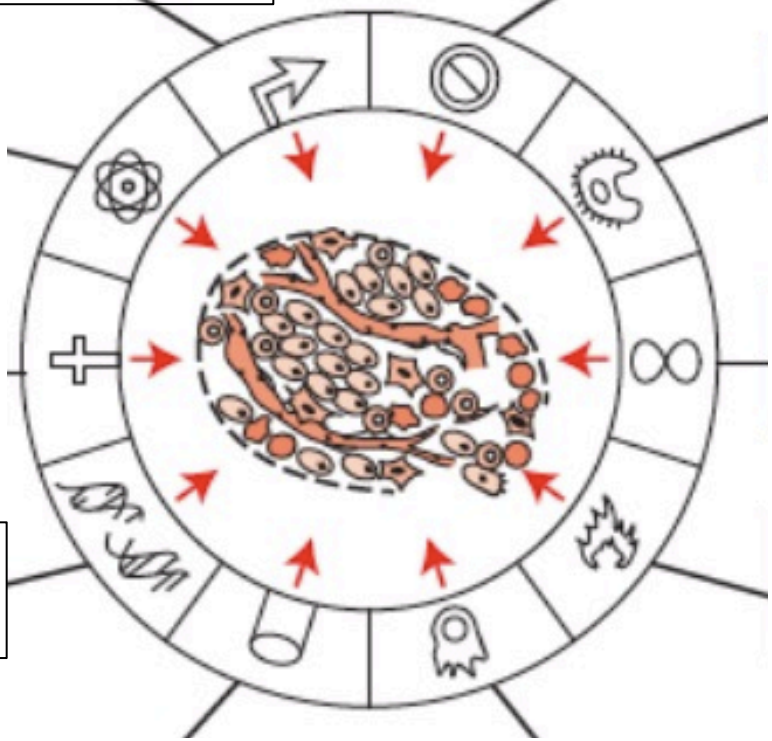
Corso di Biologia Cellulare del Cancro AA 2020-2021

L'INFIAMMAZIONE PRO-TUMORALE

L'infiammazione pro-tumorale è una enabling characteristic



Indipendenza dai segnali proliferativi

Resistenza ai segnali inibitori della proliferazione

Riprogrammazione del metabolismo cellulare

Evasione dal sitema immunitario

Evasione dai meccanismi oncosoppressivi intrinseci

Potenziale replicativo illimitato

Mutazione e instabilità genomica

Infiammazione pro-tumorale

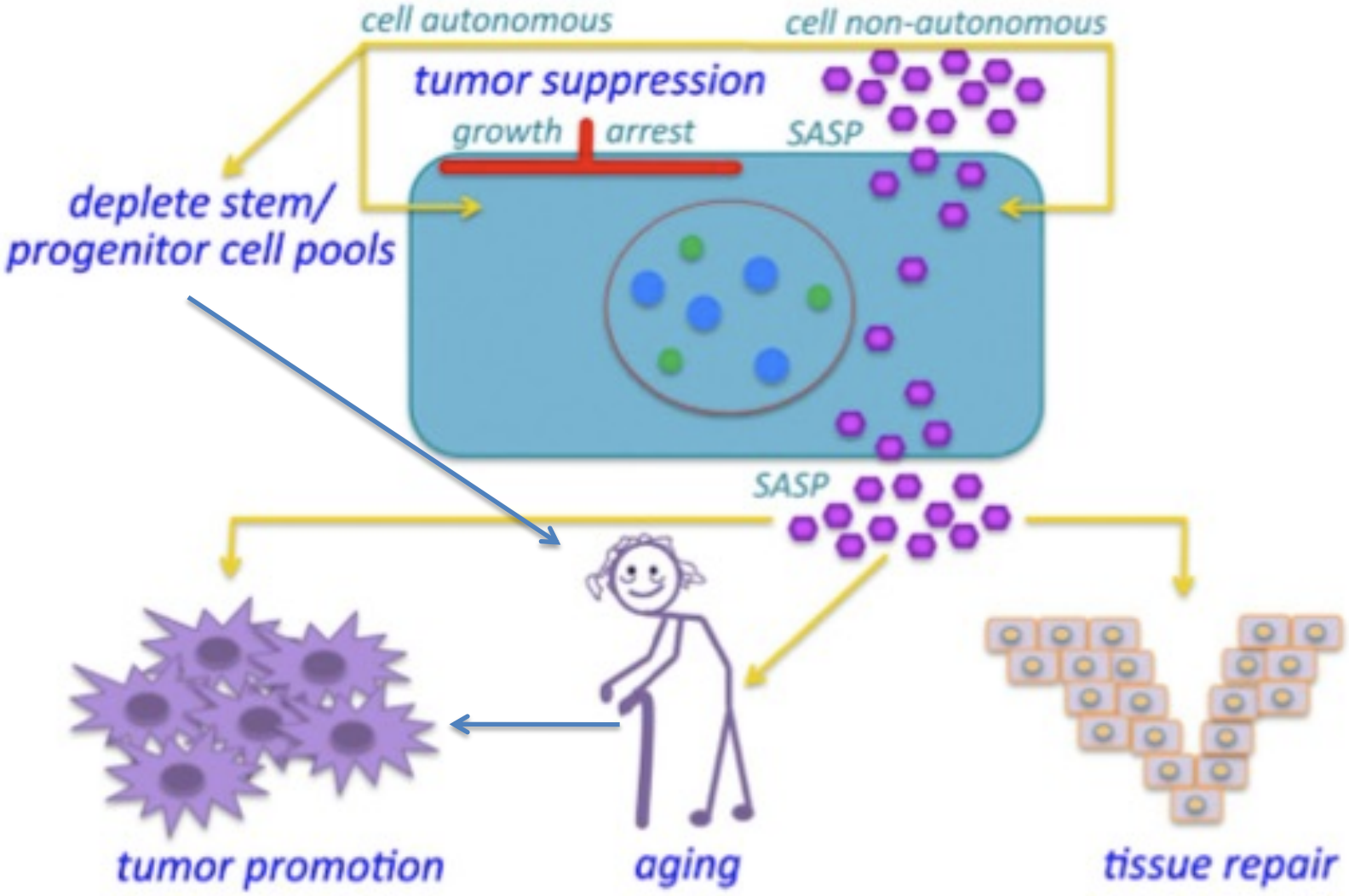
Angiogenesi

Invasione e metastasi

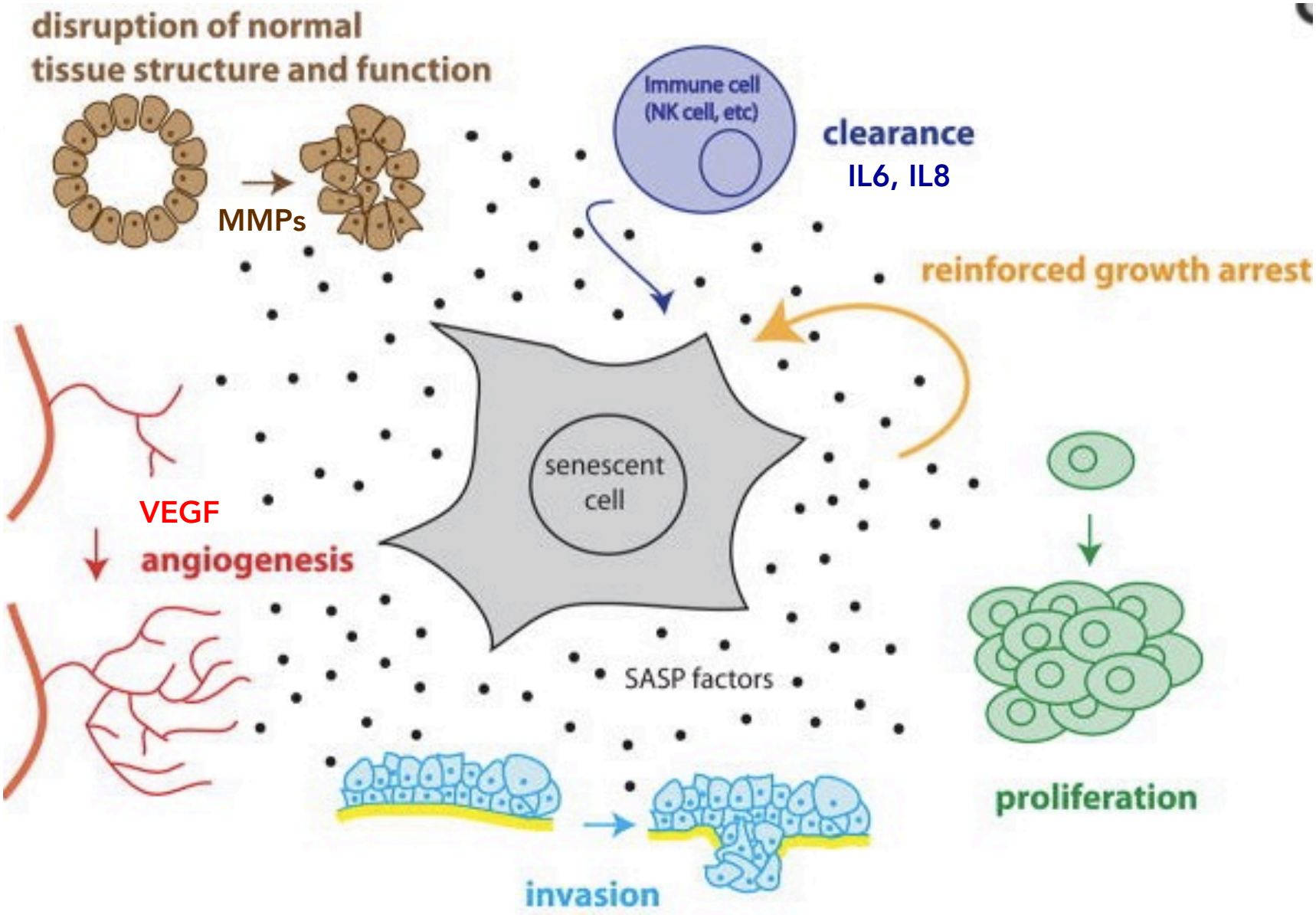
Box 1 | The evidence that links cancer and inflammation

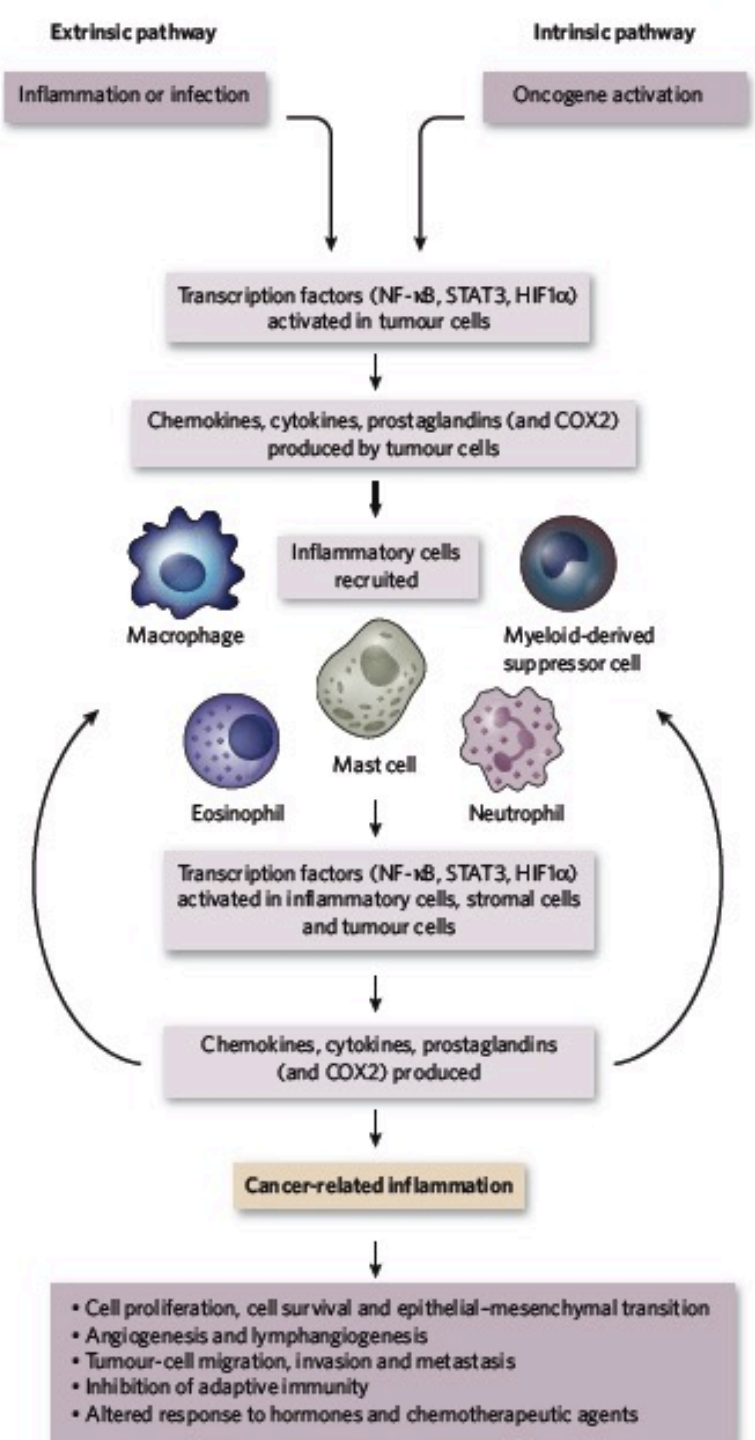
- Inflammatory diseases increase the risk of developing many types of cancer (including bladder, cervical, gastric, intestinal, oesophageal, ovarian, prostate and thyroid cancer).
- Non-steroidal anti-inflammatory drugs reduce the risk of developing certain cancers (such as colon and breast cancer) and reduce the mortality caused by these cancers.
- Signalling pathways involved in inflammation operate downstream of oncogenic mutations (such as mutations in the genes encoding RAS, MYC and RET).
- Inflammatory cells, chemokines and cytokines are present in the microenvironment of all tumours in experimental animal models and humans from the earliest stages of development.
- The targeting of inflammatory mediators (chemokines and cytokines, such as TNF-α and IL-1β), key transcription factors involved in inflammation (such as NF-κB and STAT3) or inflammatory cells decreases the incidence and spread of cancer.
- Adoptive transfer of inflammatory cells or overexpression of inflammatory cytokines promotes the development of tumours.

Un microambiente ricco di cellule senescenti è permissive per la tumorigenesi

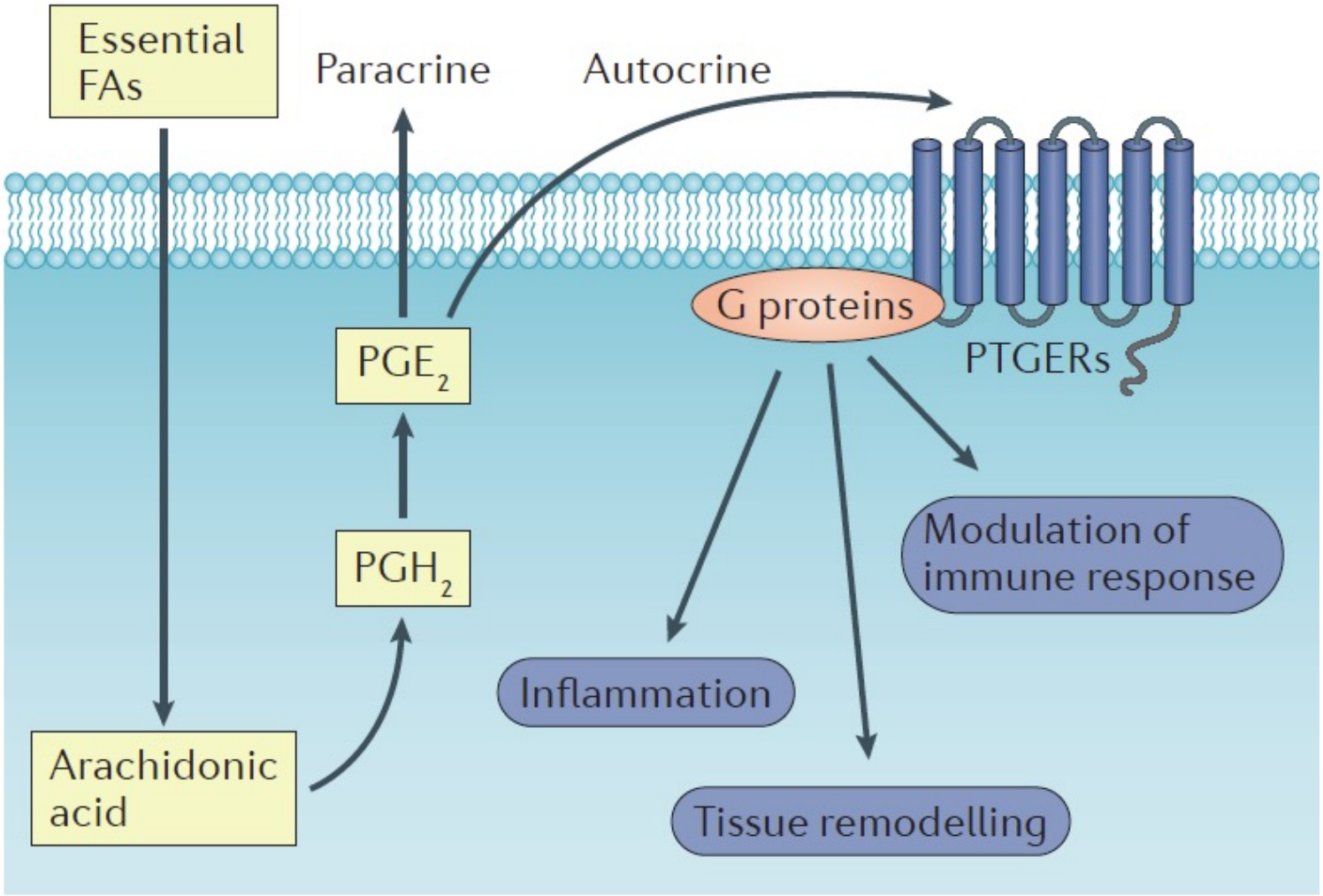


Il fenotipo secretorio delle cellule senescenti

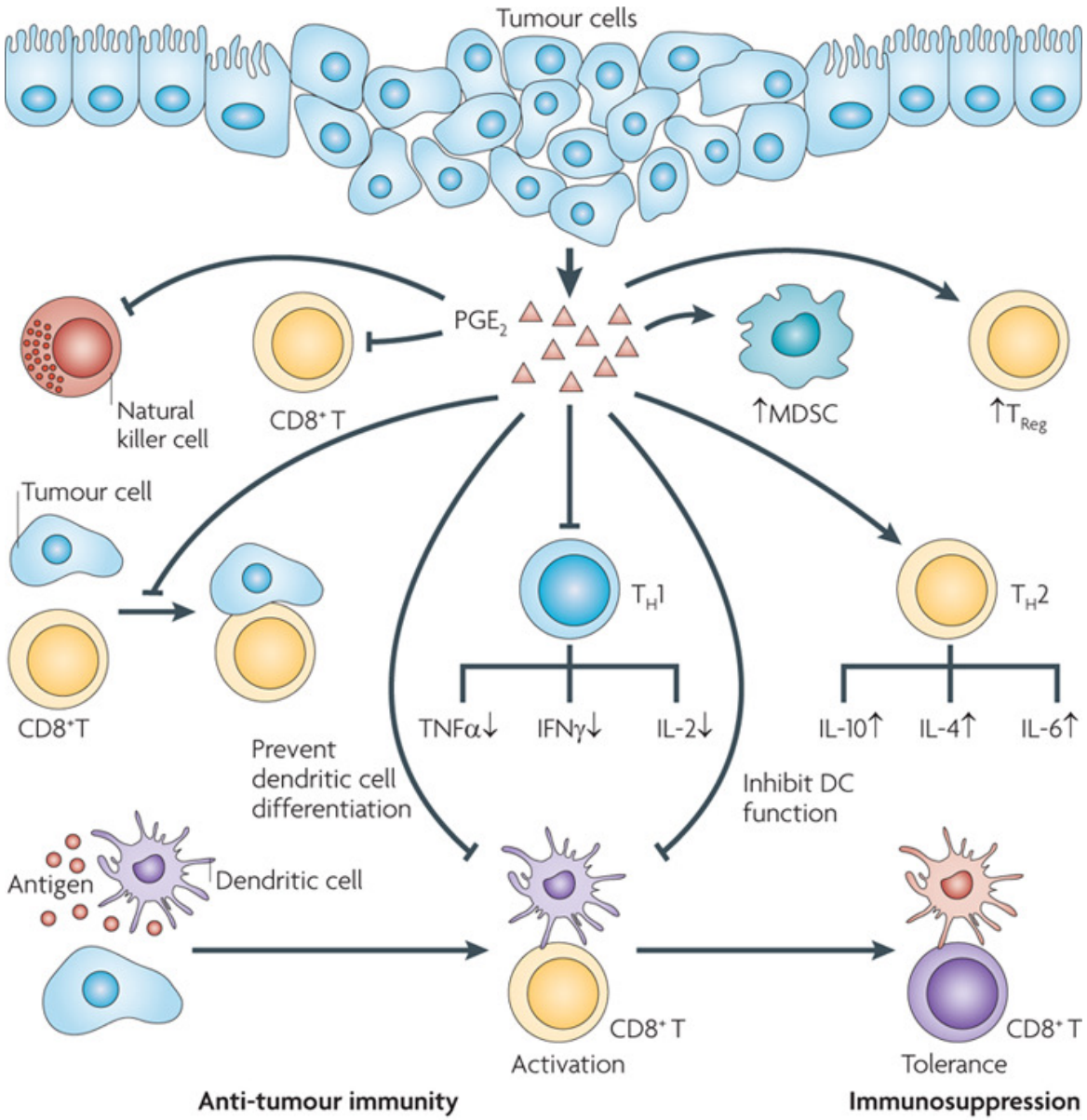



Extrinsic pathway
Intrinsic pathway
Inflammation or infection
Oncogene activation
Transcription factors (NF-κB, STAT3, HIF1α) activated in tumour cells
Chemokines, cytokines, prostaglandins (and COX2) produced by tumour cells
Inflammatory cells recruited
Macrophage
Myeloid-derived suppressor cell
Mast cell
Eosinophil
Neutrophil
Transcription factors (NF-κB, STAT3, HIF1α) activated in inflammatory cells, stromal cells and tumour cells
Chemokines, cytokines, prostaglandins (and COX2) produced
Cancer-related inflammation
• Cell proliferation, cell survival and epithelial–mesenchymal transition
• Angiogenesis and lymphangiogenesis
• Tumour-cell migration, invasion and metastasis
• Inhibition of adaptive immunity
• Altered response to hormones and chemotherapeutic agents

Le prostaglandine sono derivate dal metabolismo dei FA essenziali

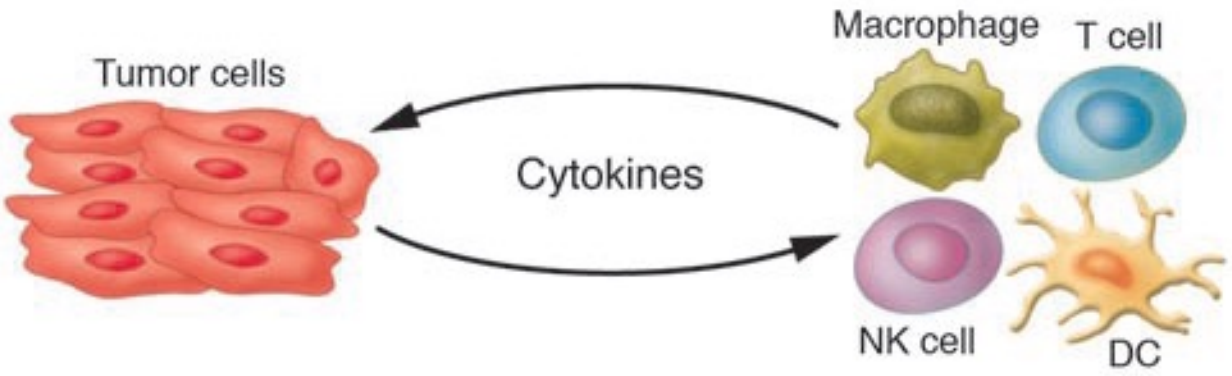


Ruolo pro-infiammatorio e immunosoppressivo della prostaglandina PGE2



Nature Reviews | Cancer

Cellule immuni-infiammatorie infiltranti il tumore



Infiltrato immune

Limita la progressione tumorale

Th1 lymphocytes
M1 macrophages
N1 neutrophils
T cytotoxic lymphocytes
NK cells

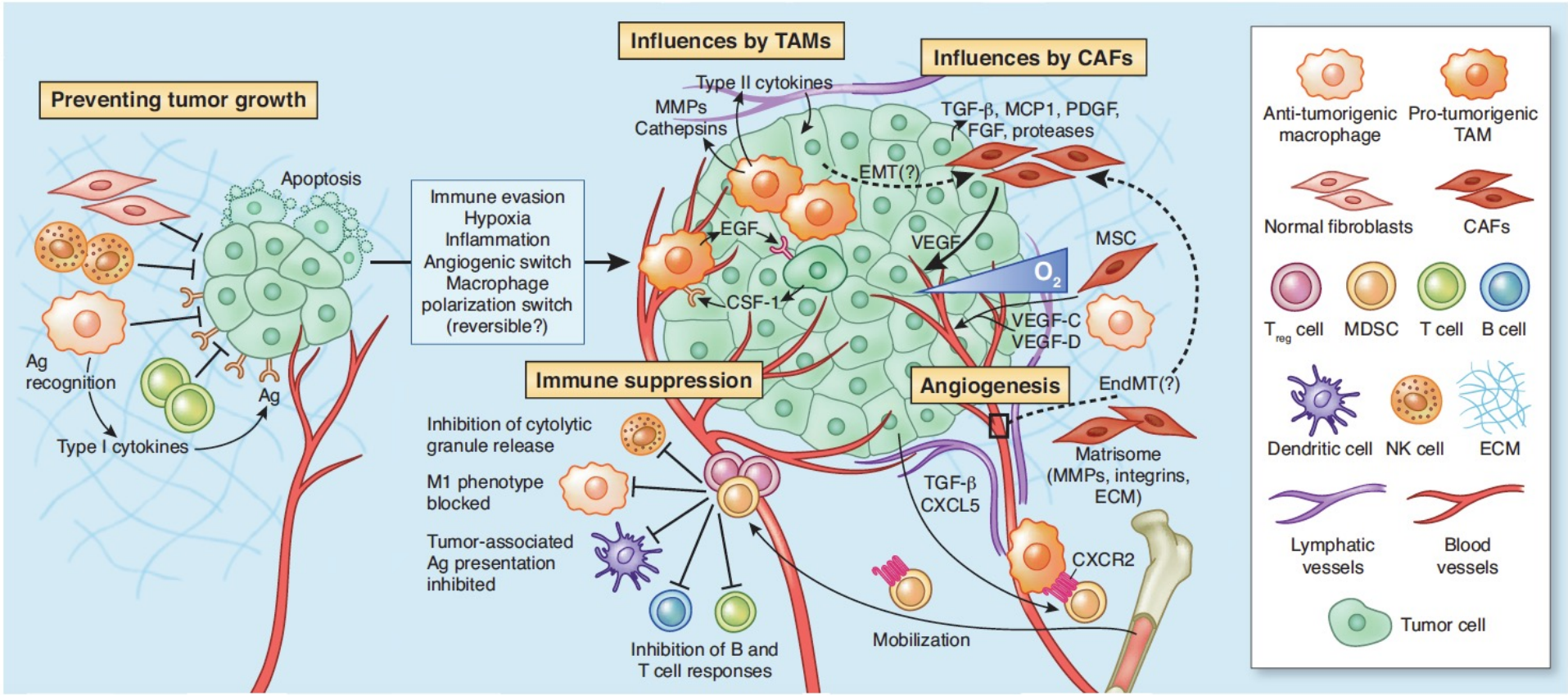
Involved in innate & adaptive immune response to pathogens

Stimola la progressione tumorale

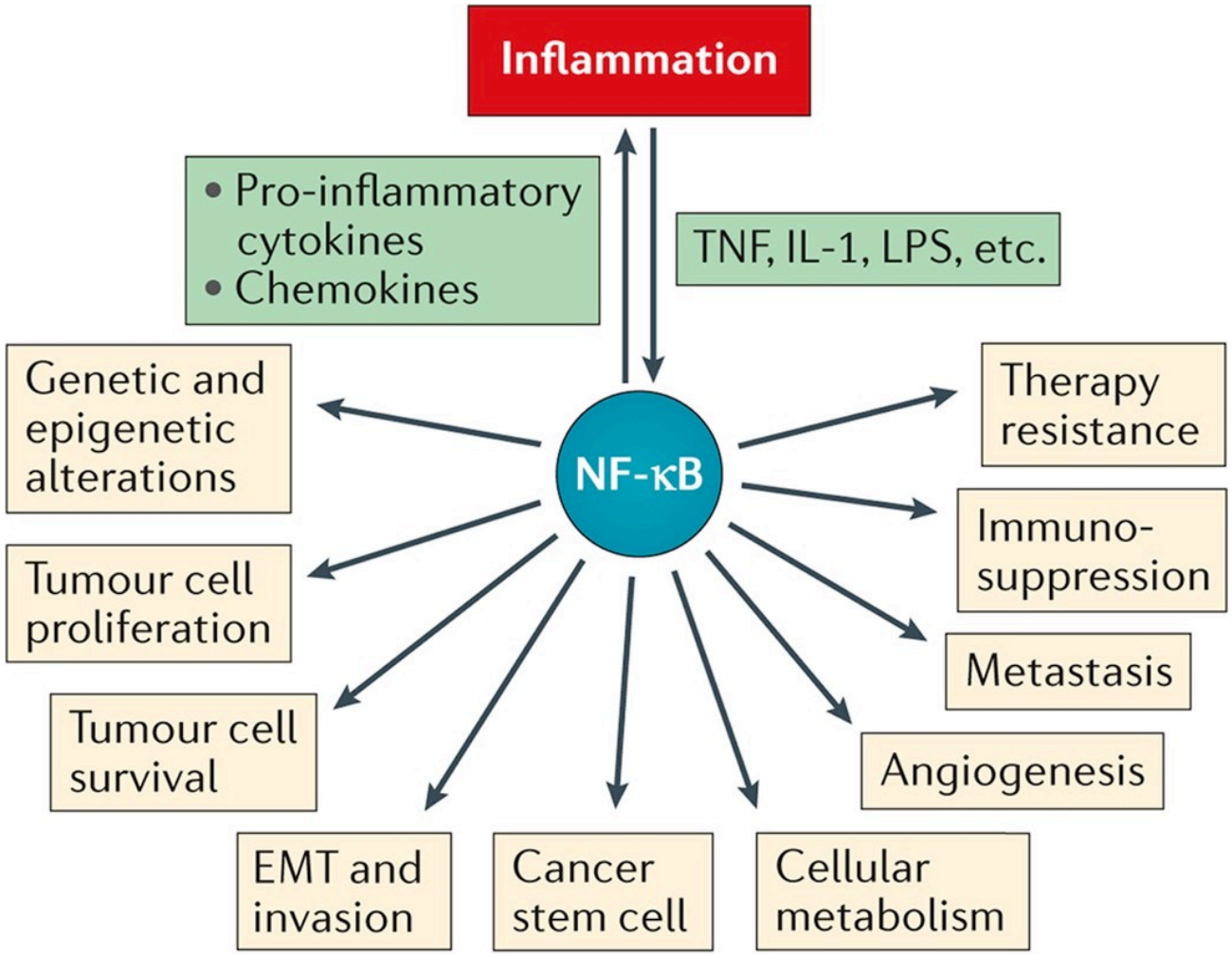
Th2 lymphocytes
M2 macrophages
N2 neutrophils
Myeloid progenitors
Regulatory T cells

Involved in wound healing & tissue housecleaning

Mantovani and Sica, 2012 - Lin and Karin, 2007 - Zou, 2005 - Grivennikov, 2010


Preventing tumor growth
Apoptosis
Ag recognition
Ag
Type I cytokines
Immune evasion
Hypoxia
Inflammation
Angiogenic switch
Macrophage polarization switch (reversible?)
Influences by TAMs
Type II cytokines
MMPs
Cathepsins
EGF
CSF-1
Influences by CAFs
TGF-β, MCP1, PDGF, FGF, proteases
EMT(?)
VEGF
MSC
O2
VEGF-C
VEGF-D
Angiogenesis
EndMT(?)
Matrisome (MMPs, integrins, ECM)
TGF-β
CXCL5
CXCR2
Immune suppression
Inhibition of cytolytic granule release
M1 phenotype blocked
Tumor-associated Ag presentation inhibited
Inhibition of B and T cell responses
Mobilization
Anti-tumorigenic macrophage
Pro-tumorigenic TAM
Normal fibroblasts
CAFs
Treg cell
MDSC
T cell
B cell
Dendritic cell
NK cell
ECM
Lymphatic vessels
Blood vessels
Tumor cell

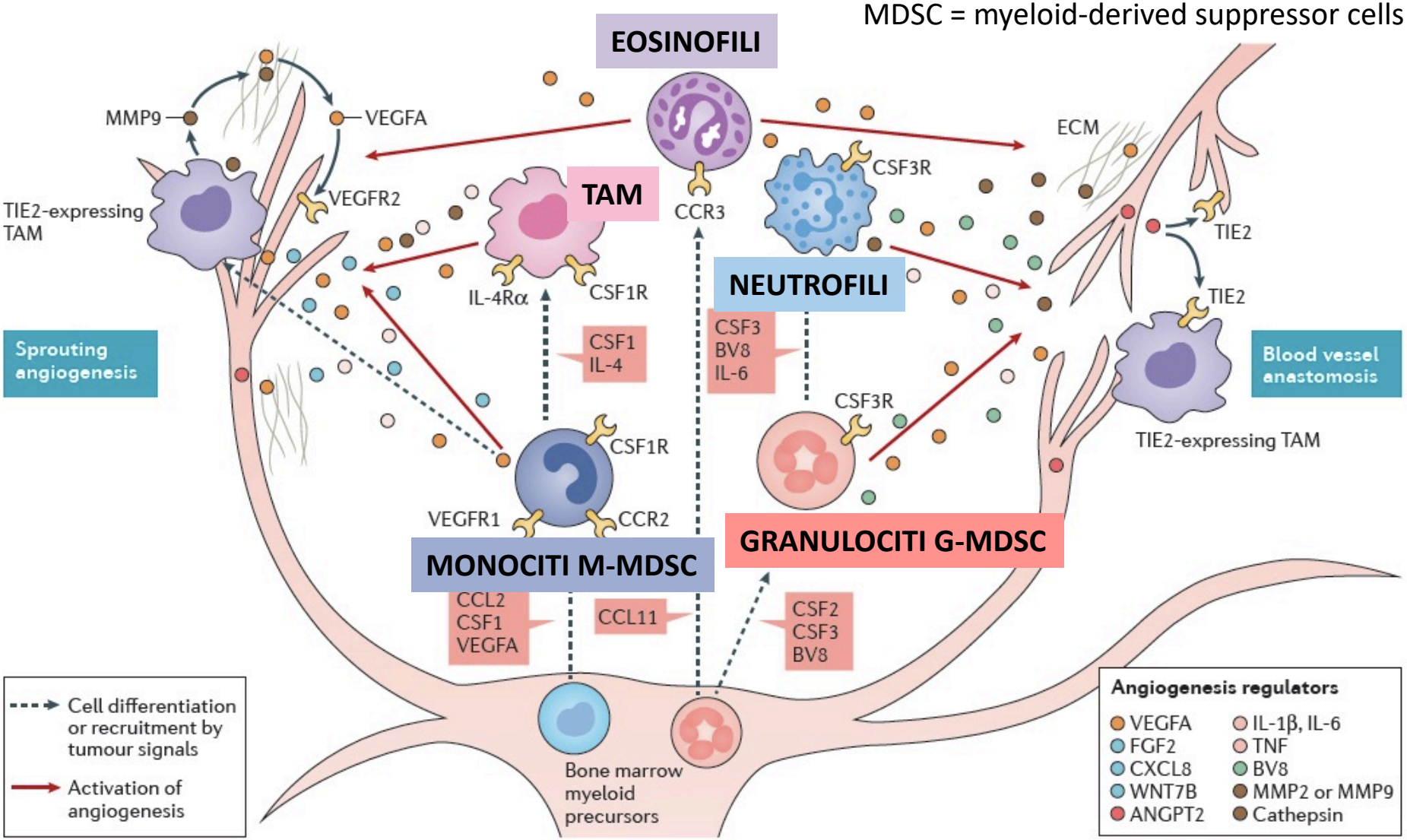
Citochine prodotte da cellule del SI inducono NF-κB pathway in cellule tumorali



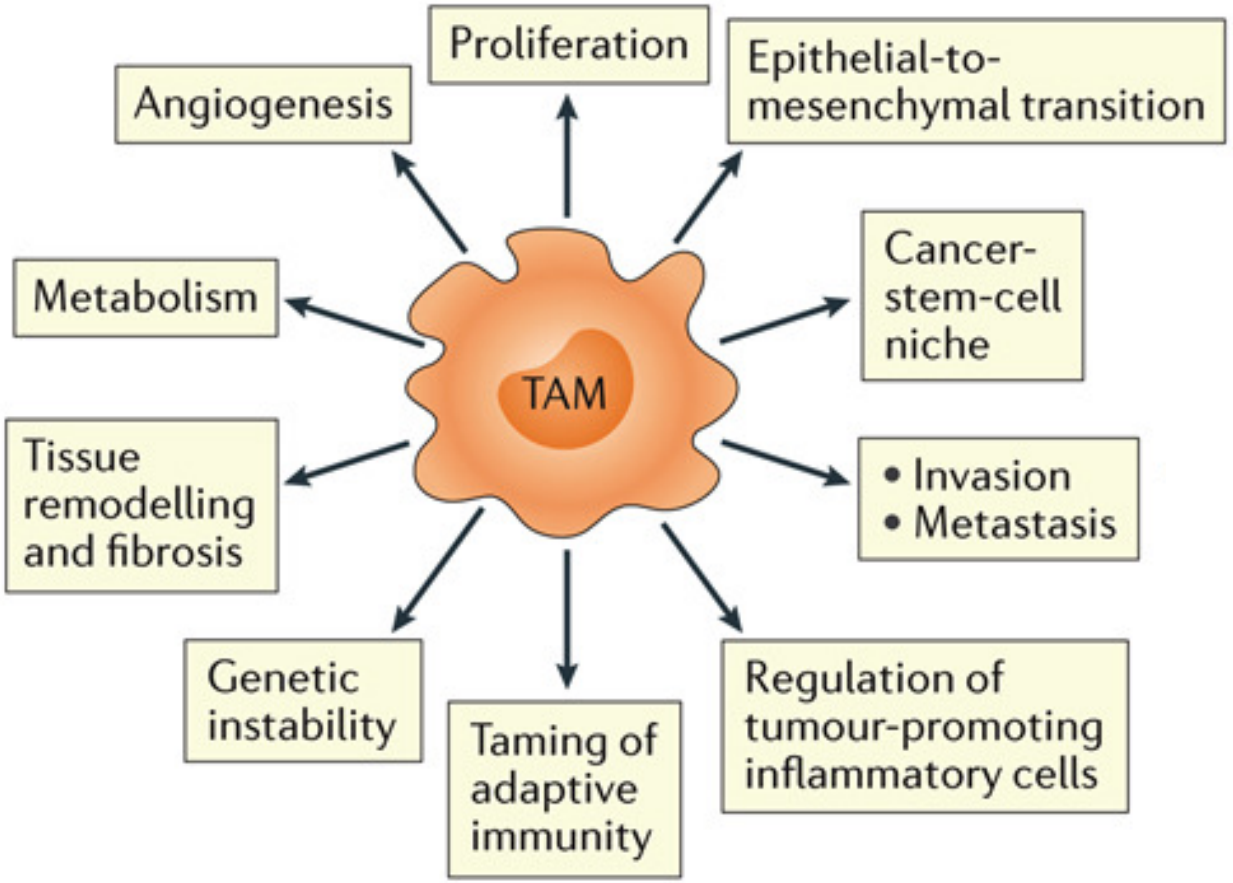
Nature Reviews | Immunology

Cellule della linea mieloide nel microambiente tumorale

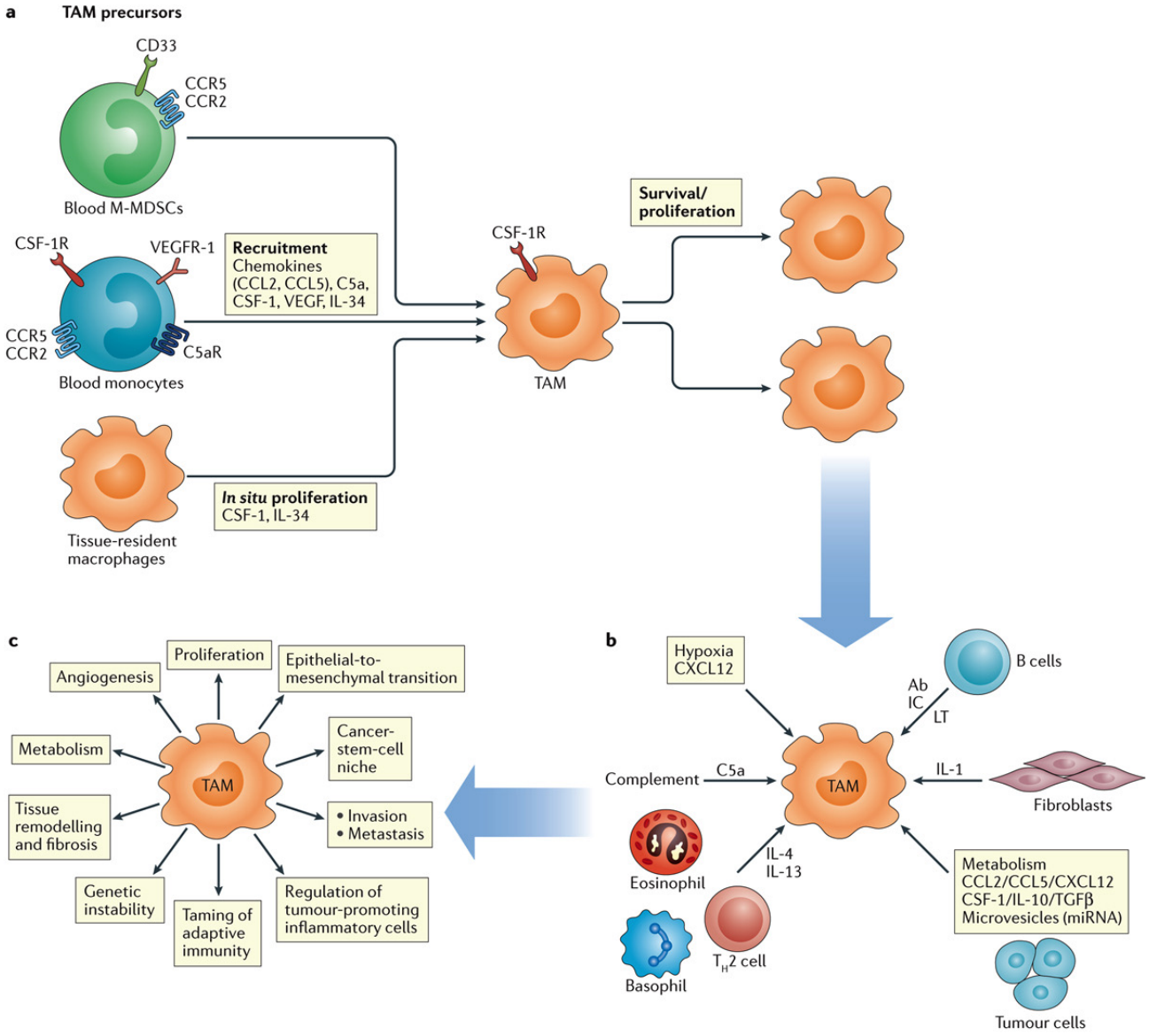
MDSC = myeloid-derived suppressor cells



TAM = TUMOR-ASSOCIATED MACROPHAGES

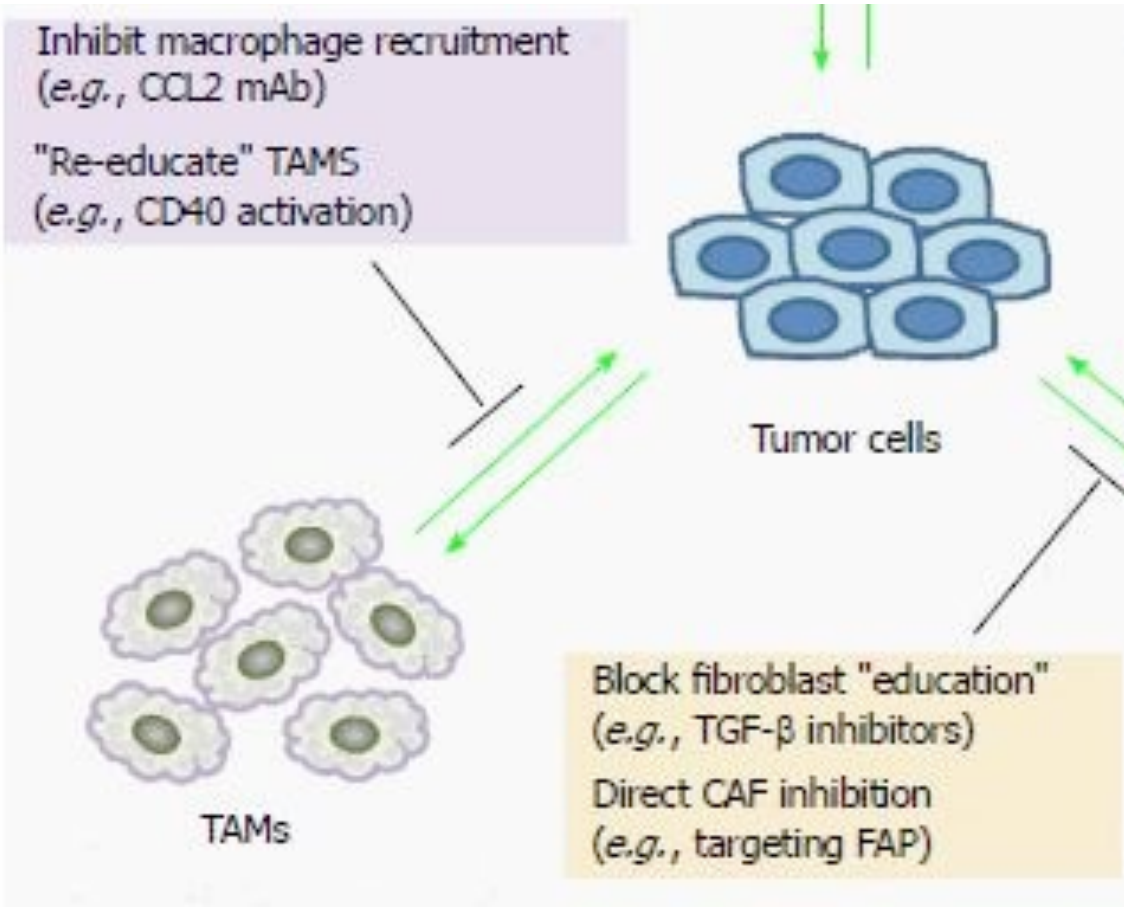


TAM = TUMOR-ASSOCIATED MACROPHAGES

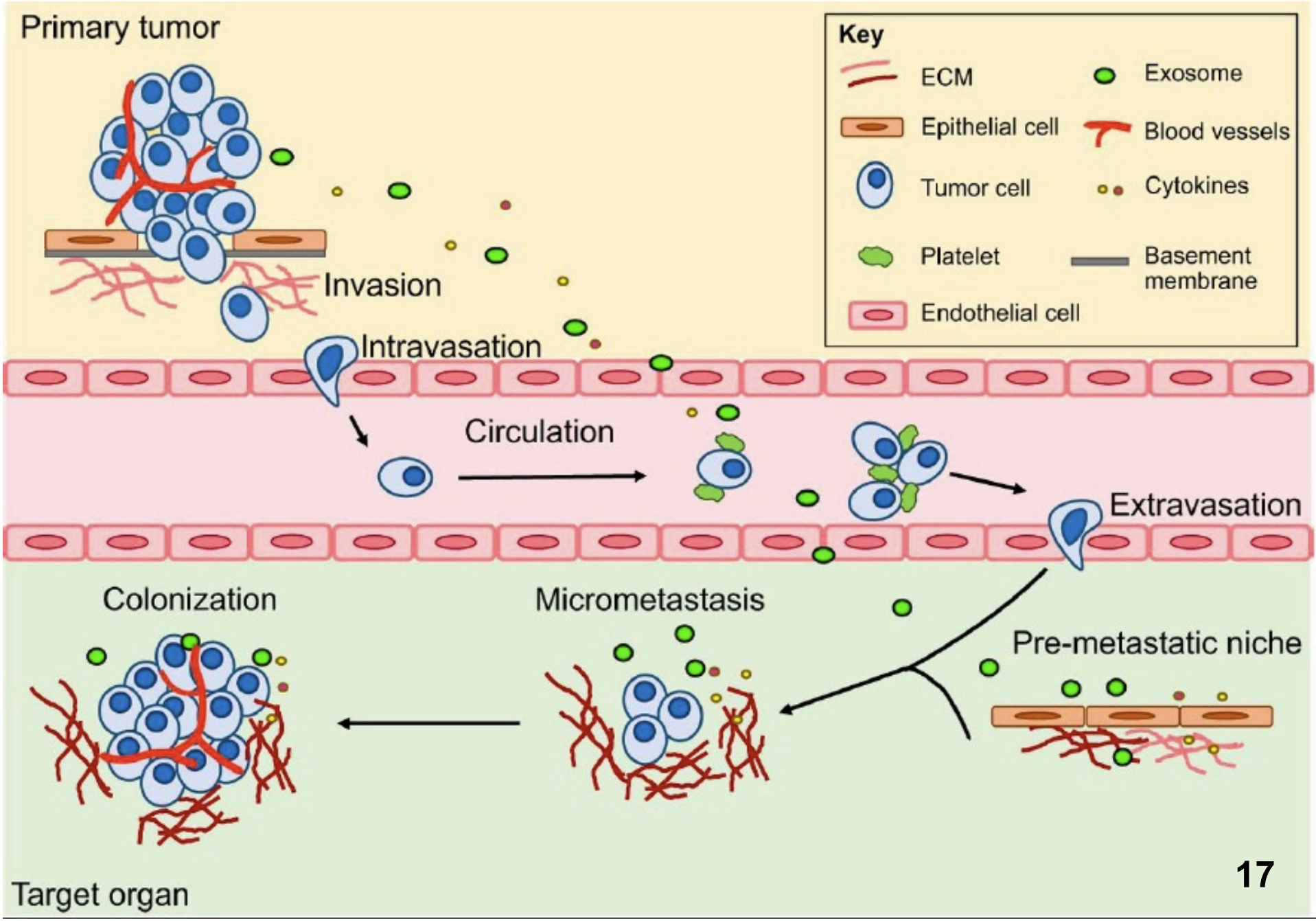


Nature Reviews | Clinical Oncology

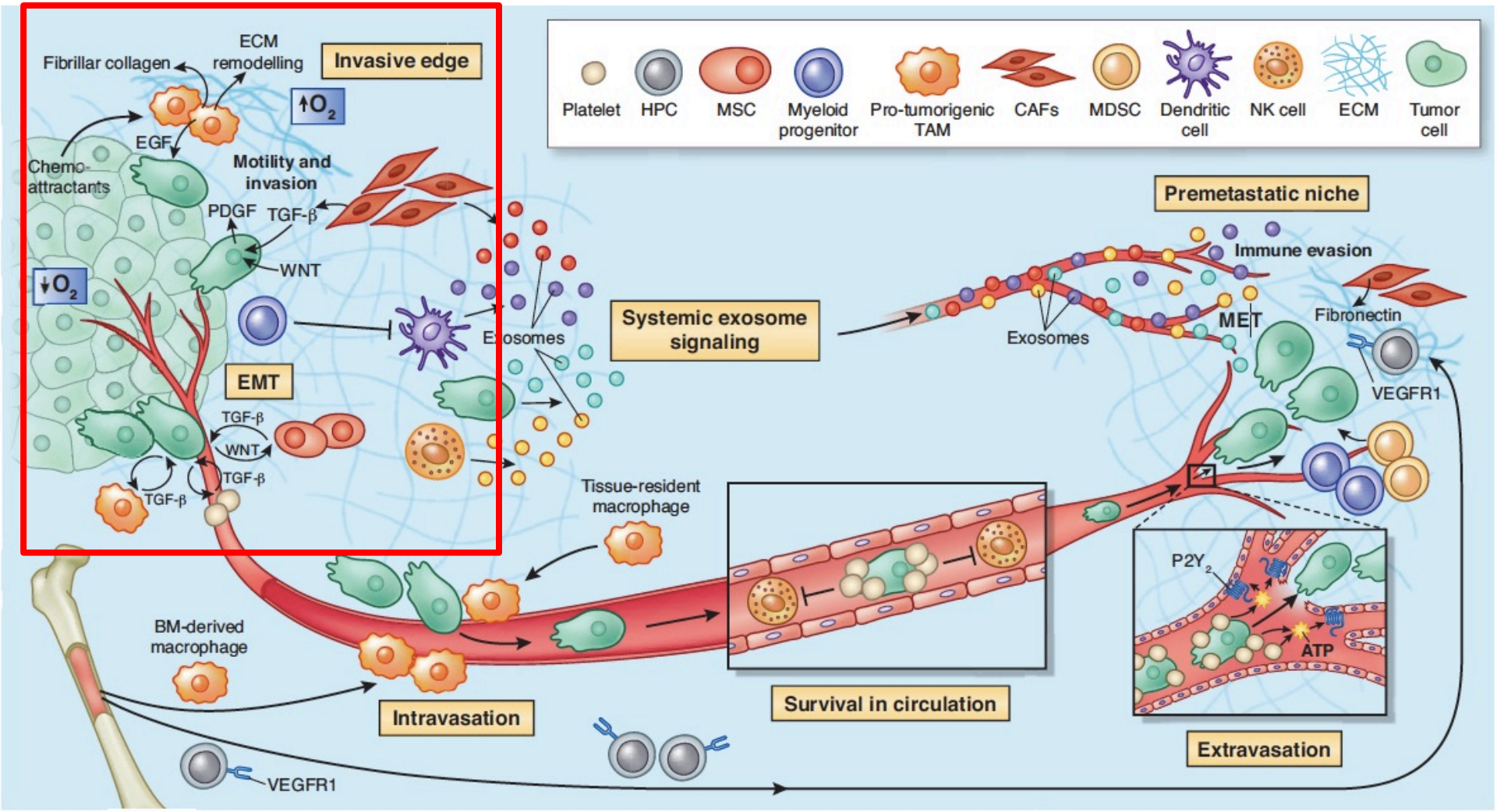
Terapie dirette contro il microambiente



LA CASCATA INVASIONE-METASTASI


Primary tumor
Key
ECM
Exosome
Epithelial cell
Blood vessels
Tumor cell
Cytokines
Platelet
Basement membrane
Endothelial cell
Invasion
Intravasation
Circulation
Extravasation
Colonization
Micrometastasis
Pre-metastatic niche
Target organ

Interazioni con il microambiente nella cascata metastatica



Il processo metastatico

- E' il processo attraverso il quale si formano **tumori secondari**, in nuovi siti, diversi da quello originale.

- Durante la cascata metastatica le cellule tumorali subiscono/attivano una serie di cambiamenti più o meno stabili, la cui conseguenza è la generazione di cellule con **competenza metastatica**.

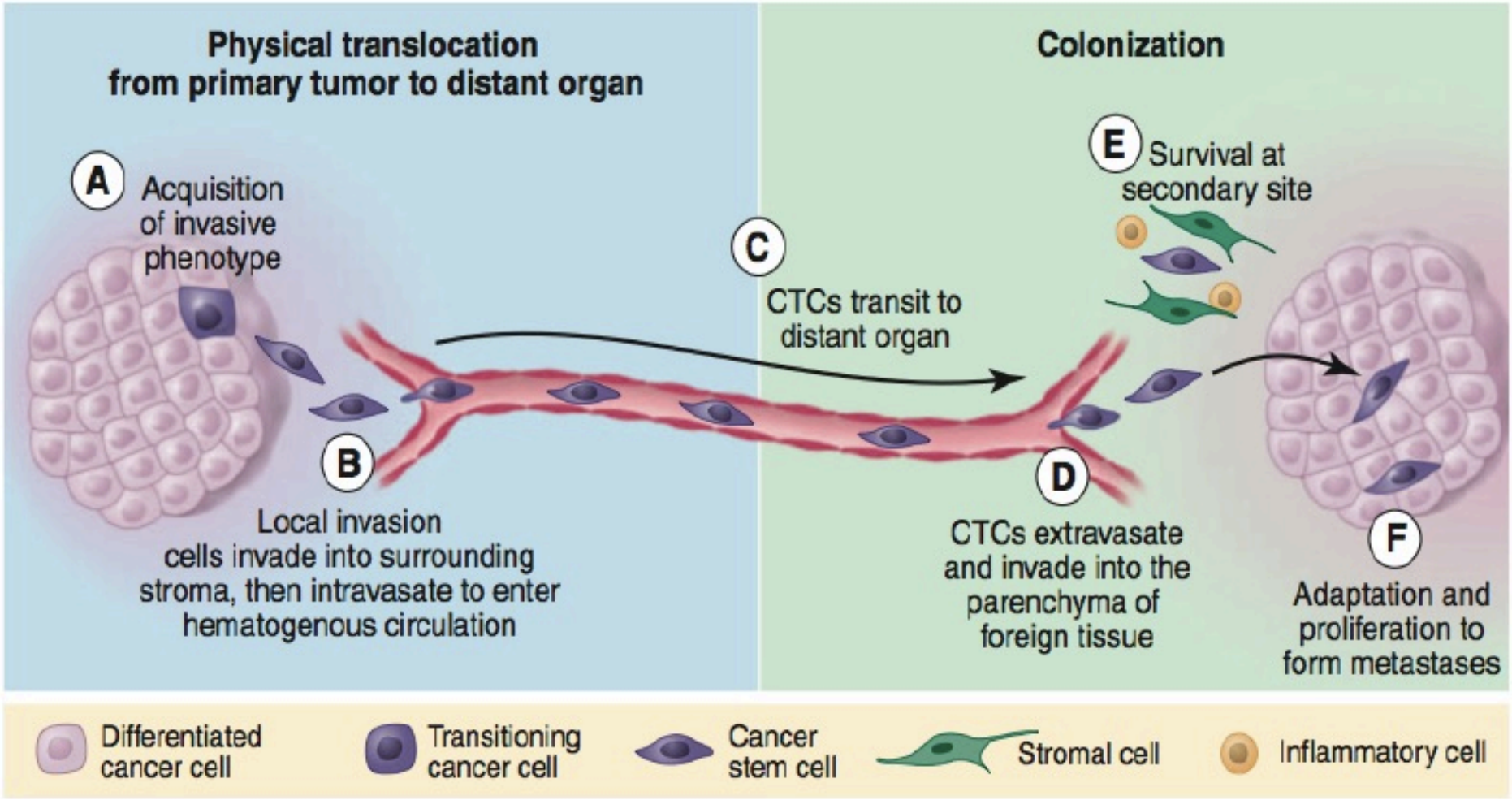
- È importante ricordare che questo processo dipende da interazioni con il microambiente.

- **Mortalità**: > 90% della mortalità associata al cancro si può attribuire alla formazione di metastasi.

- **Terapia**: la malattia metastatica è difficile da curare essendo di natura sistemica e spesso le cellule disseminate **sono resistenti agli agenti terapeutici**. Inoltre, le metastasi possono essere diverse geneticamente e fenotipicamente dal tumore primario.

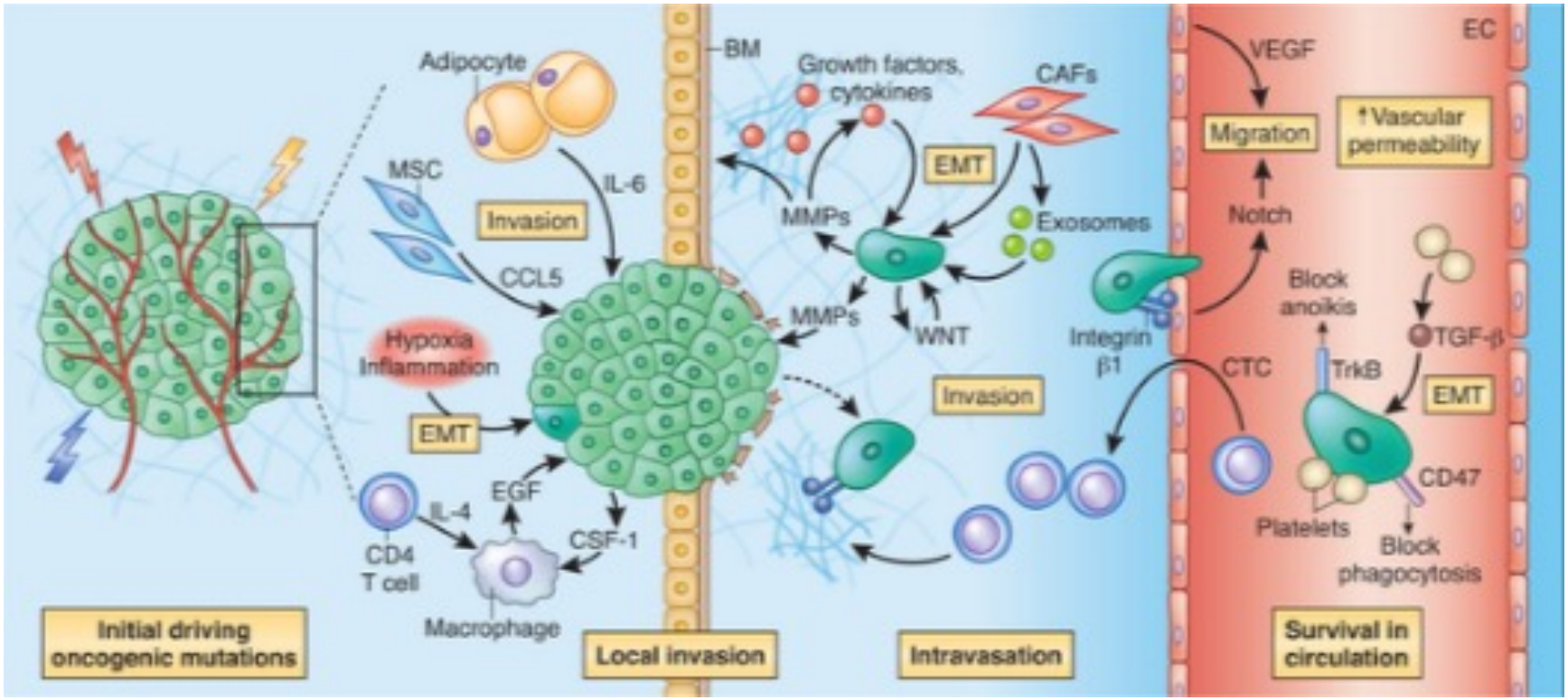
Il processo metastatico in due momenti principali

DISSEMINAZIONE **COLONIZZAZIONE**



EMT **MET**

Le fasi iniziali della disseminazione



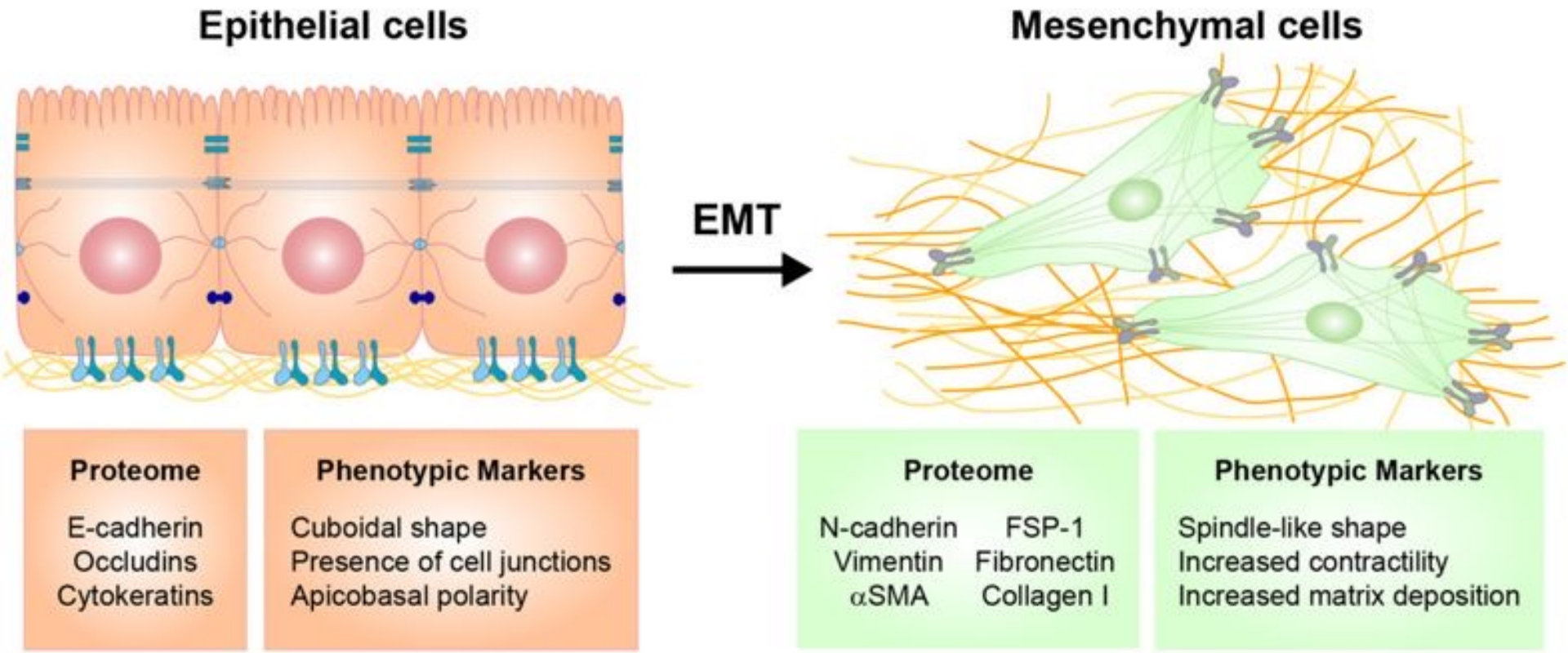
Wan, Pantel & Kang, Nat Med 2013

EMT: dedifferenziamento e acquisizione di un fenotipo motile e dotato di staminalità

Disgregazione della Membrana Basale e invasione locale Proteasi extracellulari (ad es. **MMPs**) degradano componenti della Membrana Basale e dello stroma e promuovono l'attivazione di citochine e fattori di crescita stromali (TGFb, VEGF, etc.) o legati alla membrana cellulare.

Intravasazione = Cellule tumorali invasive entrano nel sistema circolatorio attraversando l'endotelio di vasi sanguigni o linfatici. I vasi tumorali sono più permeabili e la **migrazione transendoteliale** è facilitata.

La TRANSIZIONE EPITELIO-MESENCHIMALE



Regolazione della EMT da oncogeni e segnali eterotipici

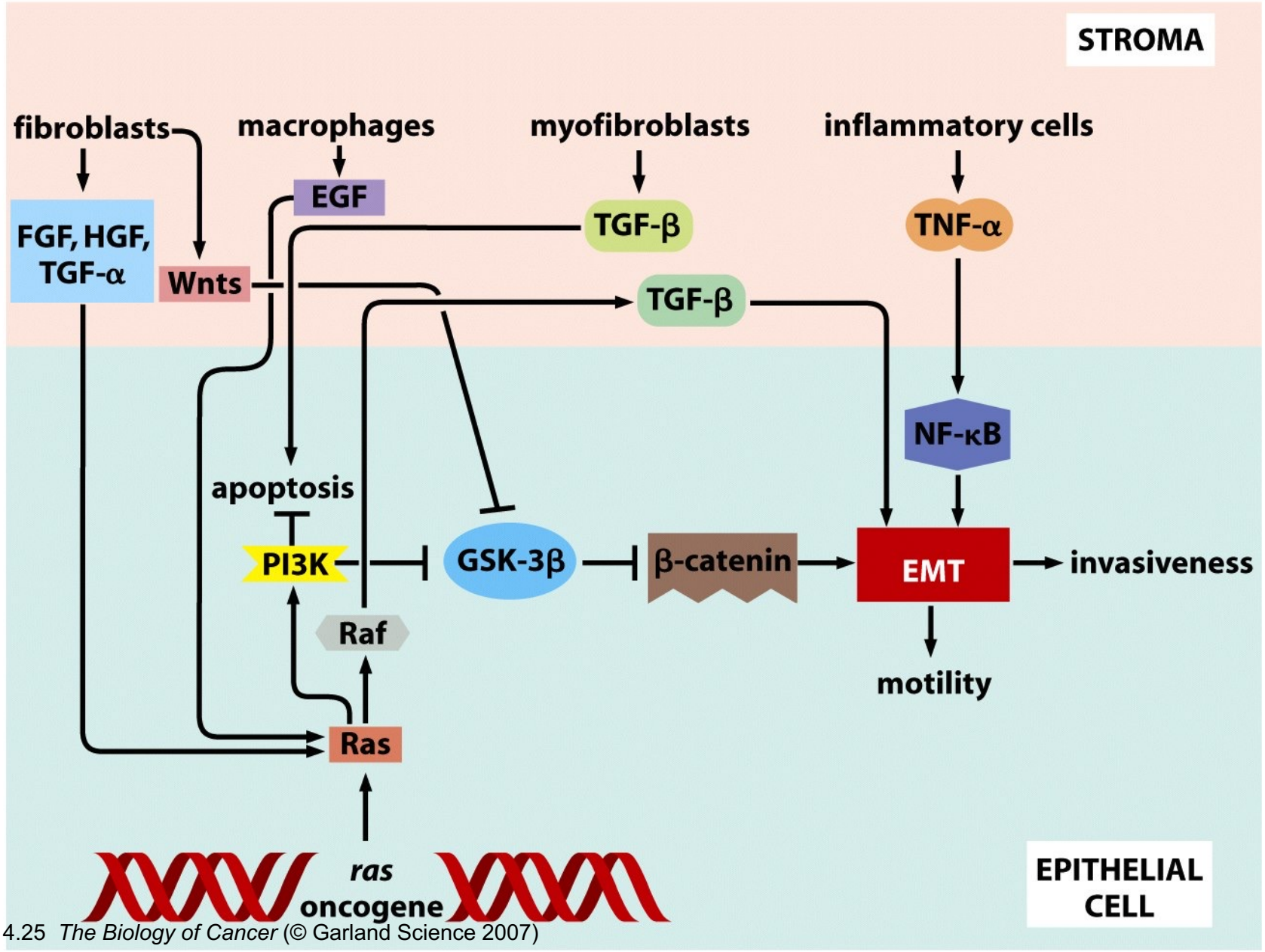
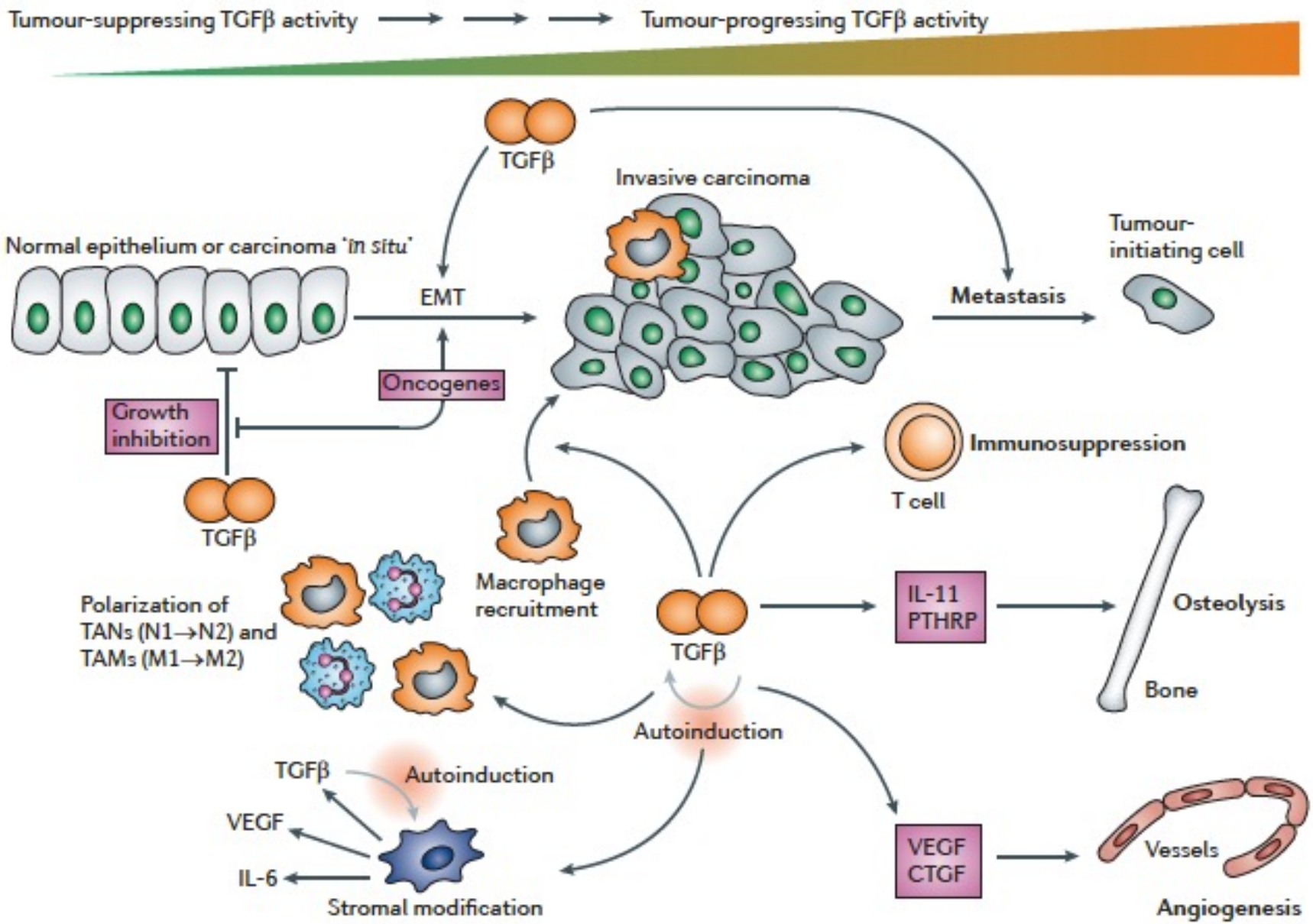


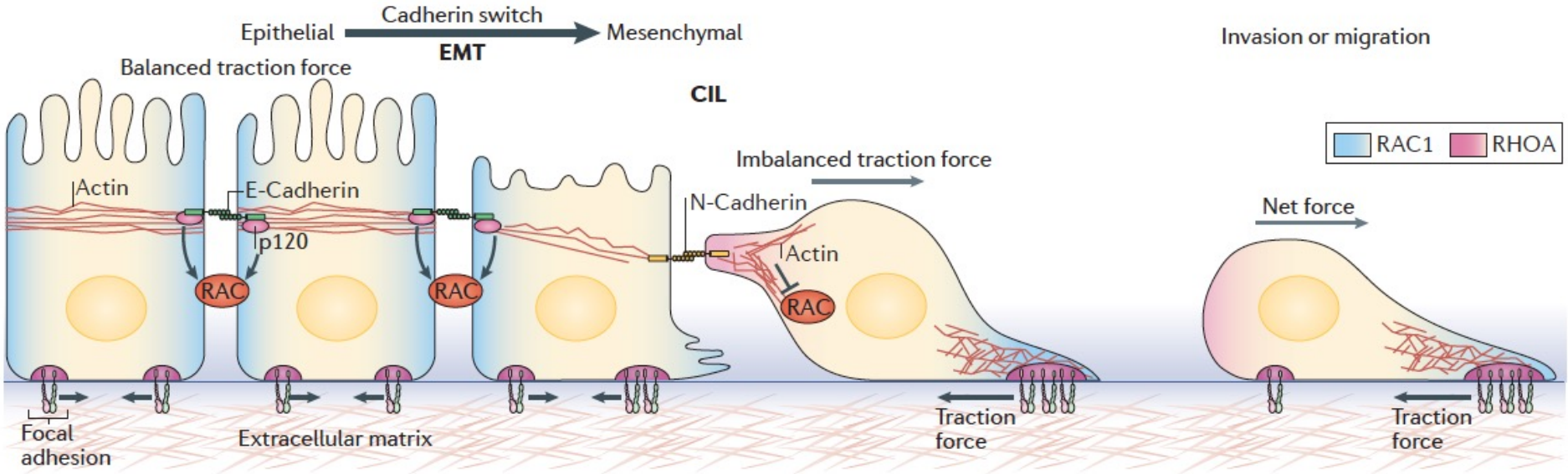
Figure 14.25 *The Biology of Cancer* (© Garland Science 2007)

Il doppio ruolo della pathway di TGFβ nel cancro



Akhurst & Hata, Nat Rev Drug Disc 2012

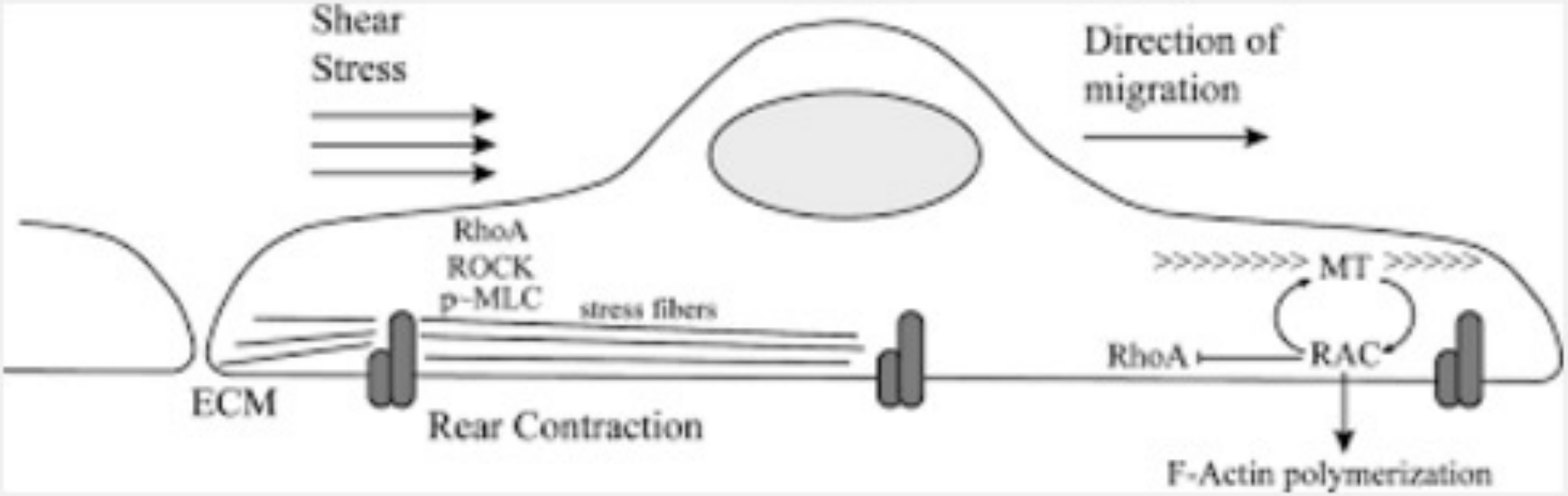
Lo switch delle caderine facilita la perdita di polarità e dell'inibizione della migrazione da contatto



E-Cadherin suppresses EMT and CIL by signalling to other adhesion components, such as p120 catenin, which polarizes the small GTPase **RAC1 towards cell–cell junctions.**

N-cadherin expression promotes polarization of **RAC1 activity towards the leading edge** of cells to generate asymmetric traction stress.

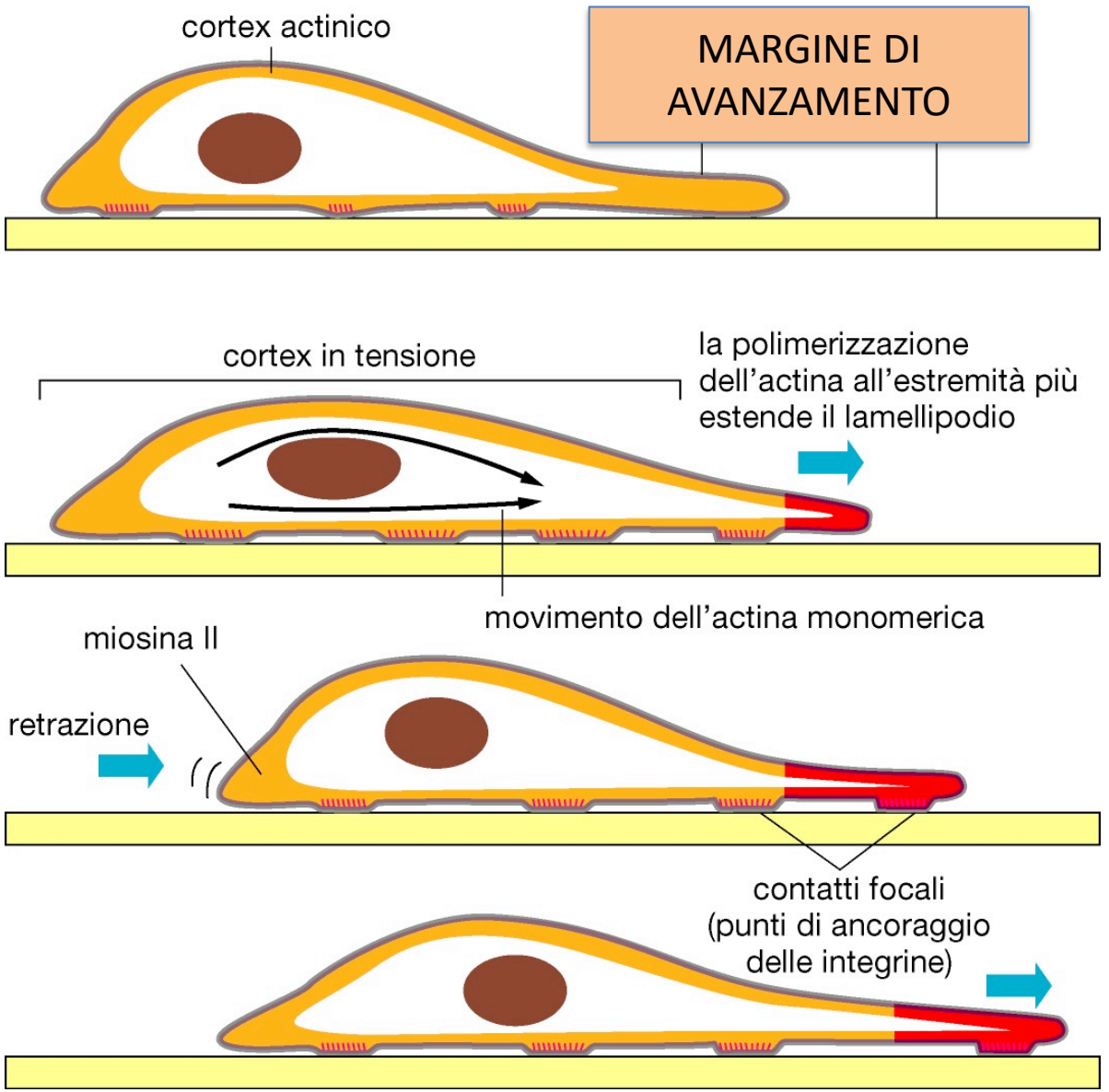
Stramer et al., Nature Revies on Cancer 2016



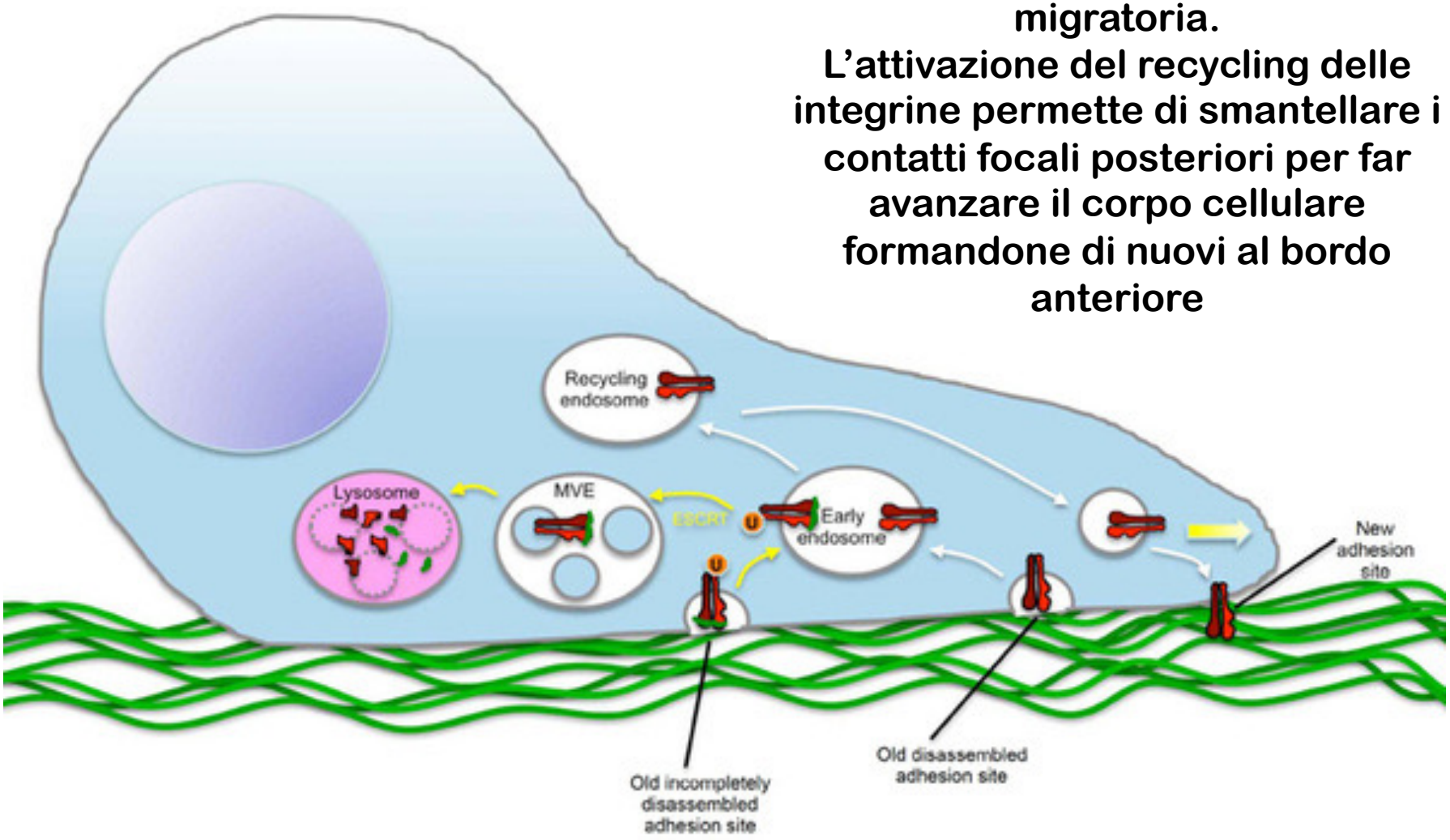
Le GTPasi Rho, Rac e cdc42 e controllano la organizzazione dell'actina e delle adesioni focali.

La migrazione dipende da **attivazione localizzata di qs proteine in piccoli, limitati domini di membrana**.

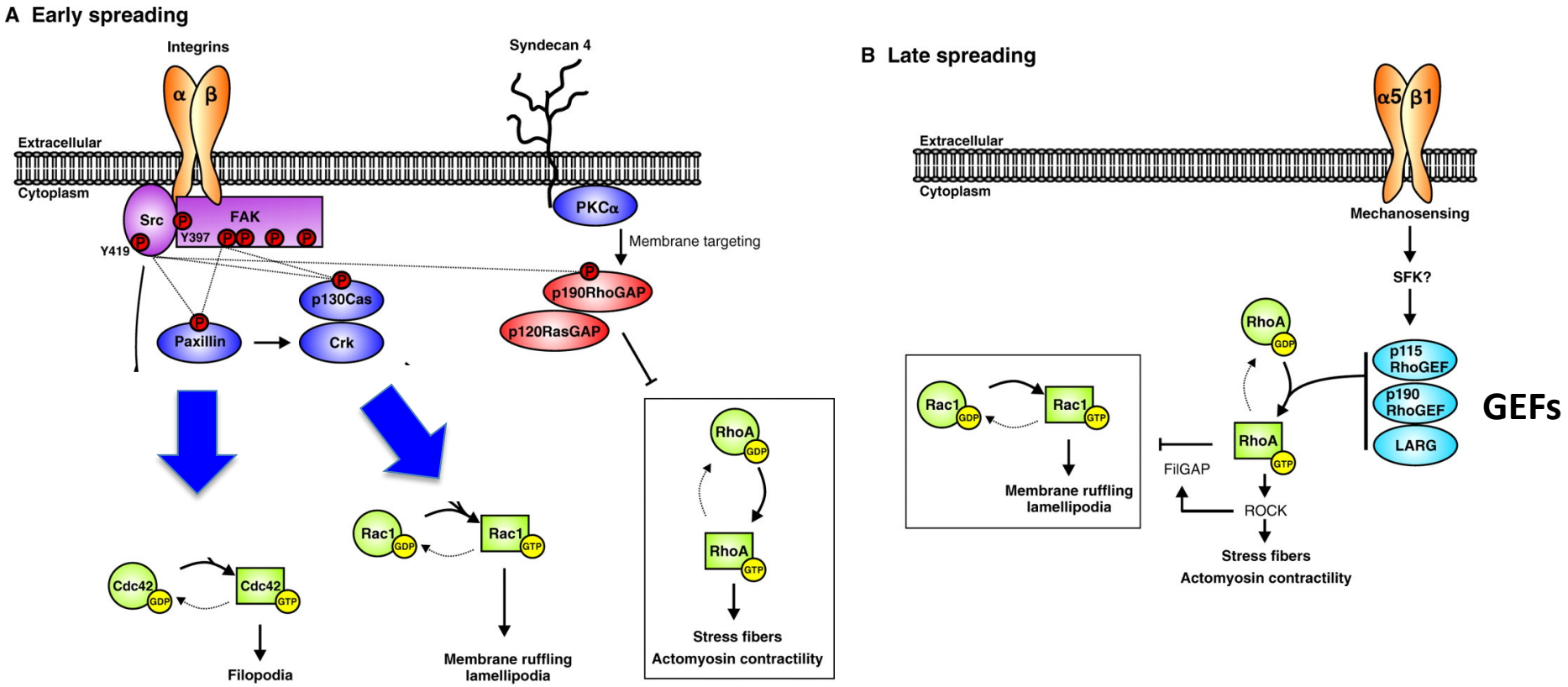
migrazione cellulare



Il pattern di espressione delle integrine al leading edge (bordo anteriore invasivo) è diverso in cellule dotate di capacità migratoria.
L'attivazione del recycling delle integrine permette di smantellare i contatti focali posteriori per far avanzare il corpo cellulare formandone di nuovi al bordo anteriore



REGOLAZIONE DI RHO DA SIGNALING DELLE INTEGRINE DURANTE LA MIGRAZIONE



Stephan Huveneers, and Erik H. J. Danen J Cell Sci 2009;122:1059-1069

Journal of Cell Science

INVASIONE: rottura della lamina basale

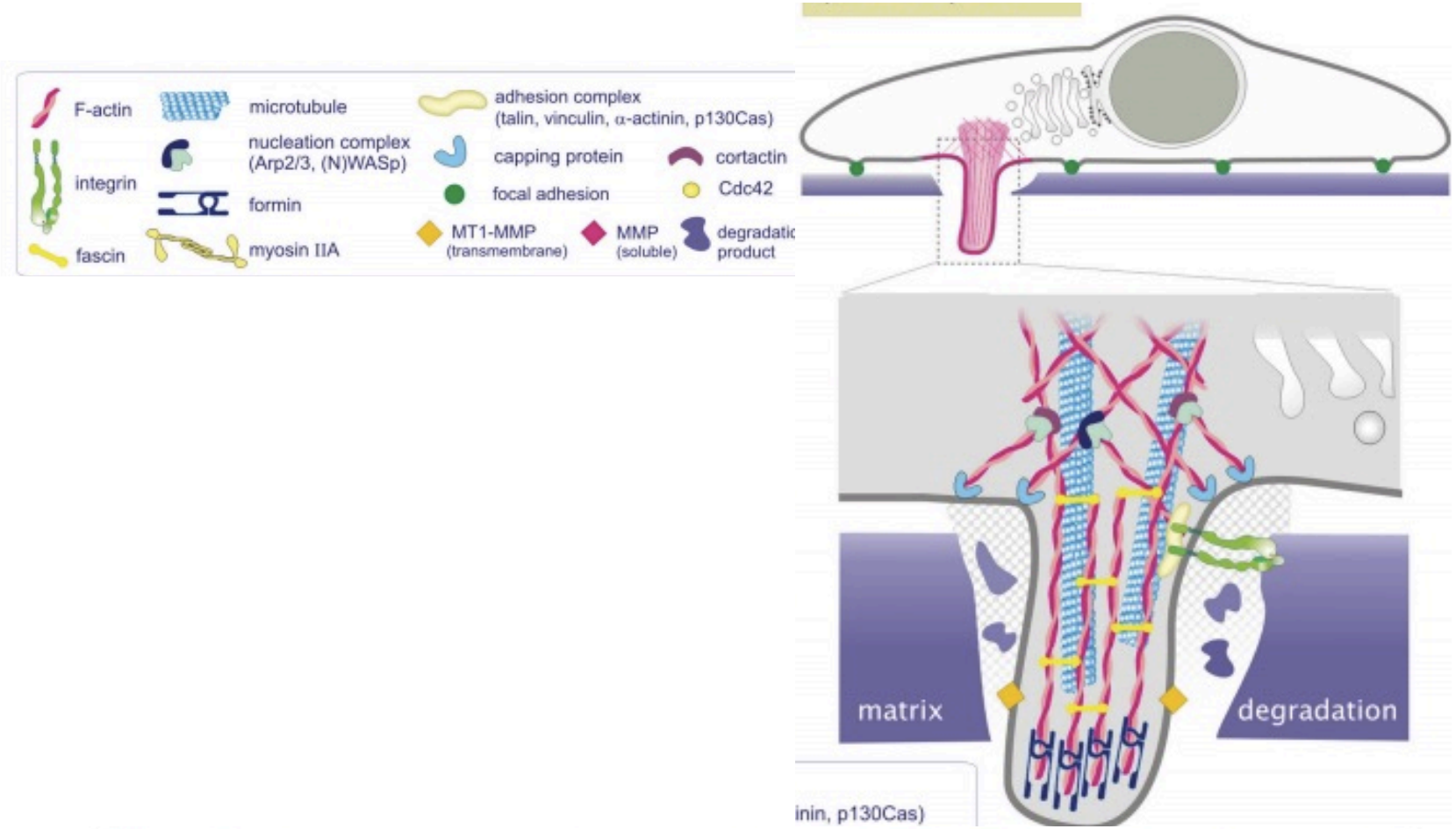
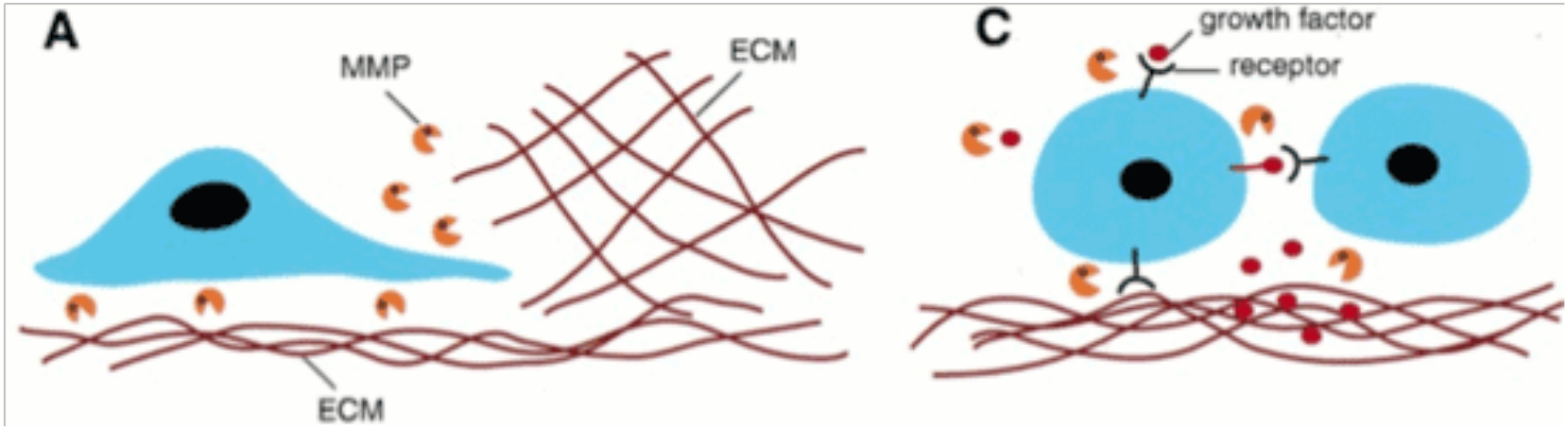


Figure 2. Schematic representation of podosomes and invadopodia. Podosomes consist of a core column of actin filaments that extends upwards from the ventral cell surface into the cytoplasm whereas invadopodia are long filopodial-like membrane extensions that penetrate into the ECM. (**A**) Schematic representation of a podosome in a macrophage: Cdc42/WASp/Arp2/3 drives actin polymerization at the face of the actin core, generating forces that push against the core and consequently promotes podosome growth. Radial actin filaments emanate from the actin core and link it to cell surface integrins and associated proteins that form the basis of the adhesive ring complex. (**B**) Schematic representation of an invadopodium in a cancerous cell: The N-WASp/Arp2/3 complex is present at the base and along the length of shafts of invadopodia but absent from the tips. The Rho effector mDia is involved in both initiation of invadopodia formation through actin nucleation and subsequent growth of invadopodia through the elongation of actin filaments. The protease activity is essential for the assembly of protrusive actin structures. Invadopodia lack the strict organization of core and ring structure found in podosomes.

La degradazione localizzata della ECM favorisce la disseminazione

Serin proteasi e metalloproteasi



Le MMPs liberano fattori di crescita e TGFβ sequestrati nella ECM

3 famiglie (24 membri):

MMPs, ADAM, ADAMTS — **famiglie di enzimi zinco-dipendenti con diversa specificità di substrato**

INIBITORI: TIMPs (endogenous tissue inhbitors)

Gli inibitori delle metalloproteasi MPIs

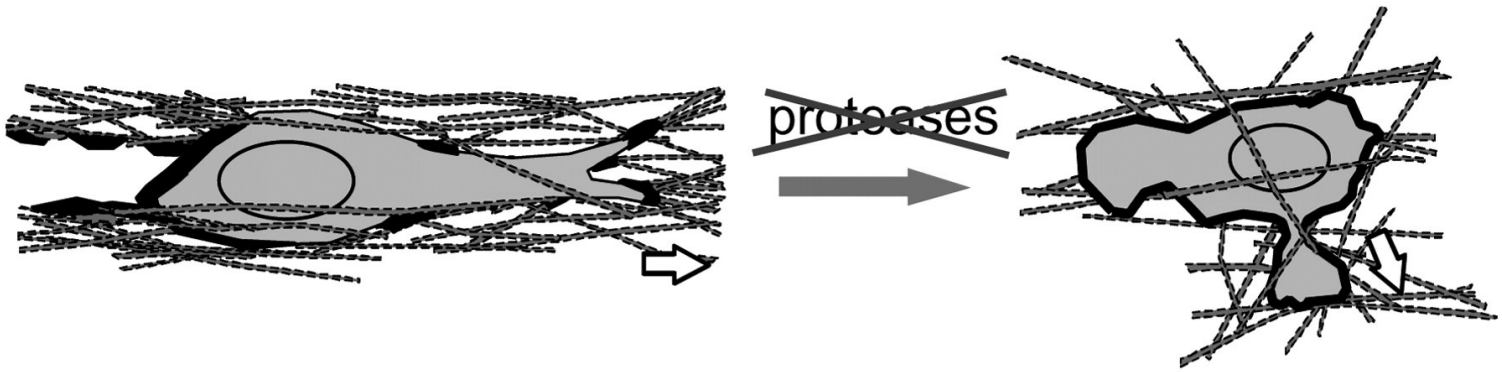
Review

Molecular Cancer Therapeutics

Matrix Metalloproteinase Inhibitors in Cancer Therapy: Turning Past Failures Into Future Successes

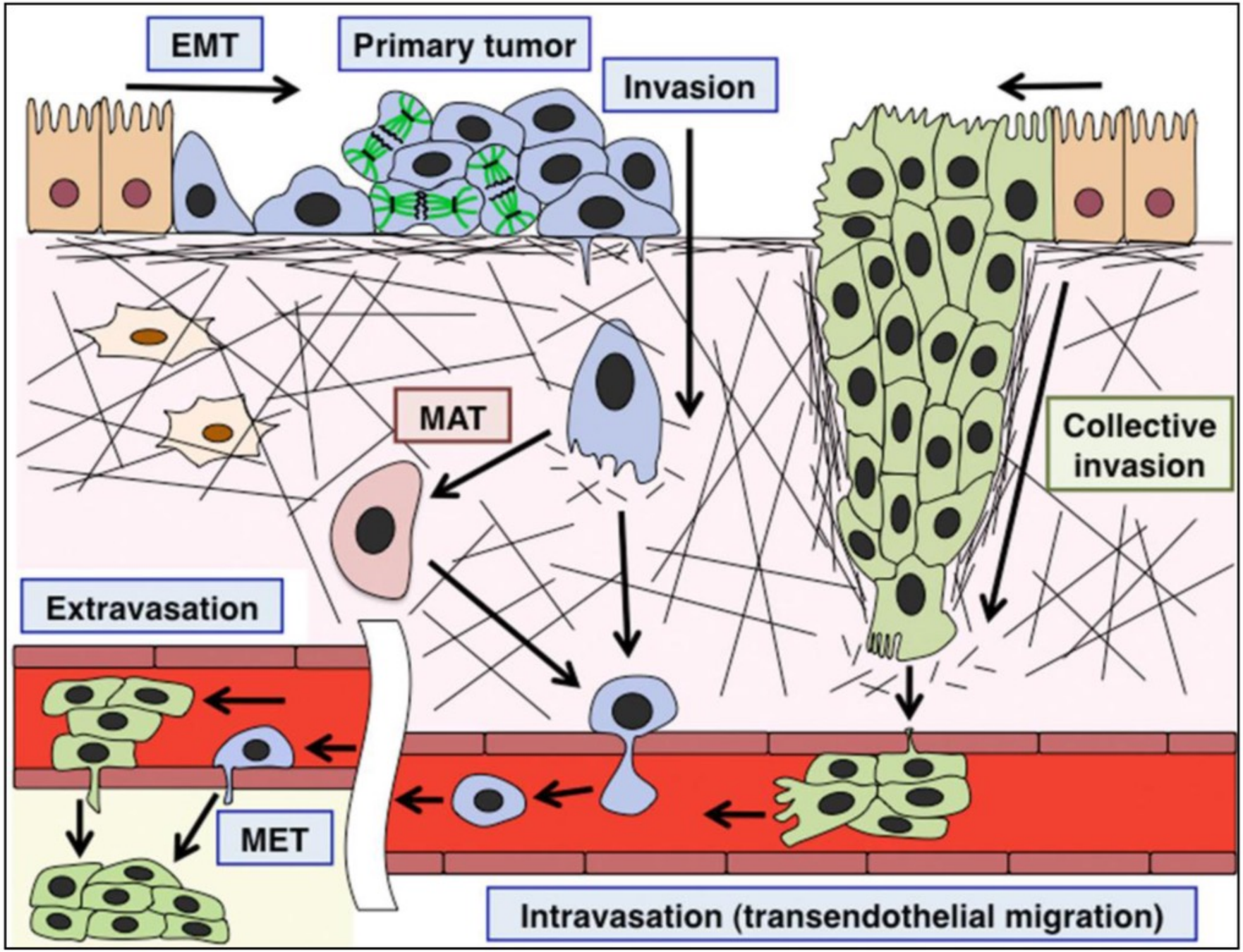
Arthur Winer, Sylvia Adams, and Paolo Mignatti

MMPs e modalità di migrazione

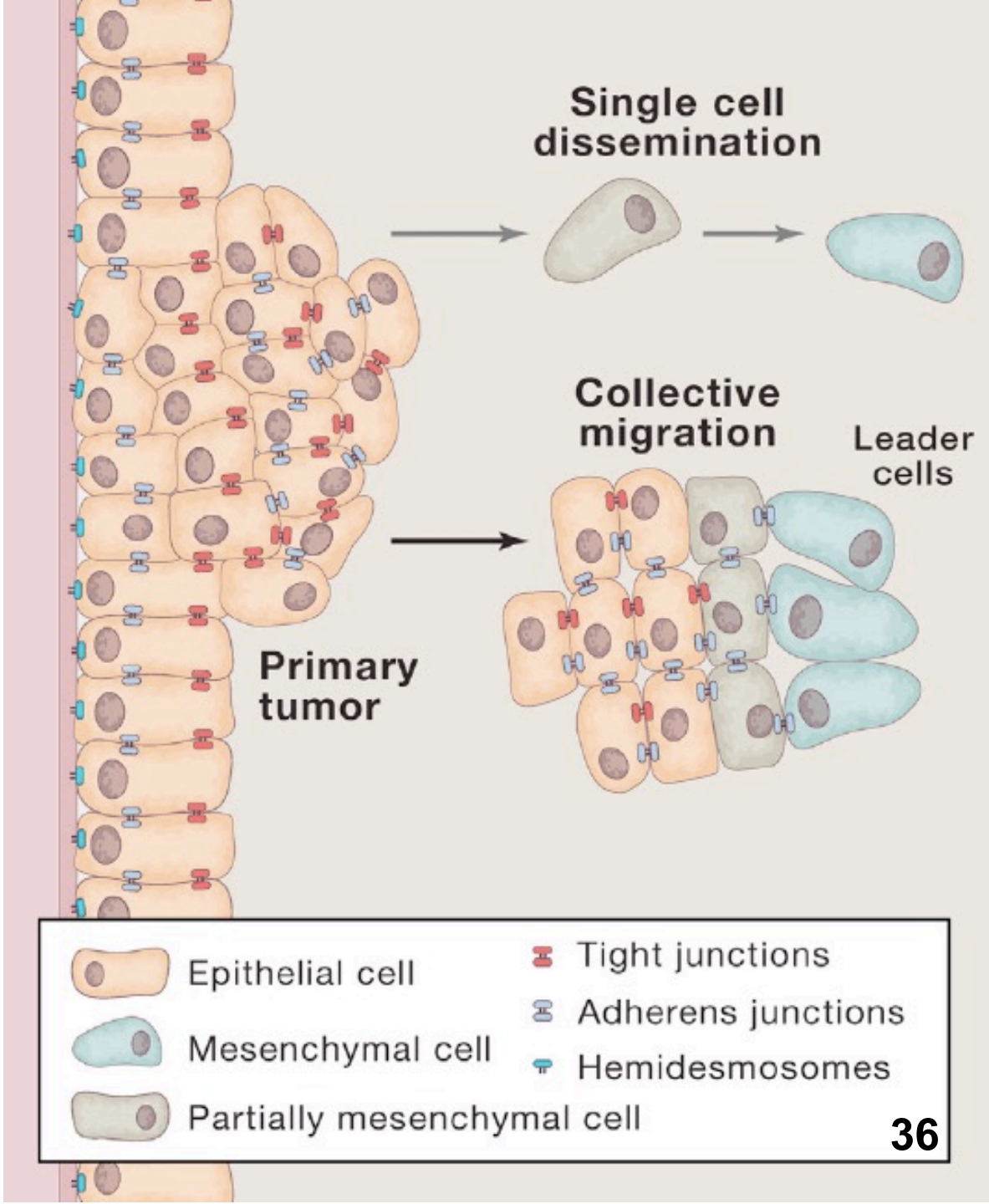


	mesenchymal	amoeboid
migration strategy	path generating	path finding
mechanism for overcoming tissue barriers	proteolytic matrix defect	morphological adaptation (constriction ring)
composition of cell-matrix interactions	focalized; integrins and MT1-MMP coclustered	diffuse; integrins non-clustered; MT1-MMP internalized and dissociated from integrins

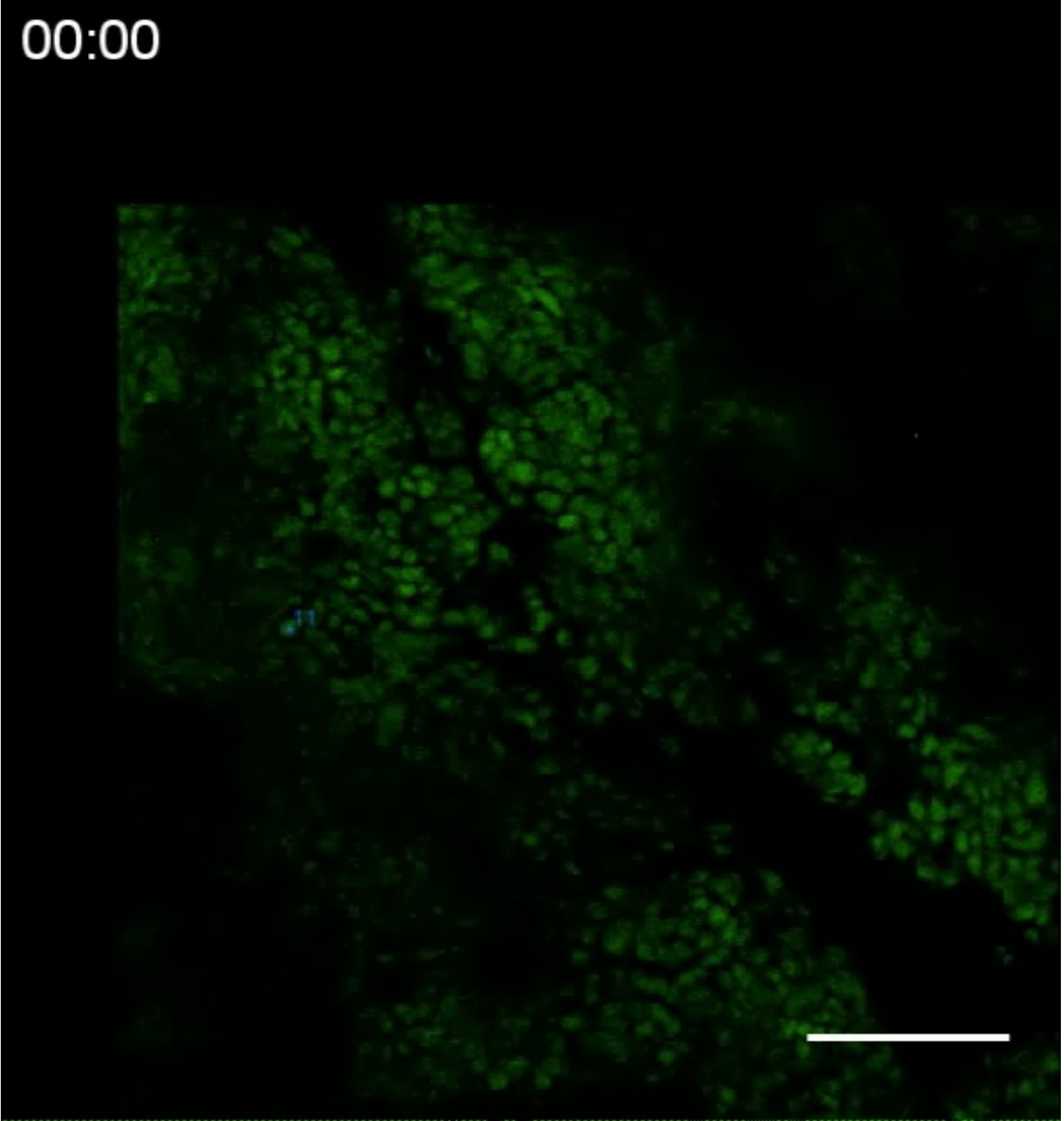
Katarina Wolf et al. J Cell Biol 2003;160:267-277


EMT
Primary tumor
Invasion
MAT
Collective invasion
Extravasation
MET
Intravasation (transendothelial migration)

La migrazione collettiva

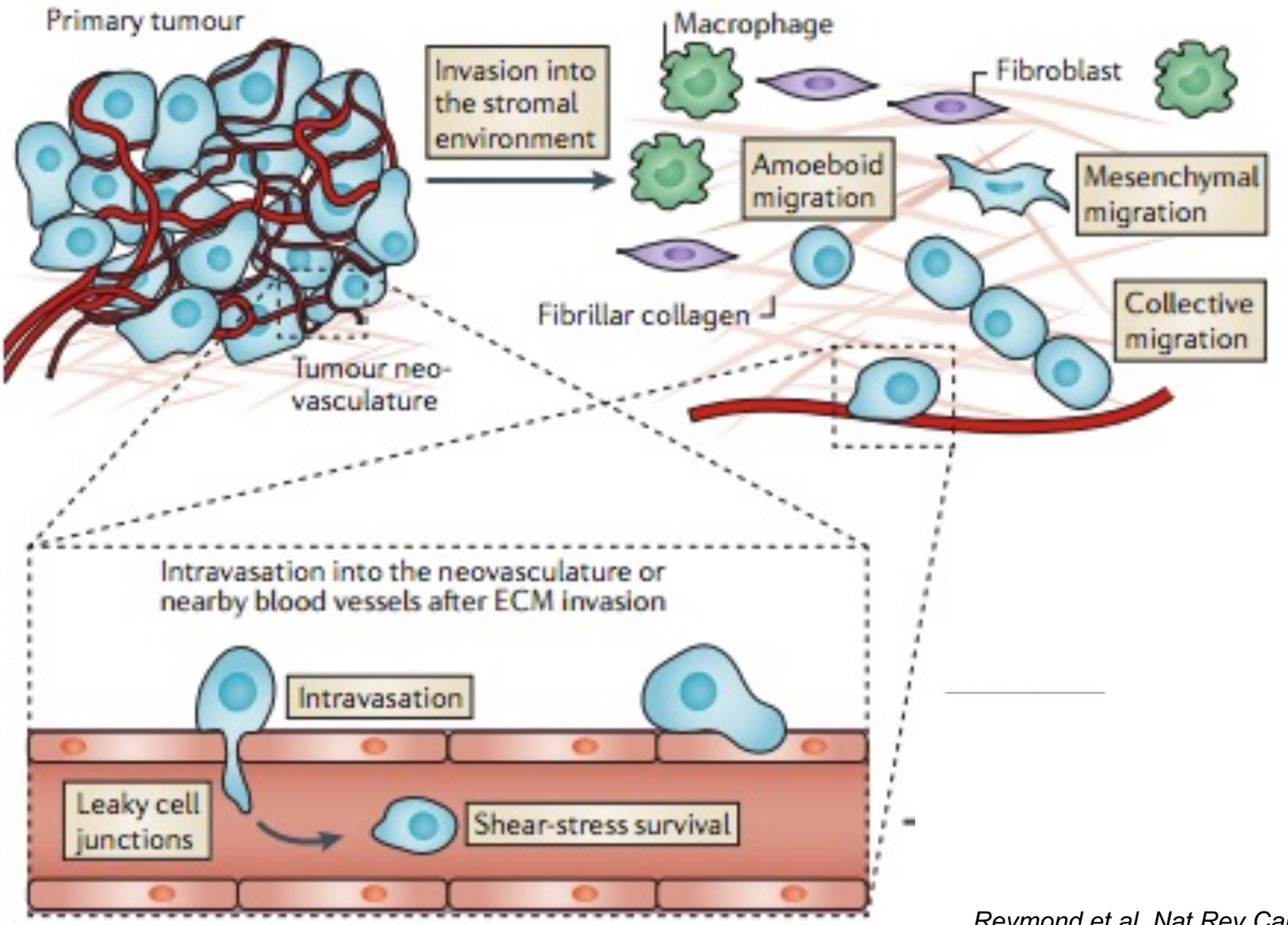


Lambert et al Cell 2017



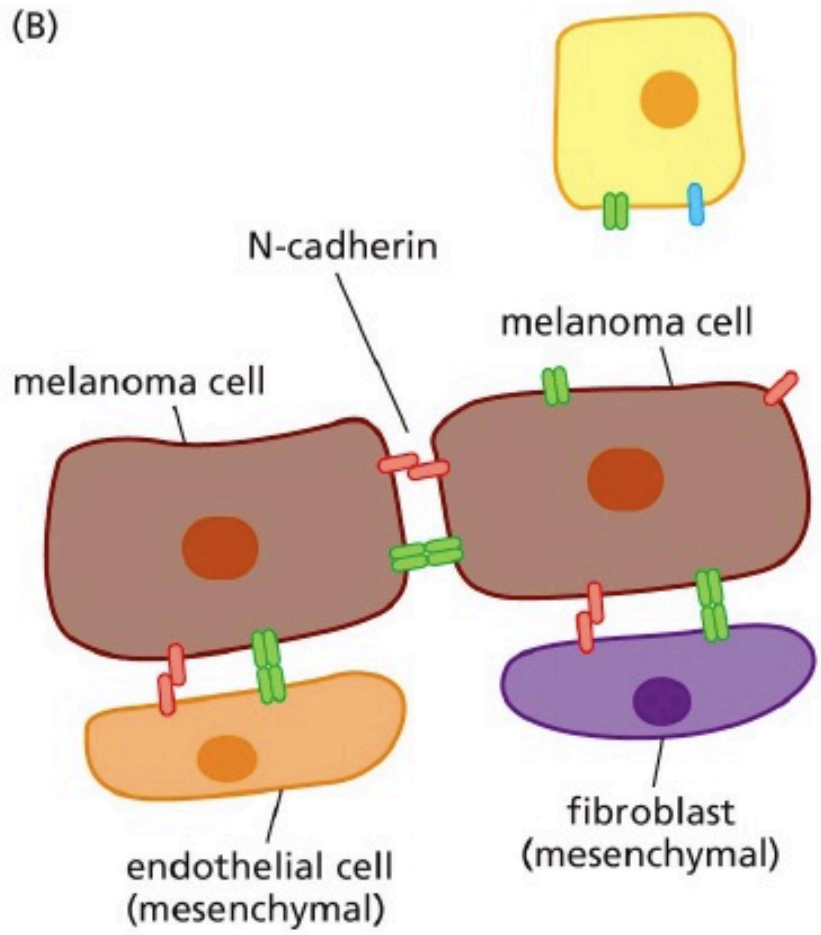
Journal of Cell Science 2019 132: jcs 220277 doi: 10.1242/jcs.220277

Invasione dello stroma e intravasazione



Reymond et al. Nat Rev Cancer 2013

Lo SWITCH delle caderine facilita l'intravasazione



When melanocytes become transformed in melanoma cells they shift from **E-Cadherin to N- Cadherin** thus extricating from keratinocytes and making more interactions via N-cadherin to stromal cells facilitating cell migration and invasion.