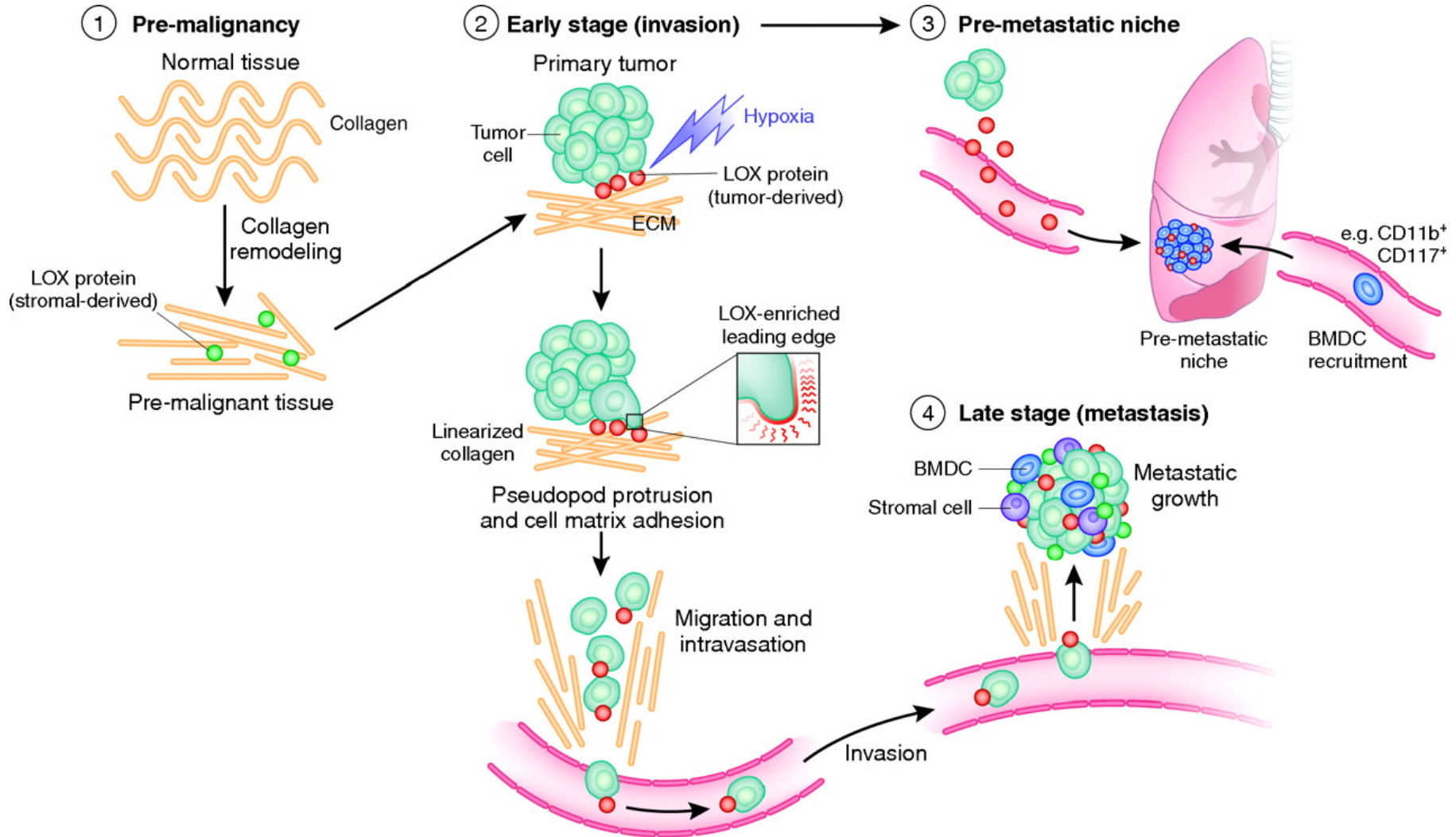
citochine
fattori di crescita
stimoli meccanici



Rimodellamento della ECM nella tumorigenesi



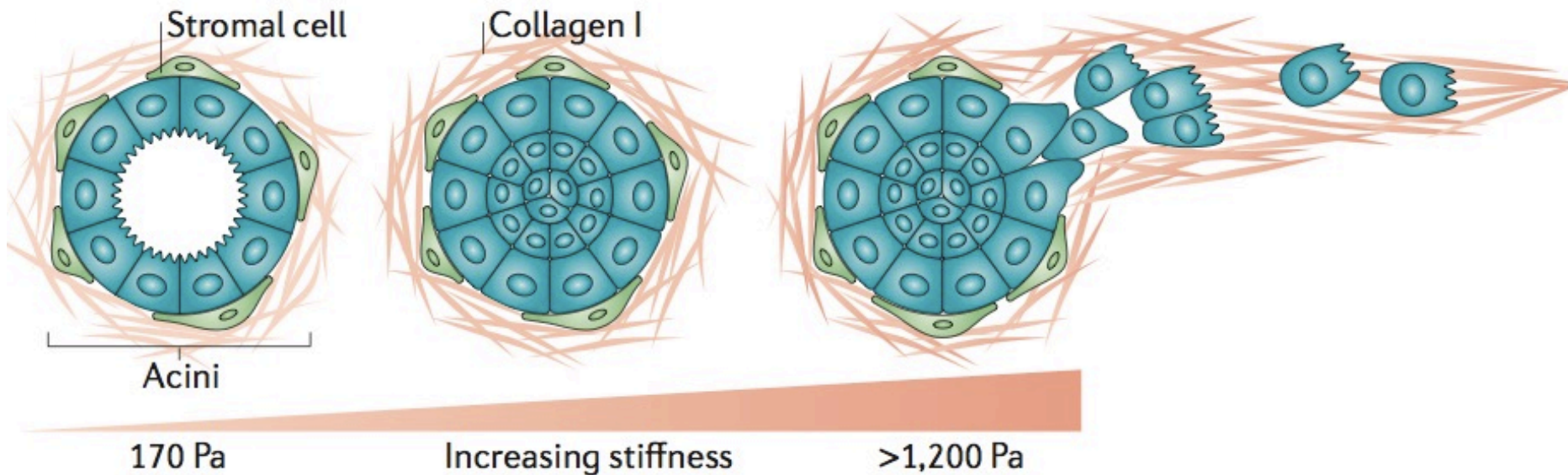
Le lisil-ossidasi LOX nel rimodellamento della ECM



APPROCCI TERAPEUTICI: LOX inhibitors

- The lysyl oxidase (LOX) family of proteins are secreted amine oxidases, the primary function of which is the covalent crosslinking of collagens and elastin in the extracellular matrix. The function of these enzymes is required for the structural integrity of many tissues.
- Preclinical studies involving the targeting of LOX or LOXL2 by small irreversible competitive inhibitors, as well as specific function-blocking antibodies to prevent metastasis, have been efficacious. So far, no detrimental side effects or tumour progression (owing to the proposed tumour suppressive roles of these proteins) have been noted with the use of specific antibody inhibitors.
- Targeting the LOX family is an exciting prospect in the development of new drugs to prevent the progression and metastasis of cancer.

Alterazioni delle proprietà meccaniche e dell'architettura della ECM regolano il comportamento cellulare

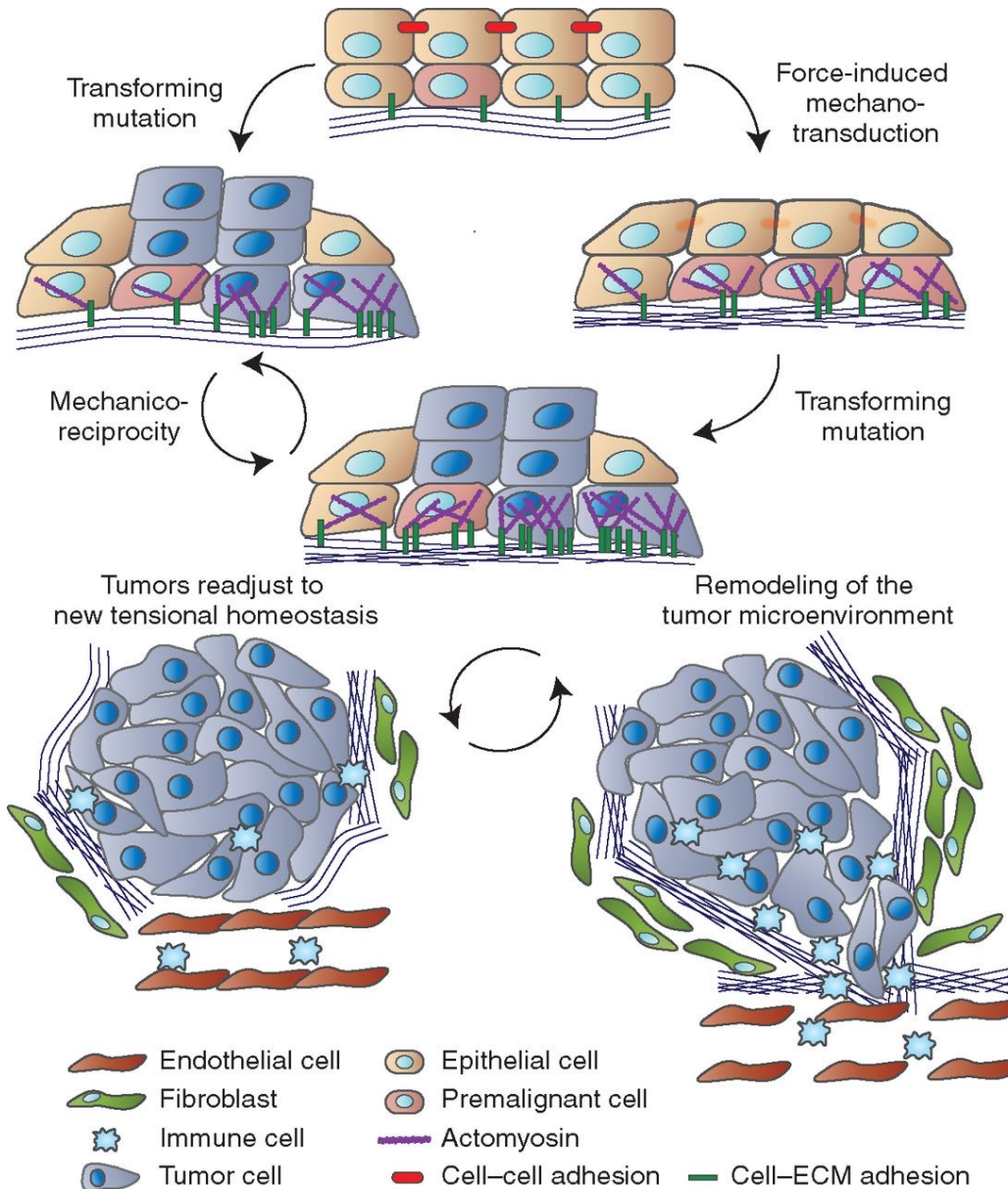


Soft ECM

Stiff ECM

Inibizione dell'apoptosi = mancata
formazione del lume
Destabilizzazione delle giunzioni aderenti
Perdita di polarità e adesione = ECM
Migrazione e invasione

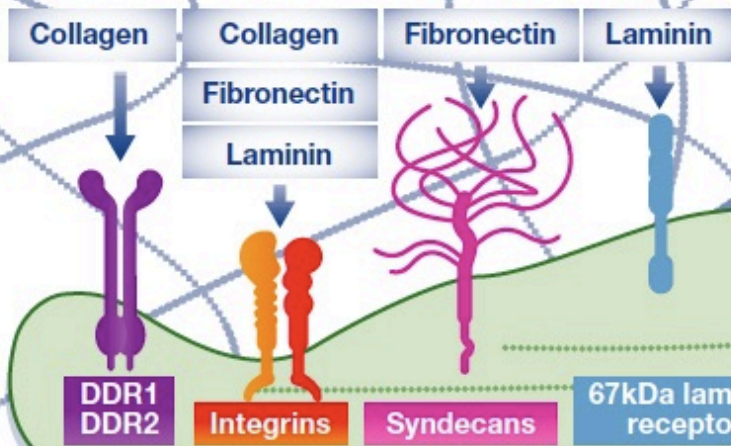
Desmoplasia ed evoluzione tumorale



Jason J. Northey et al.
 Cancer Discov
 2017;7:1224-1237

La ECM supporta il signaling di proliferazione e sopravvivenza

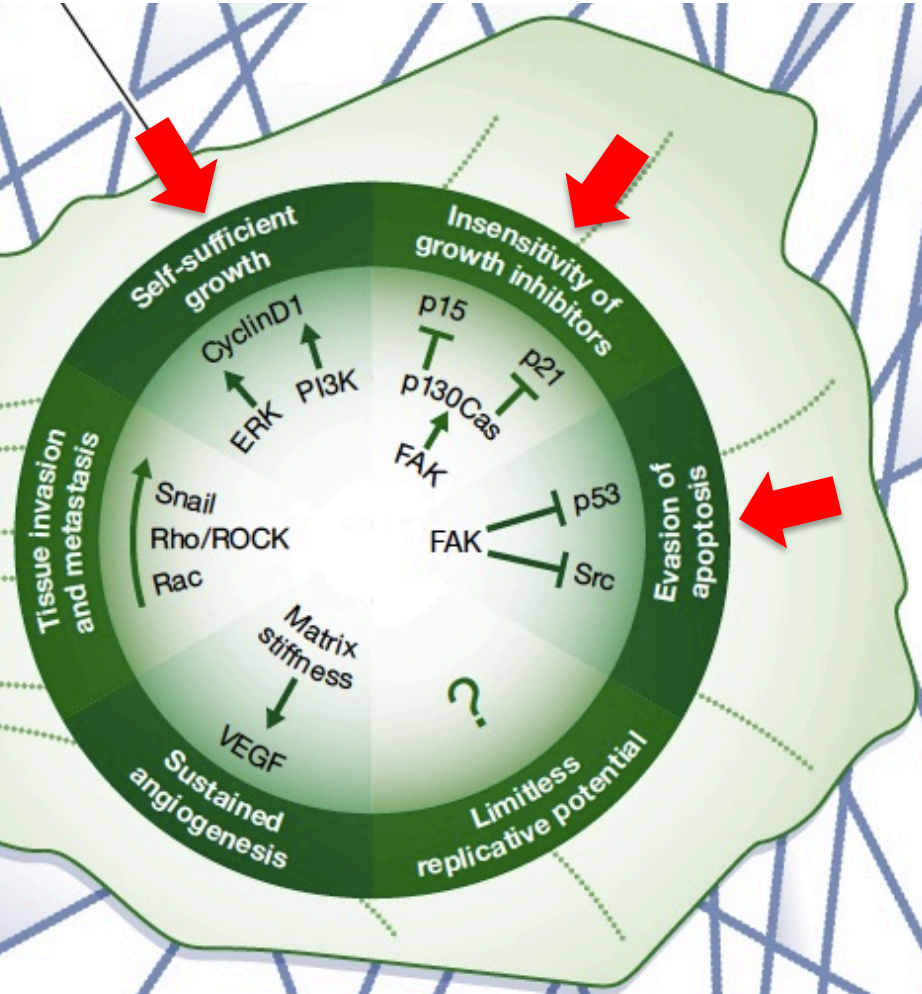
Ligandi per recettori di membrana



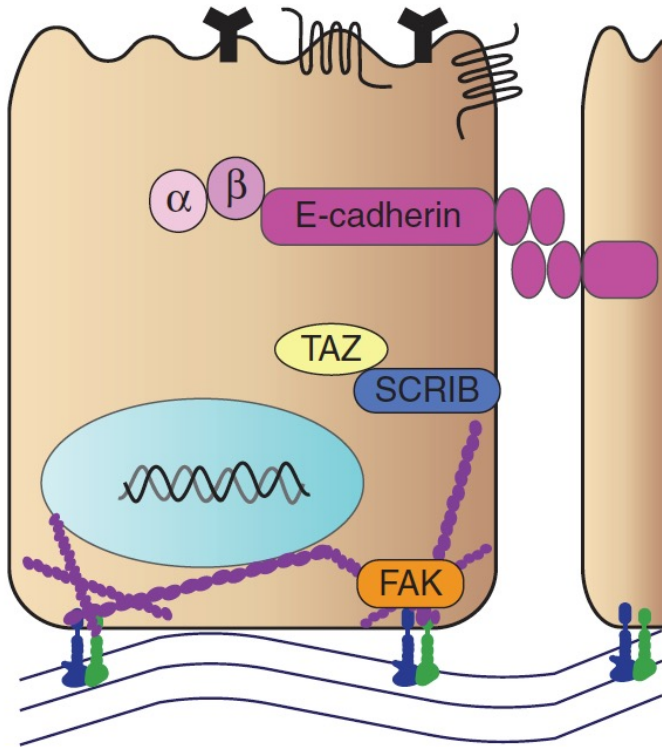
INDUCED INTRACELLULAR SIGNALING

pH
struttura
idratazione

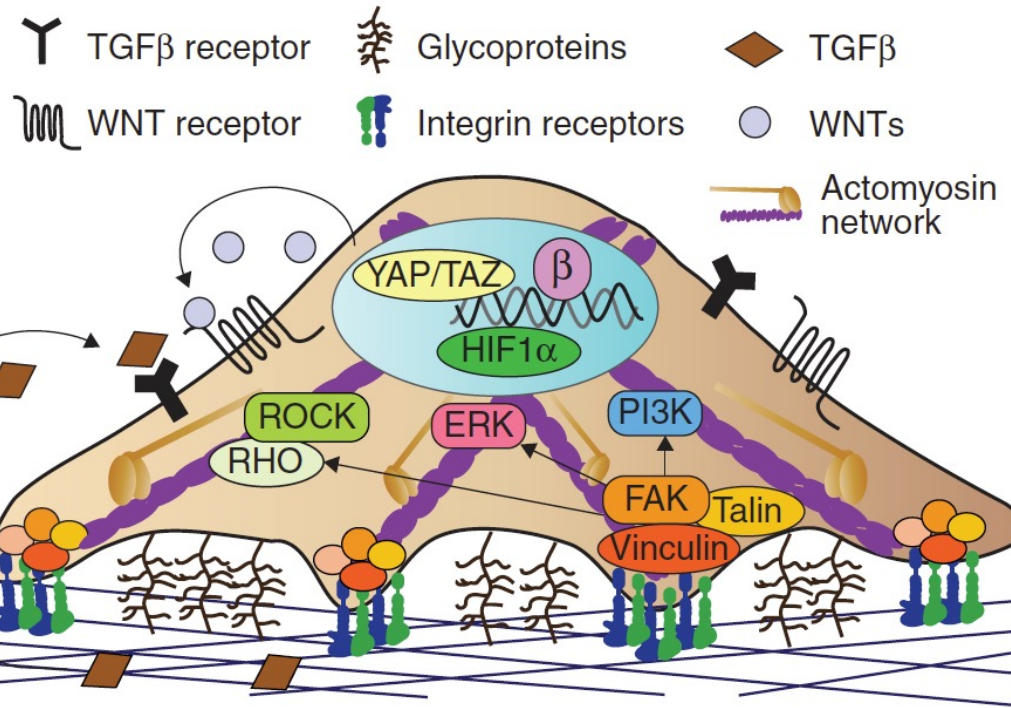
citochine
fattori di crescita
stimoli meccanici



Il signalling delle integrine attiva pathways di proliferazione e sopravvivenza



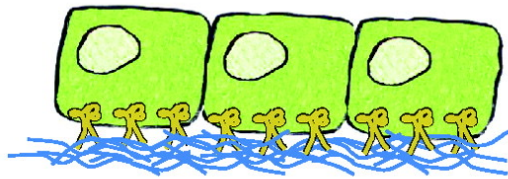
Low tension



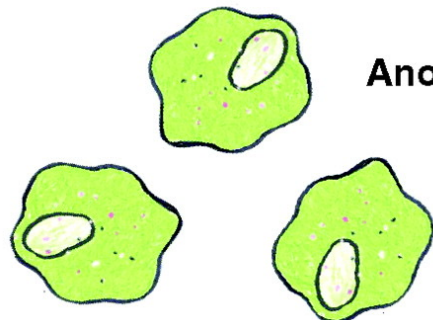
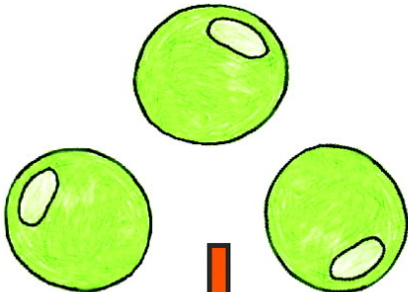
High tension

- Y TGFβ receptor
- WNT receptor
- Glycoproteins
- Integrin receptors
- TGFβ
- WNTs
- Actomyosin network

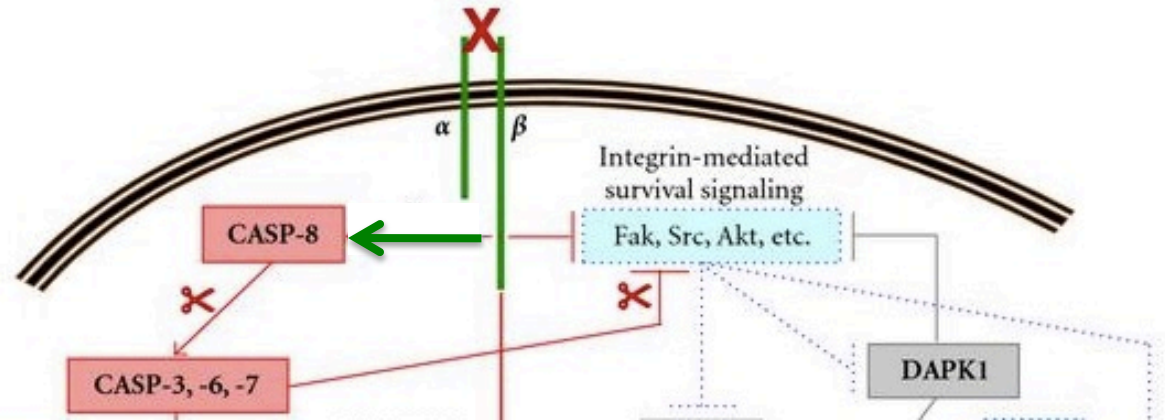
Sopravvivenza: il signaling delle integrine inibisce l'anoikis.



Loss of
integrin
attachment

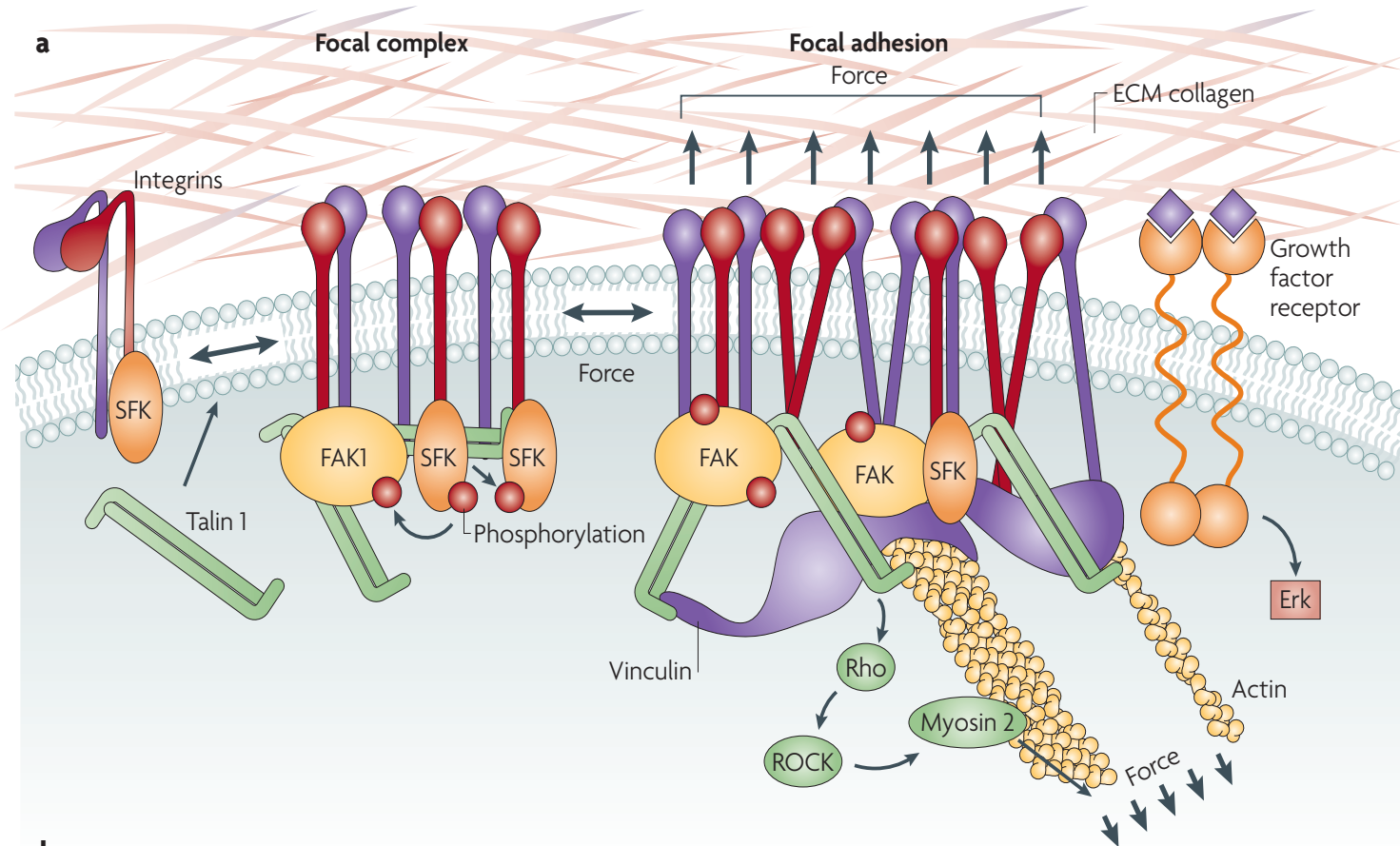


Anoikis



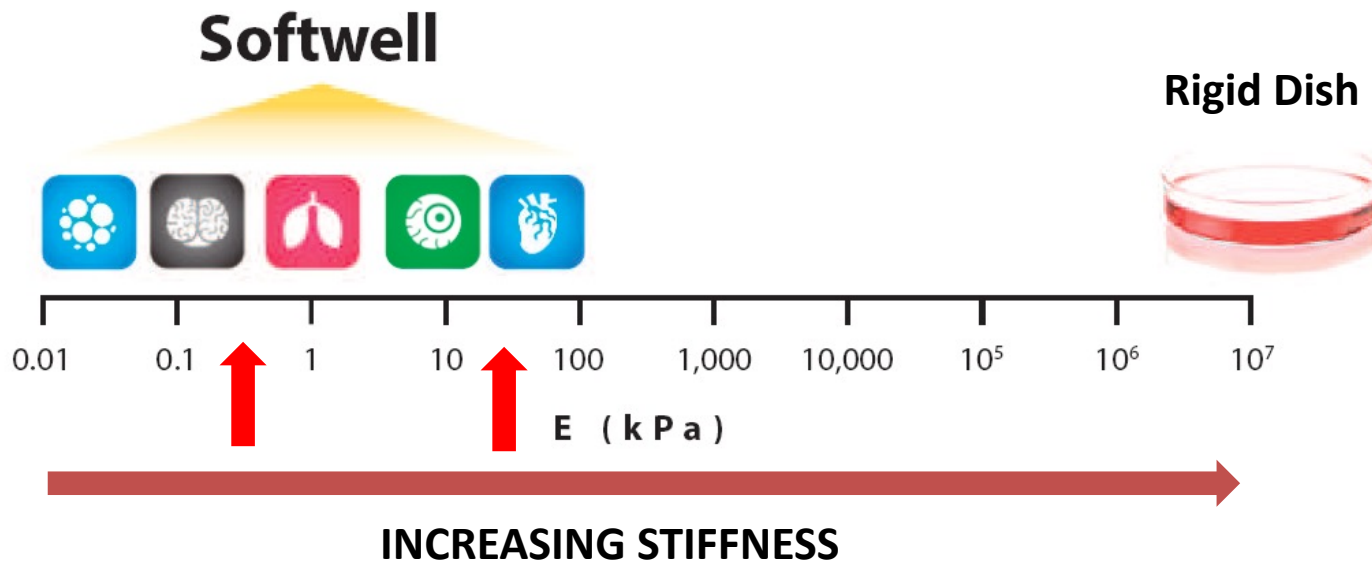
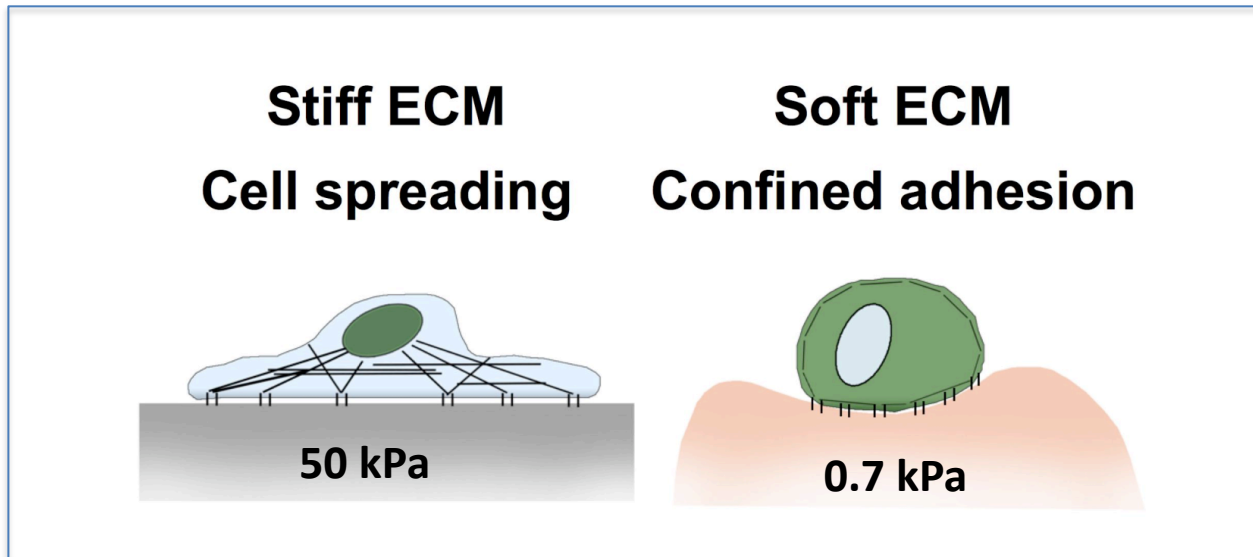
Se prive del loro ligando le integrine reclutano e attivano la caspasi 8 alla membrana, oltre a non attivare FAK-PI3K

RhoA agisce da meccanotrasduttore di stimoli dalla ECM attraverso il controllo della tensione del citoscheletro actomiosinico

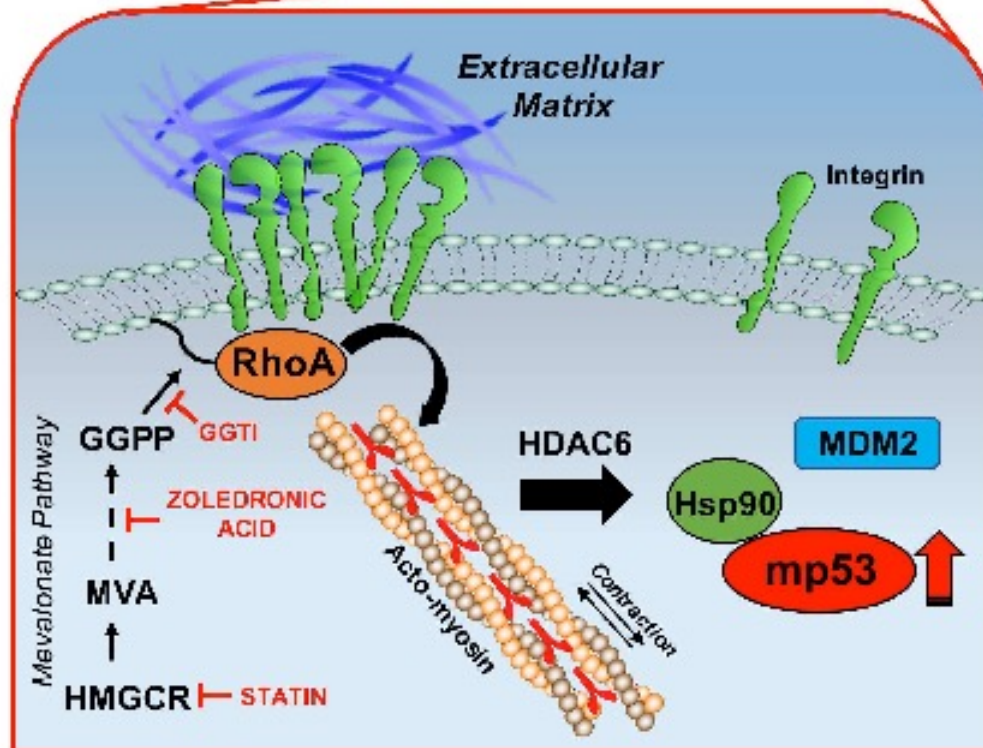
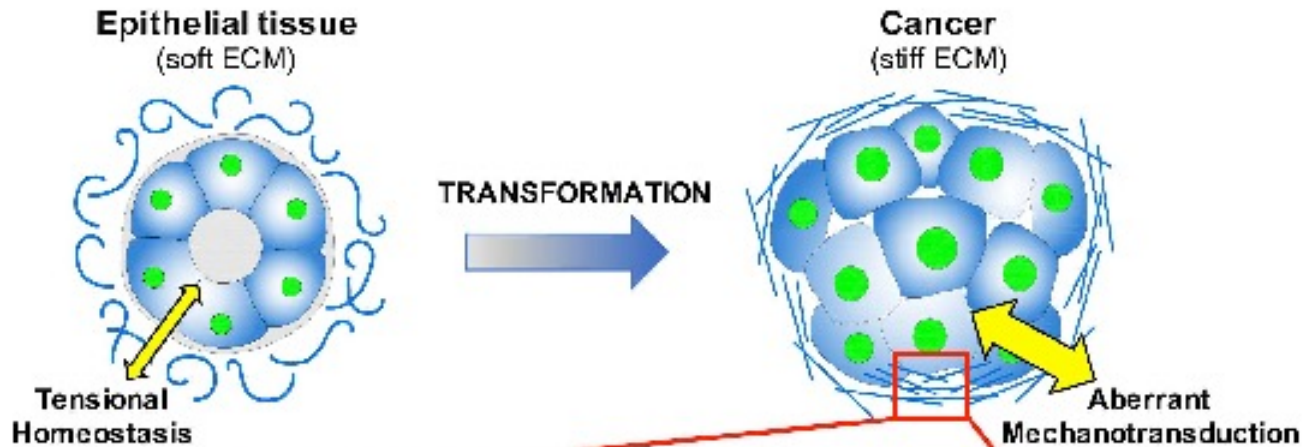


Impatto su: sopravvivenza, proliferazione e progressione tumorale

Meccanotrasduzione: risposte cellulari alla rigidità della ECM

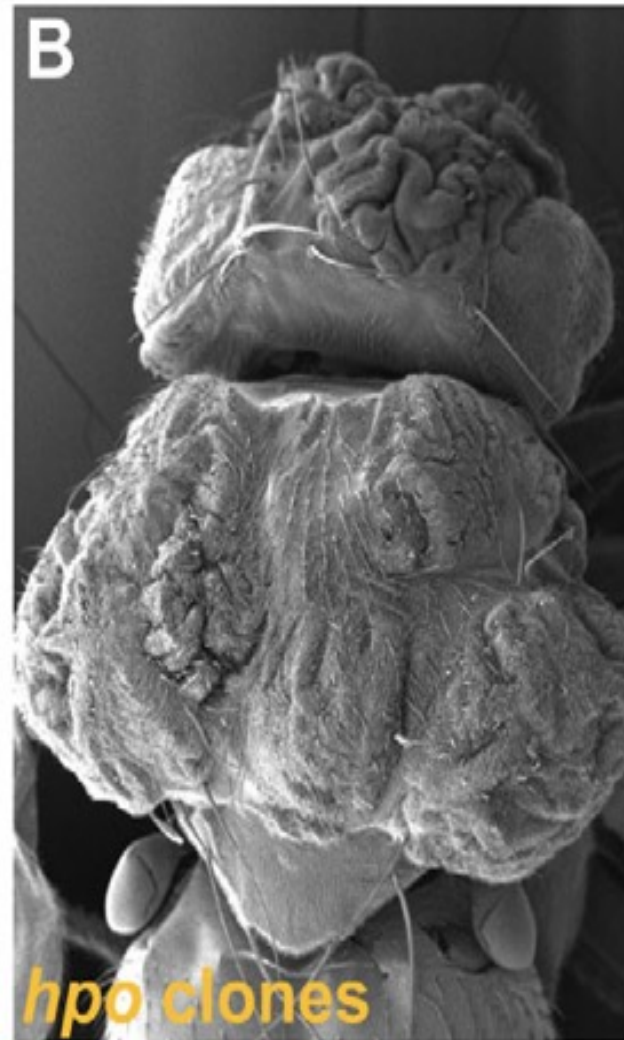


La meccano-trasduzione induce la stabilizzazione di mutp53

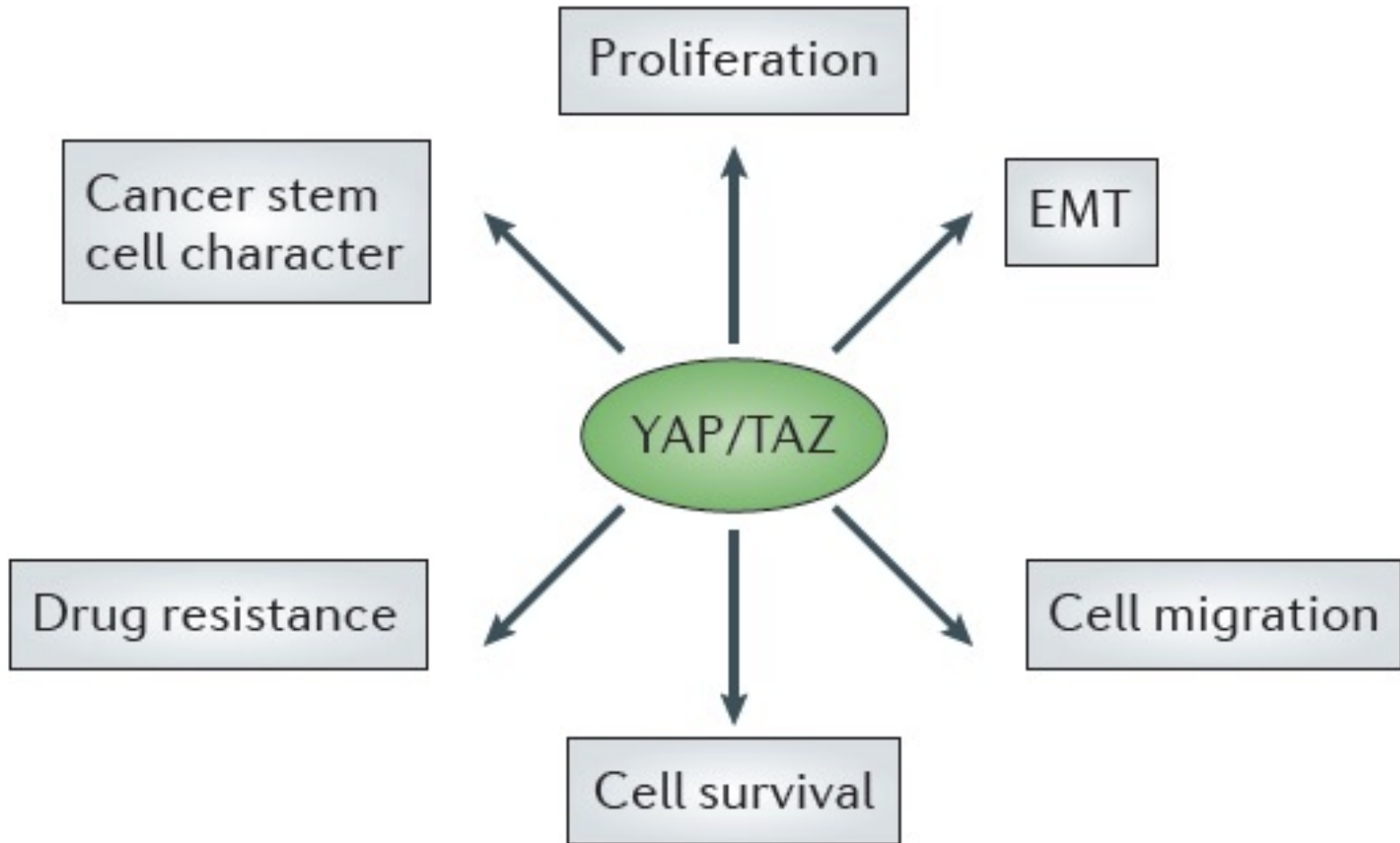


**La ECM stimola la proliferazione e la staminalità attraverso
l'attivazione degli oncogeni YAP/TAZ**

**YAP/TAZ sono effettori della HIPPO pathway,
coinvolta nella regolazione dell'omeostasi tissutale**

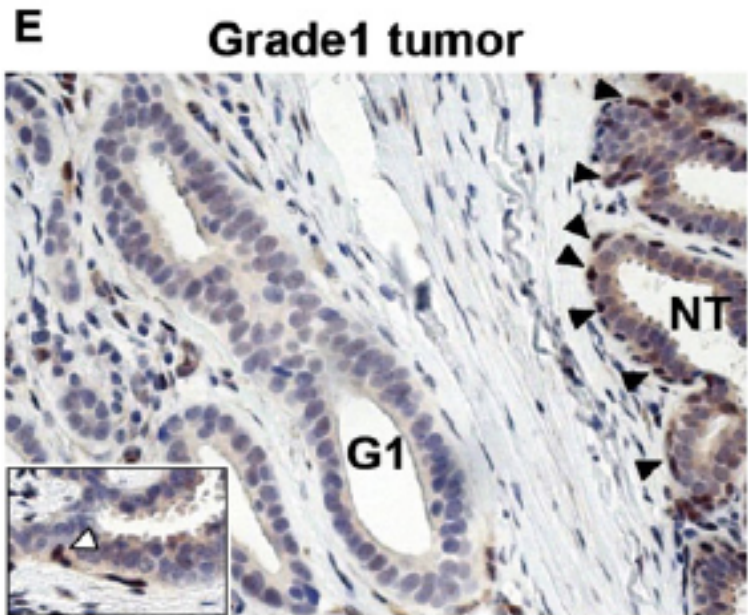


Roles of YAP/TAZ in cancer

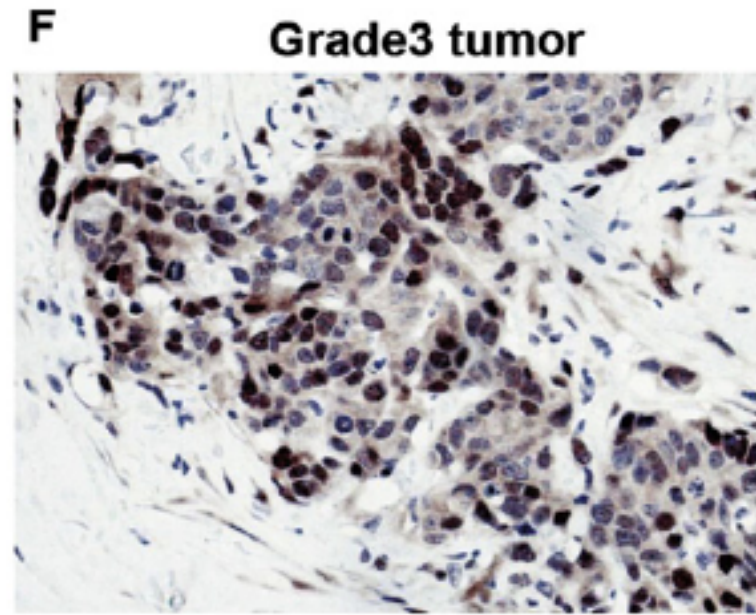


The Hippo Transducer TAZ Confers Cancer Stem Cell-Related Traits on Breast Cancer Cells

Michelangelo Cordenosi,^{1,*} Francesca Zanconato,¹ Luca Azzolin,¹ Mattia Forcato,² Antonio Rosato,³ Chiara Frasson,⁴ Masafumi Inui,¹ Marco Montagner,¹ Anna R. Parenti,⁵ Alessandro Poletti,⁶ Maria Grazia Daidone,⁷ Sirio Dupont,¹ Giuseppe Basso,⁴ Silvio Biccato,² and Stefano Piccolo^{1,*}



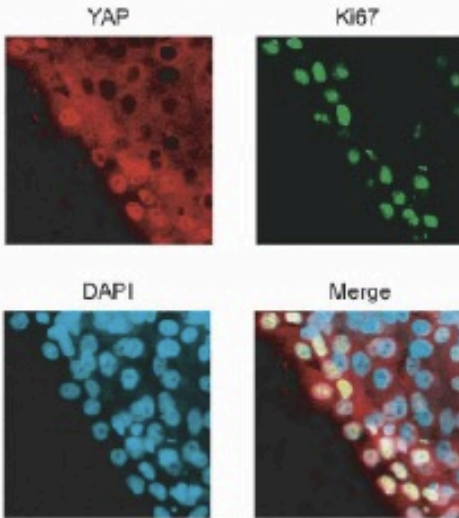
TAZ



TAZ

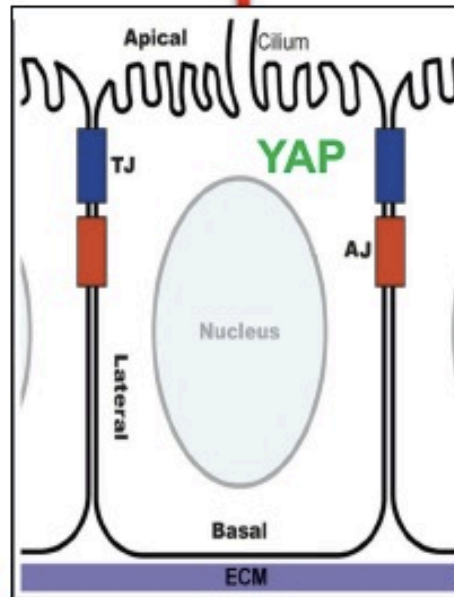
YAP/TAZ sono sensori delle caratteristiche fisiche della cellula: forma, polarità, adesione e forze meccaniche (architettura tissutale)

Contact Inhibition

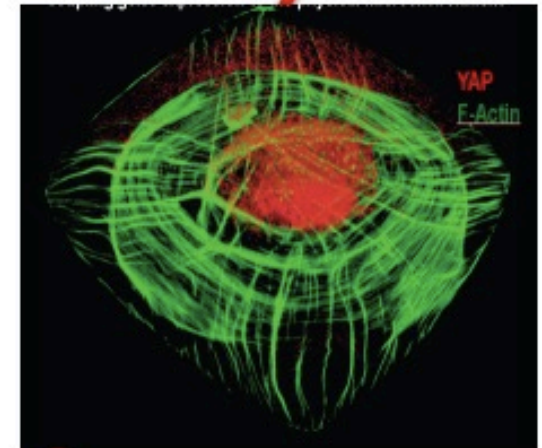


Zhao et al. Gene and Development 2007

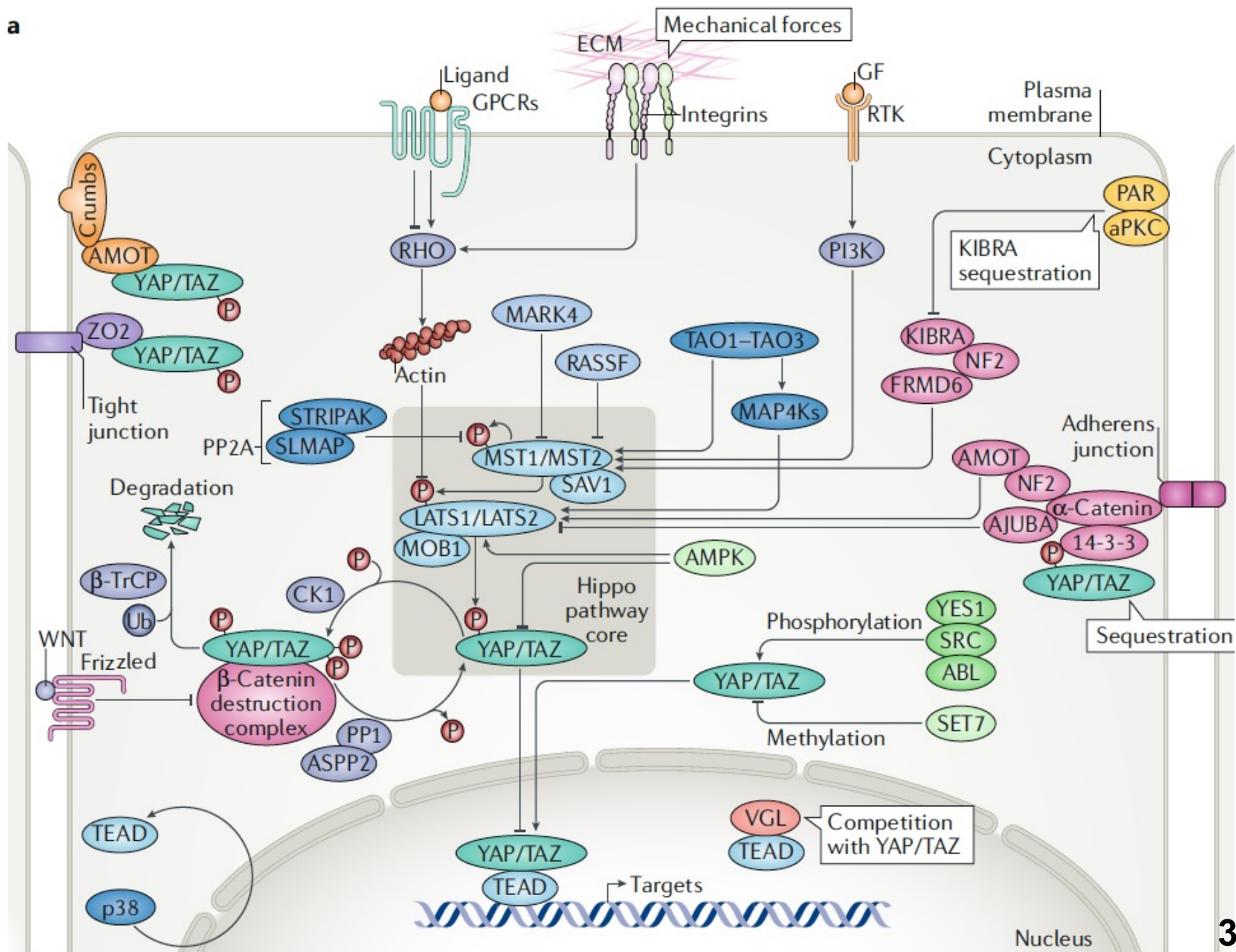
Cell Polarity

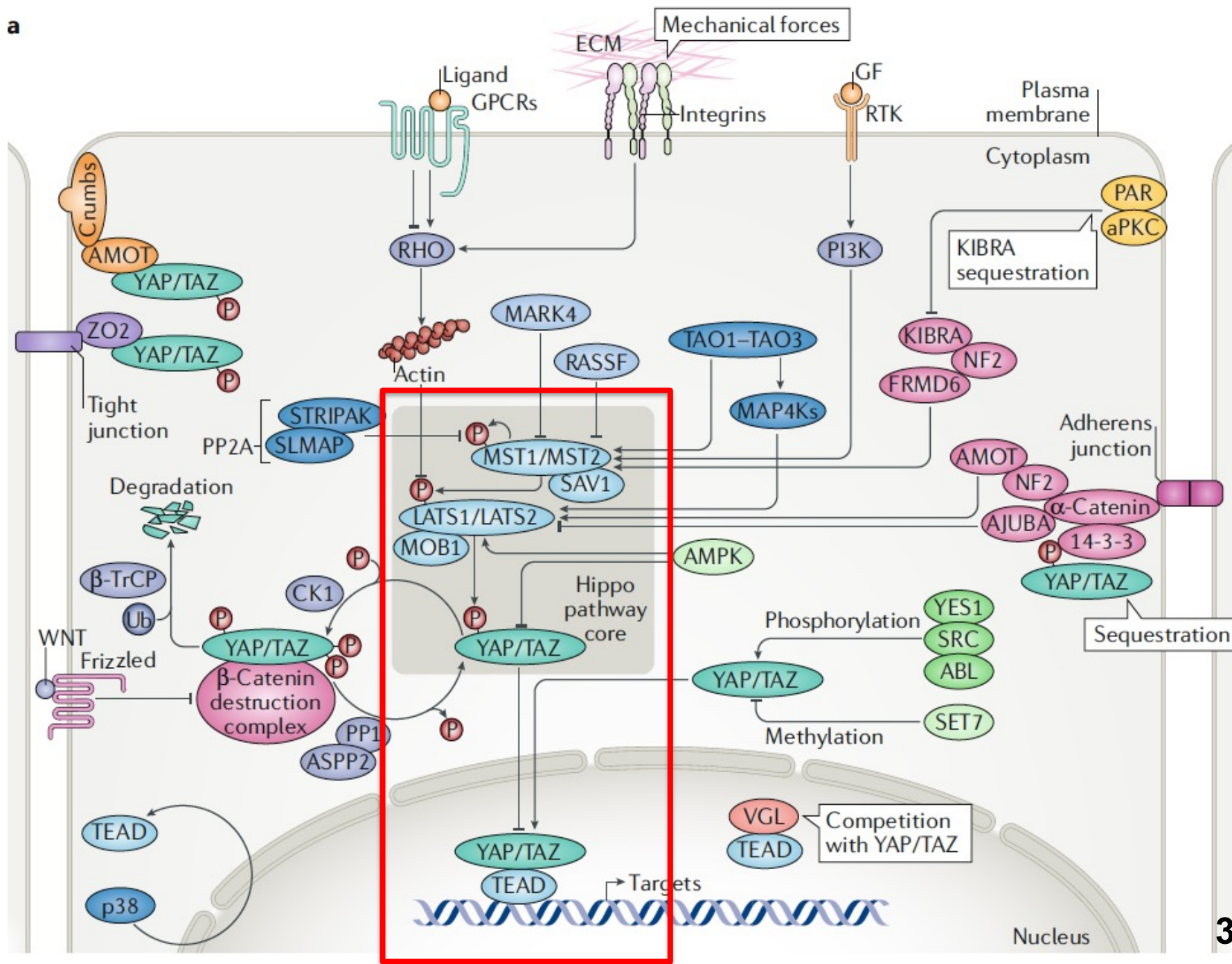


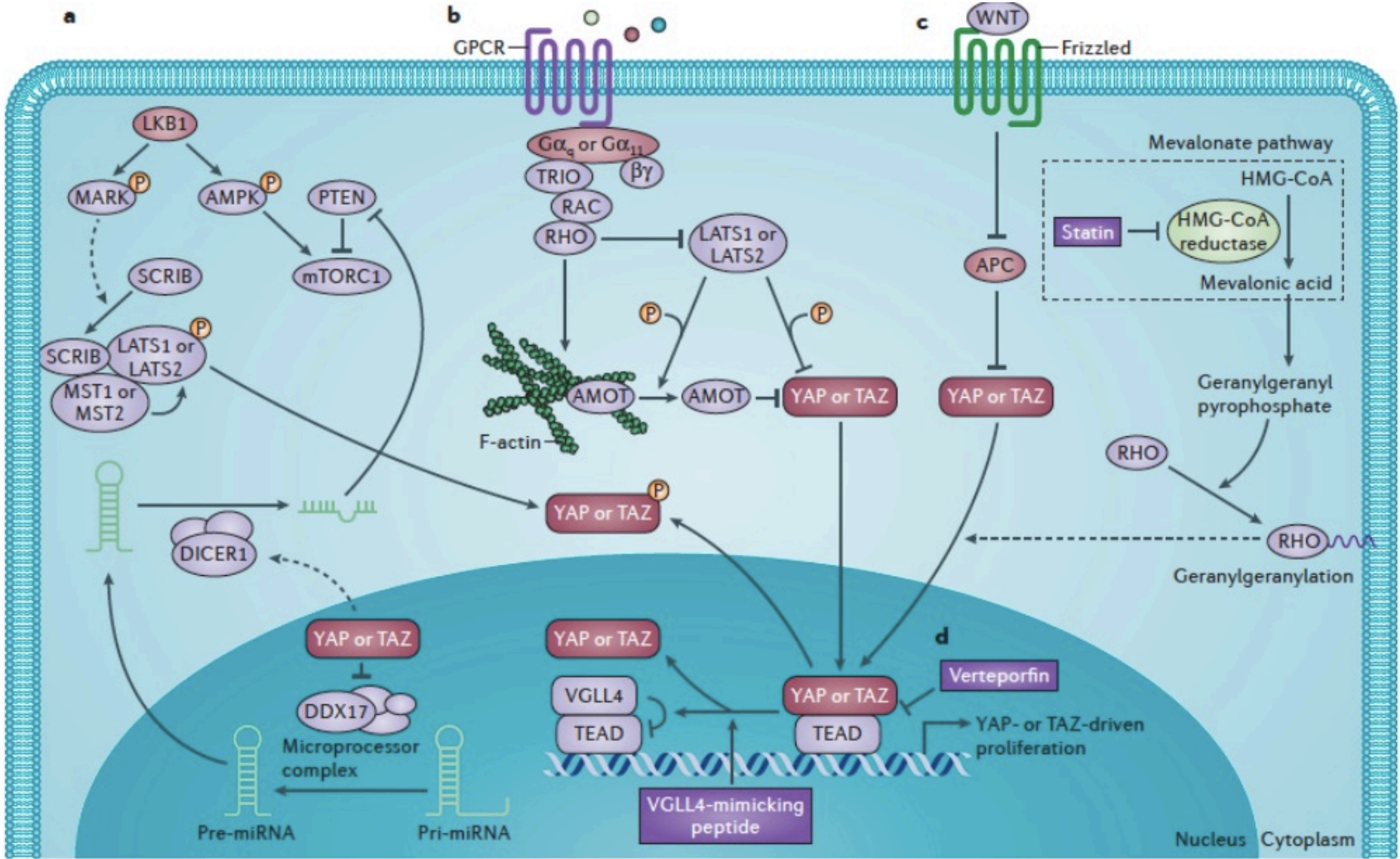
Mechanical Signals

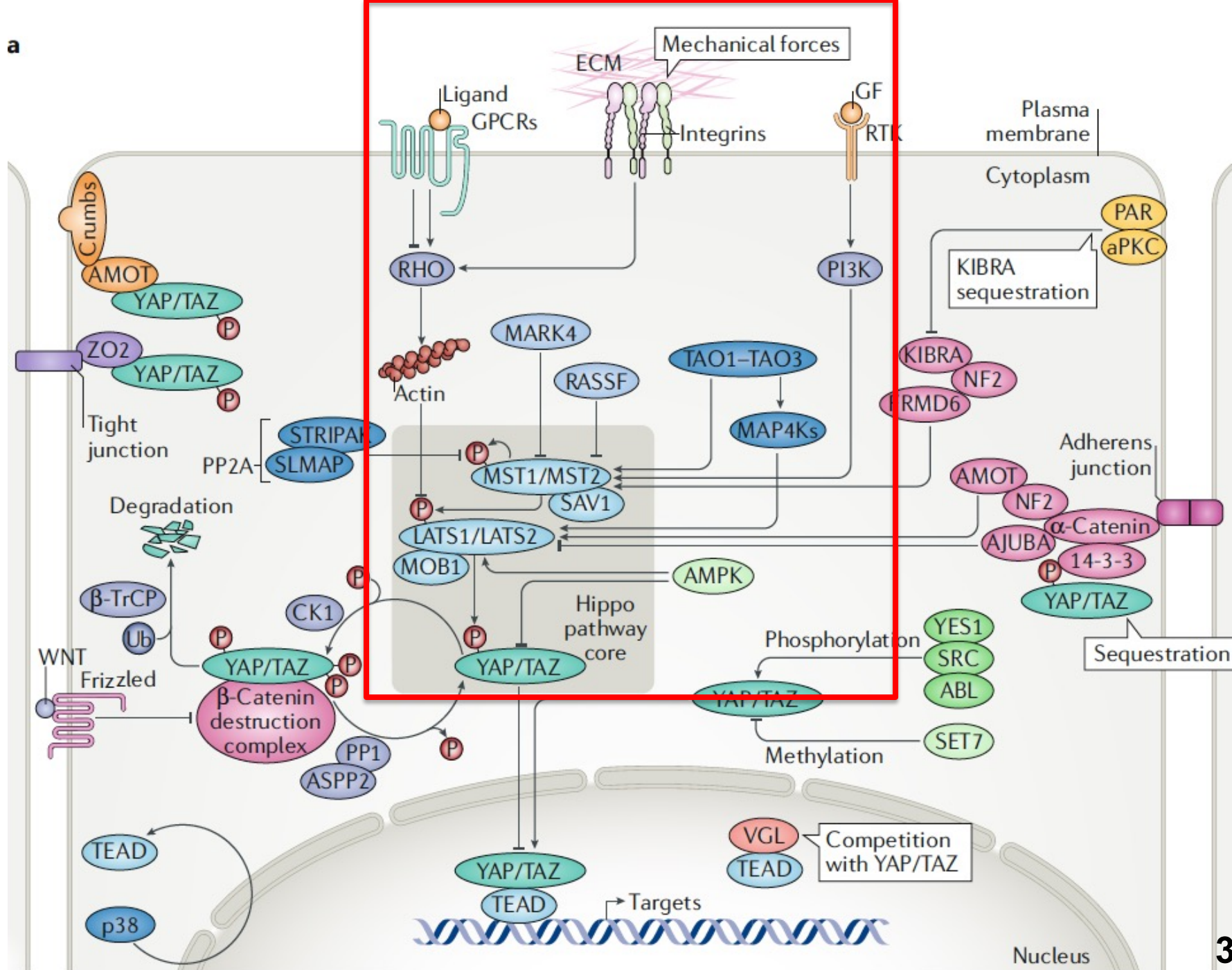


YAP/TAZ

a

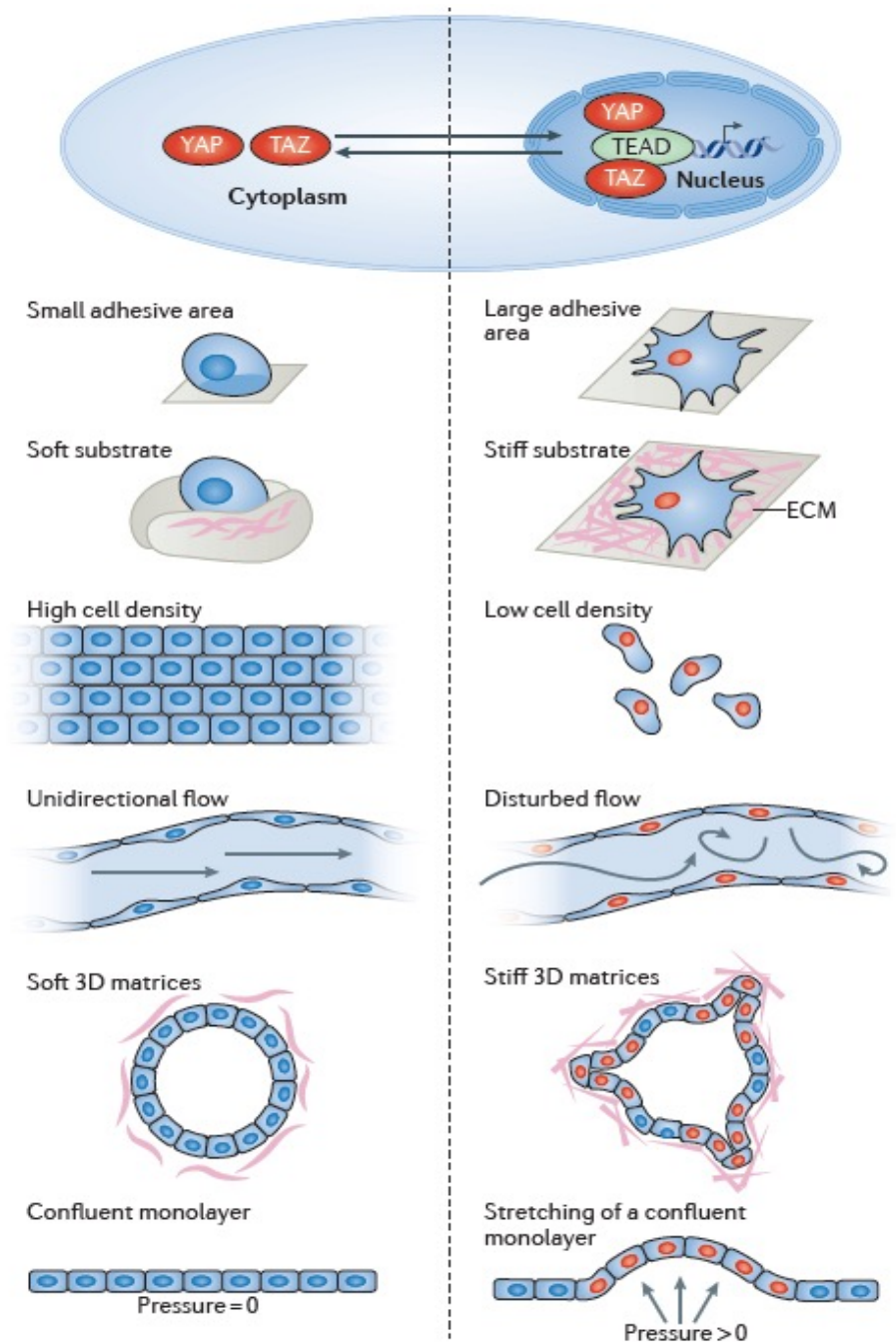
a



a

Mechanical stimuli coming from the extracellular matrix = **mechanical stresses**, include **stretching, change in pressure or fluid flux rate, variation of the available adhesive area, modification of ECM stiffness.**

These physical characteristics **impact on the organization and structure of the actin cytoskeleton.**



La rigidità della ECM ingaggia il citoscheletro actinico ad attivare YAP/TAZ

