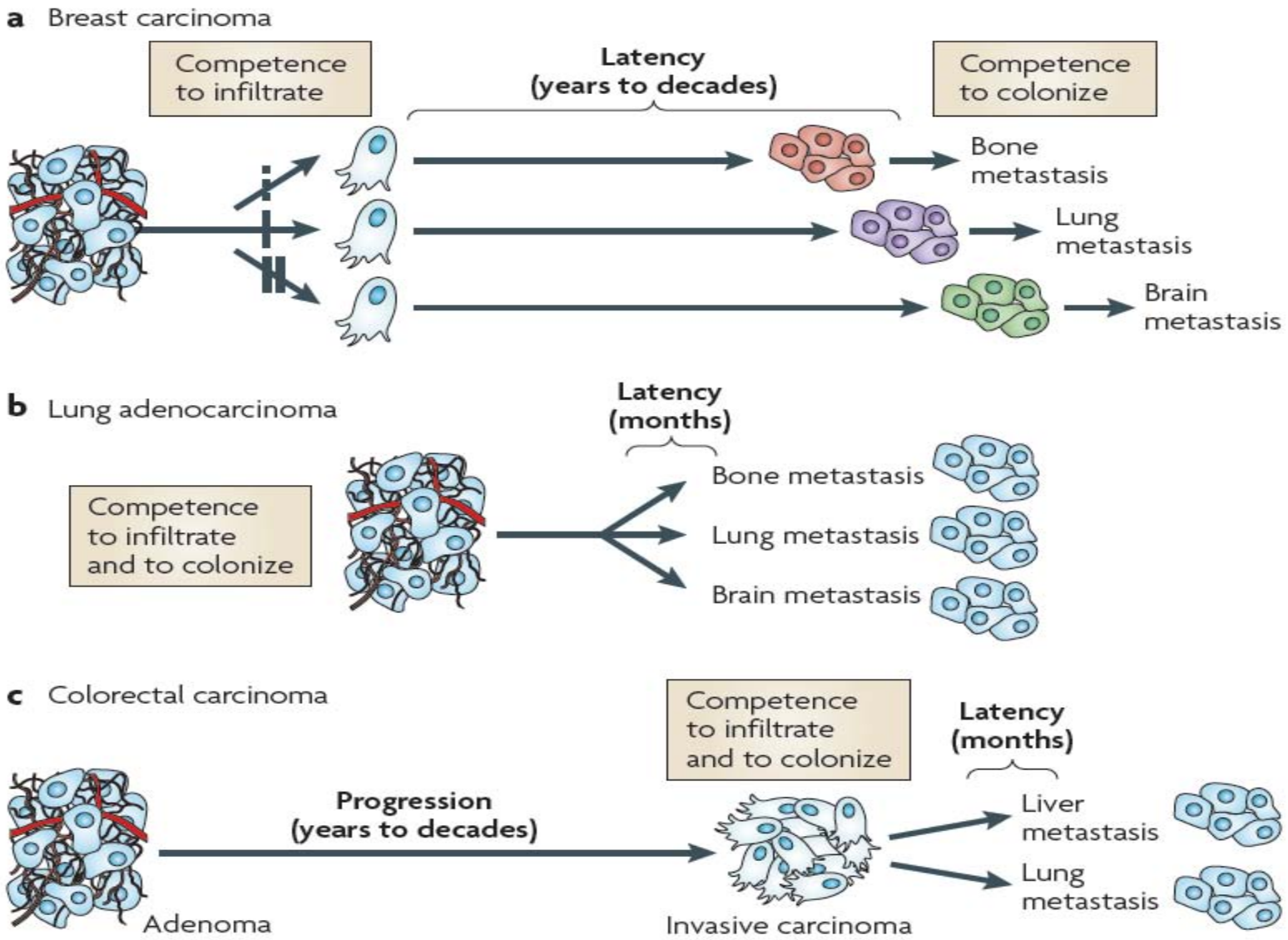
CƠ CHẾ PHÂN TỬ CỦA HIỆN TƯỢNG DI CĂN TẾ BÀO UNG THƯ

TS. BS Hoàng Anh Vũ
Đại học Y Dược TPHCM

NỘI DUNG

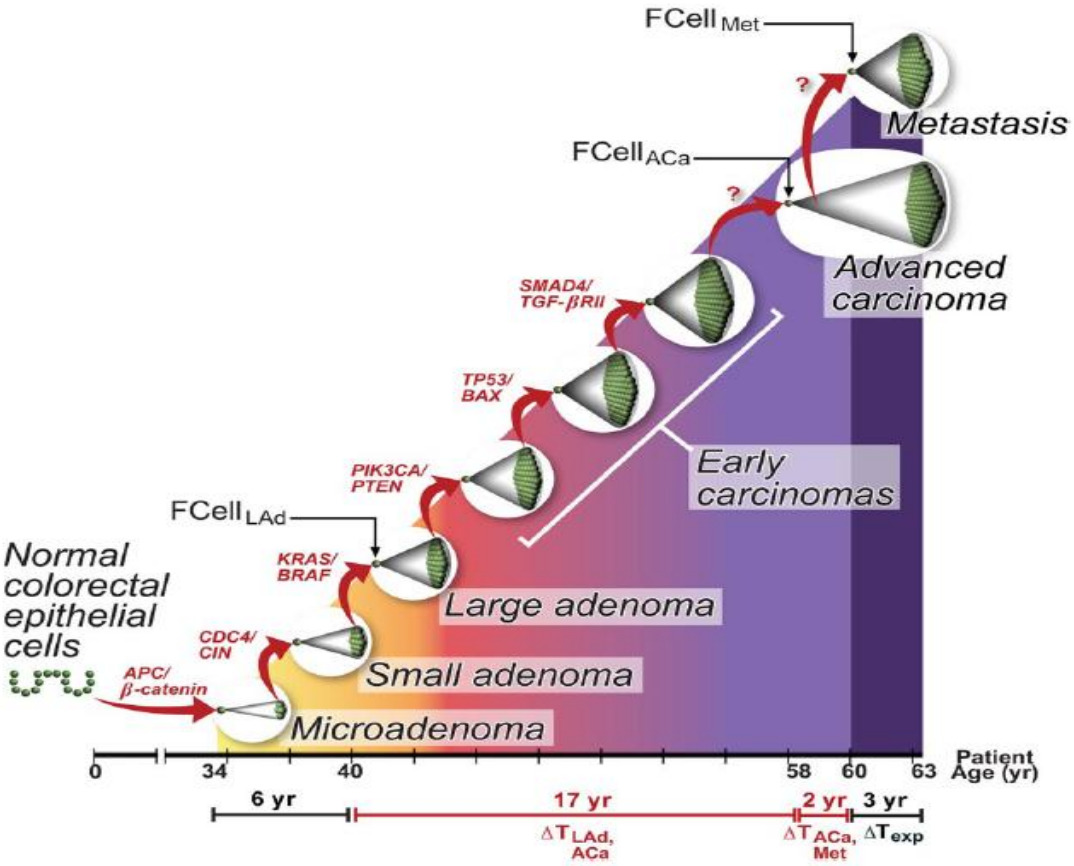
1. Các nhóm gen di căn
2. Hiện tượng EMT: vai trò của E-cadherin và N-cadherin
3. Tính bám dính của tế bào: vai trò của FAK và SRC

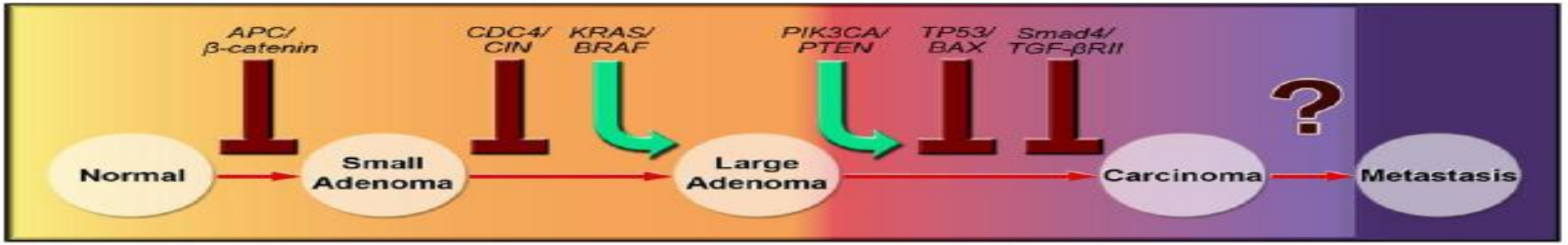
THỜI GIAN TIỀM ẨN CỦA DI CĂN



(Nguyen DX, *Nat Rev Cancer* 2009)

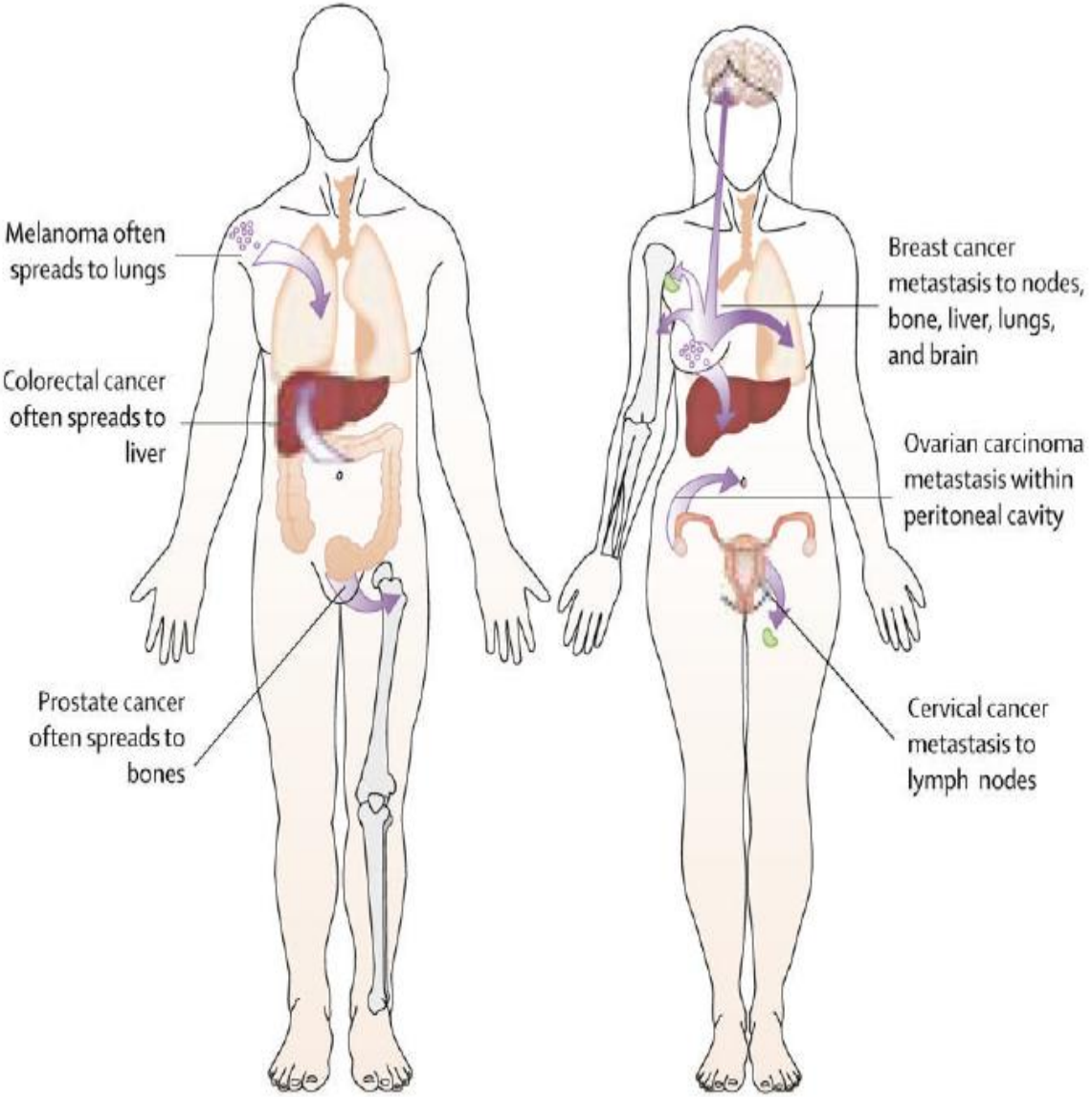
MÔ HÌNH UNG THƯ ĐẠI TRỰC TRÀNG

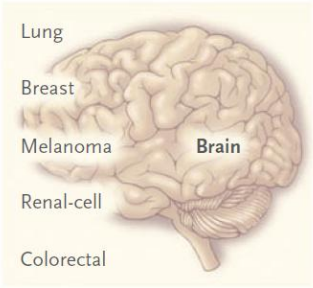


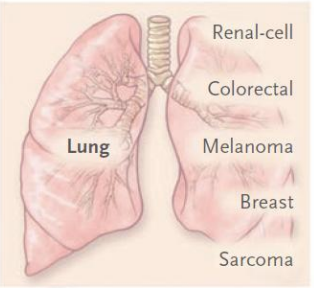


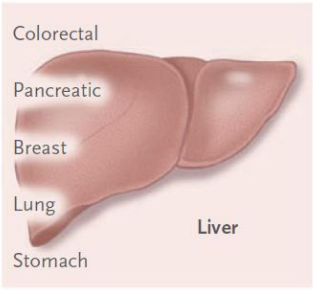
(Jones S, PNAS 2008)

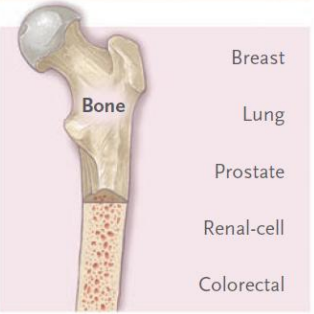
ĐÍCH ĐẾN CỦA DI CĂN Ở CÁC LOẠI UNG THƯ











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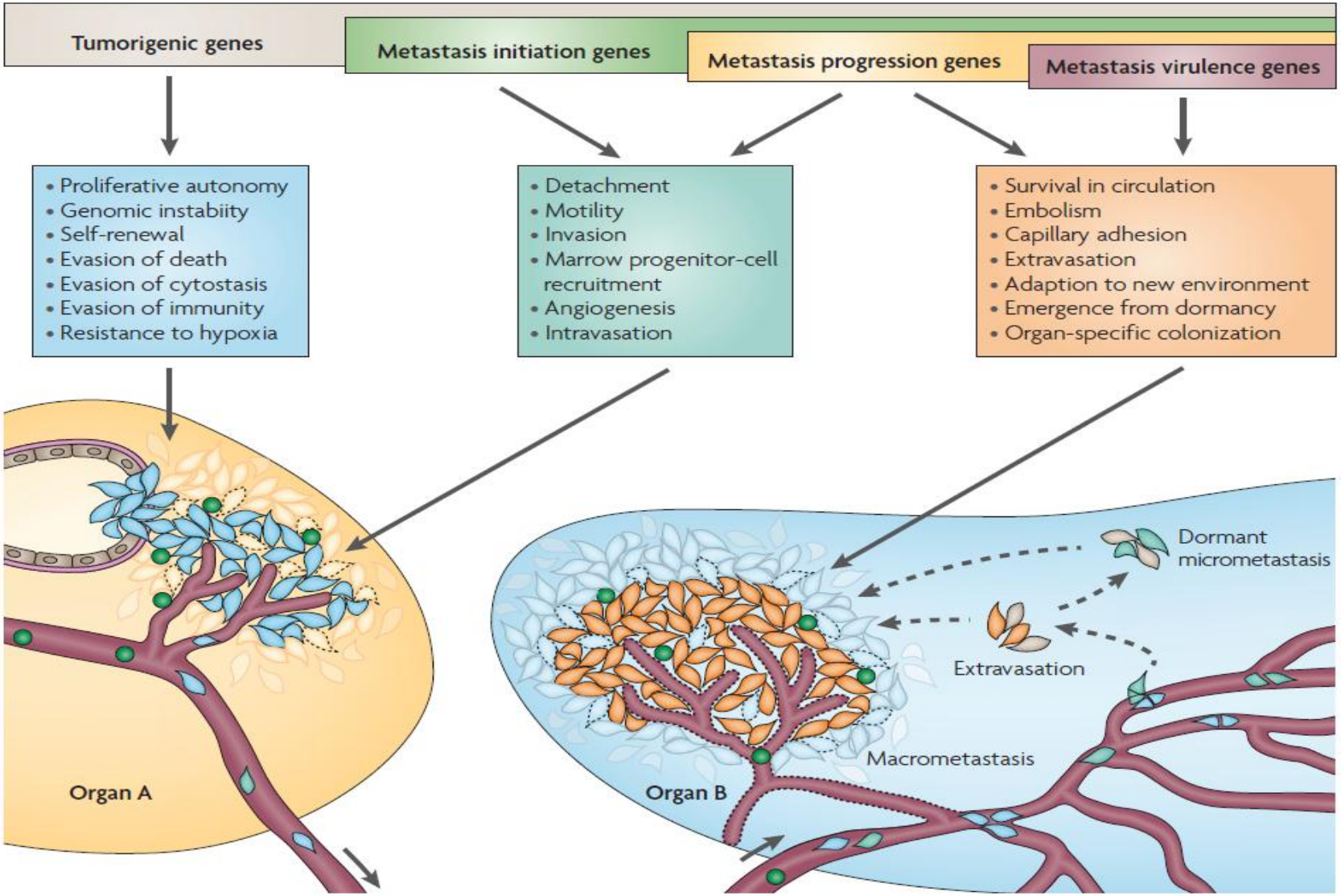

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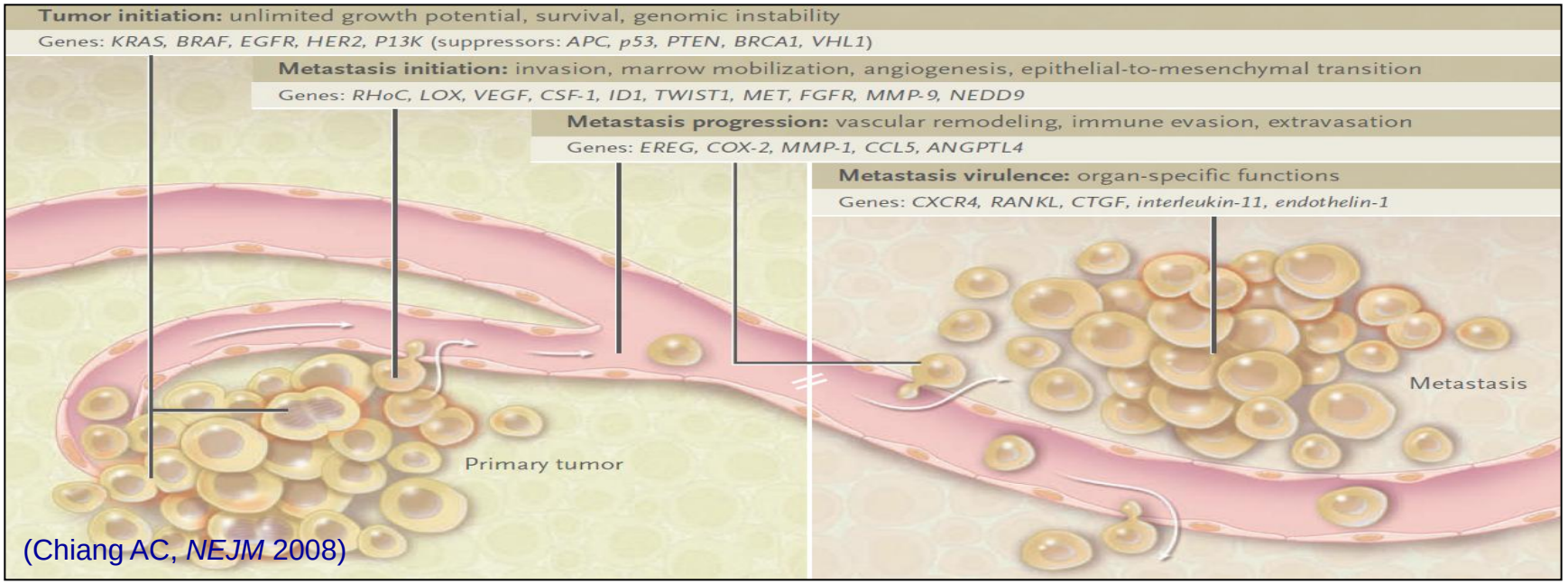
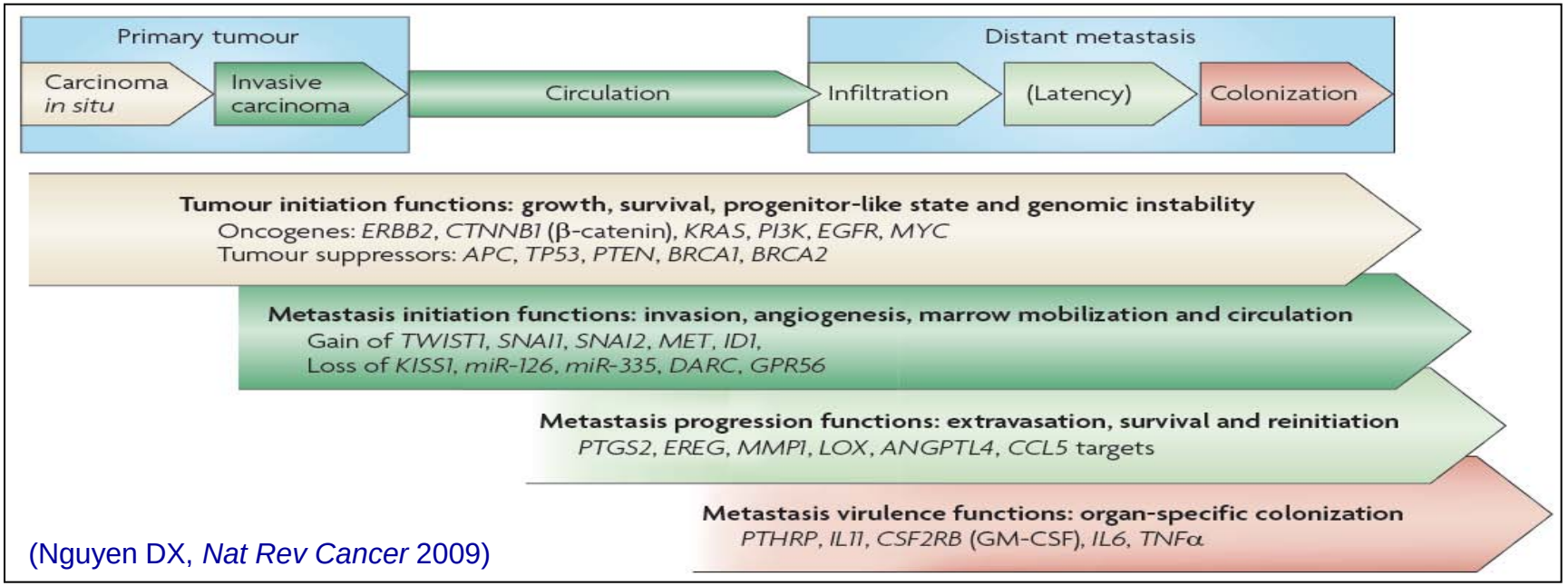
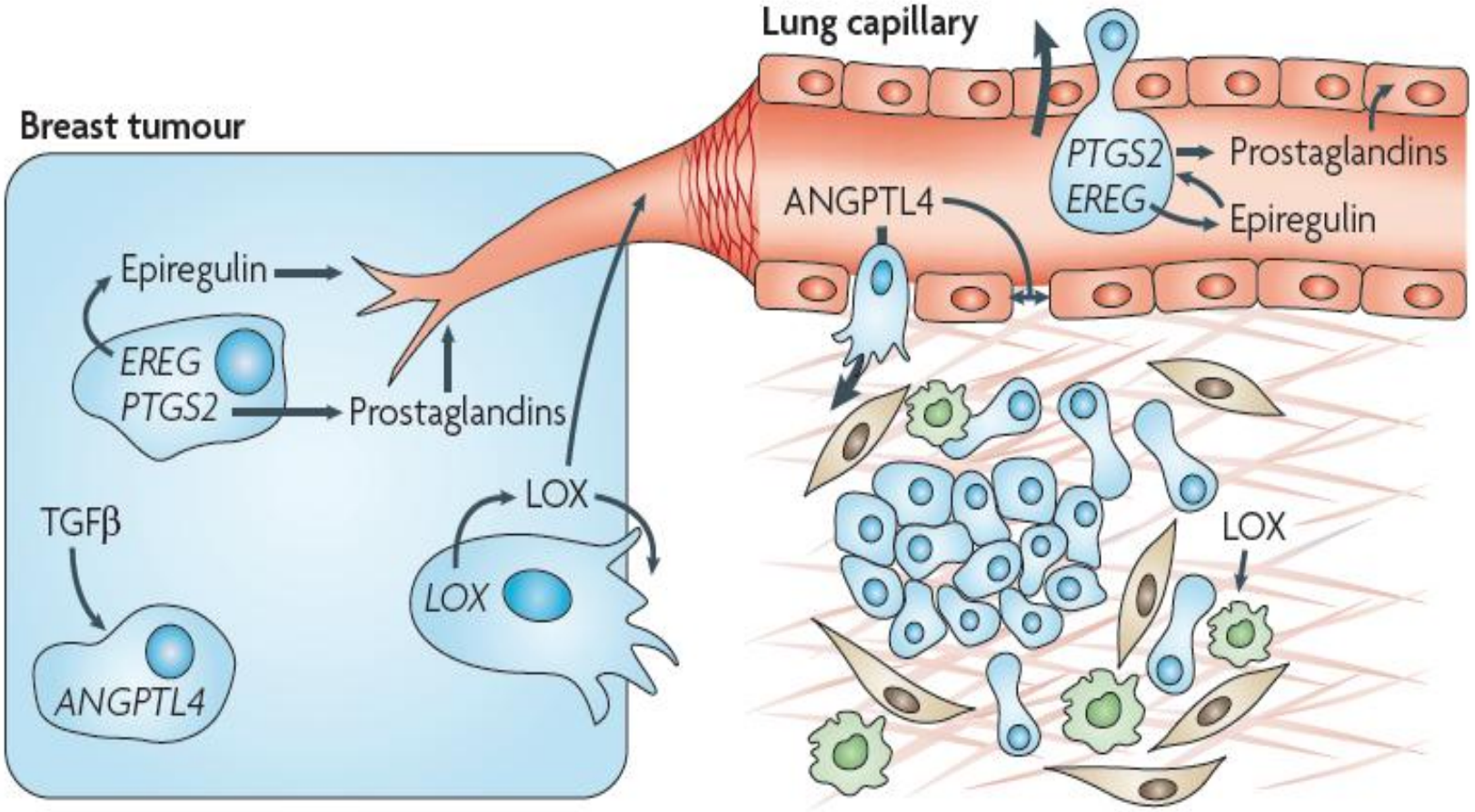


(Chiang AC, *NEJM* 2008)



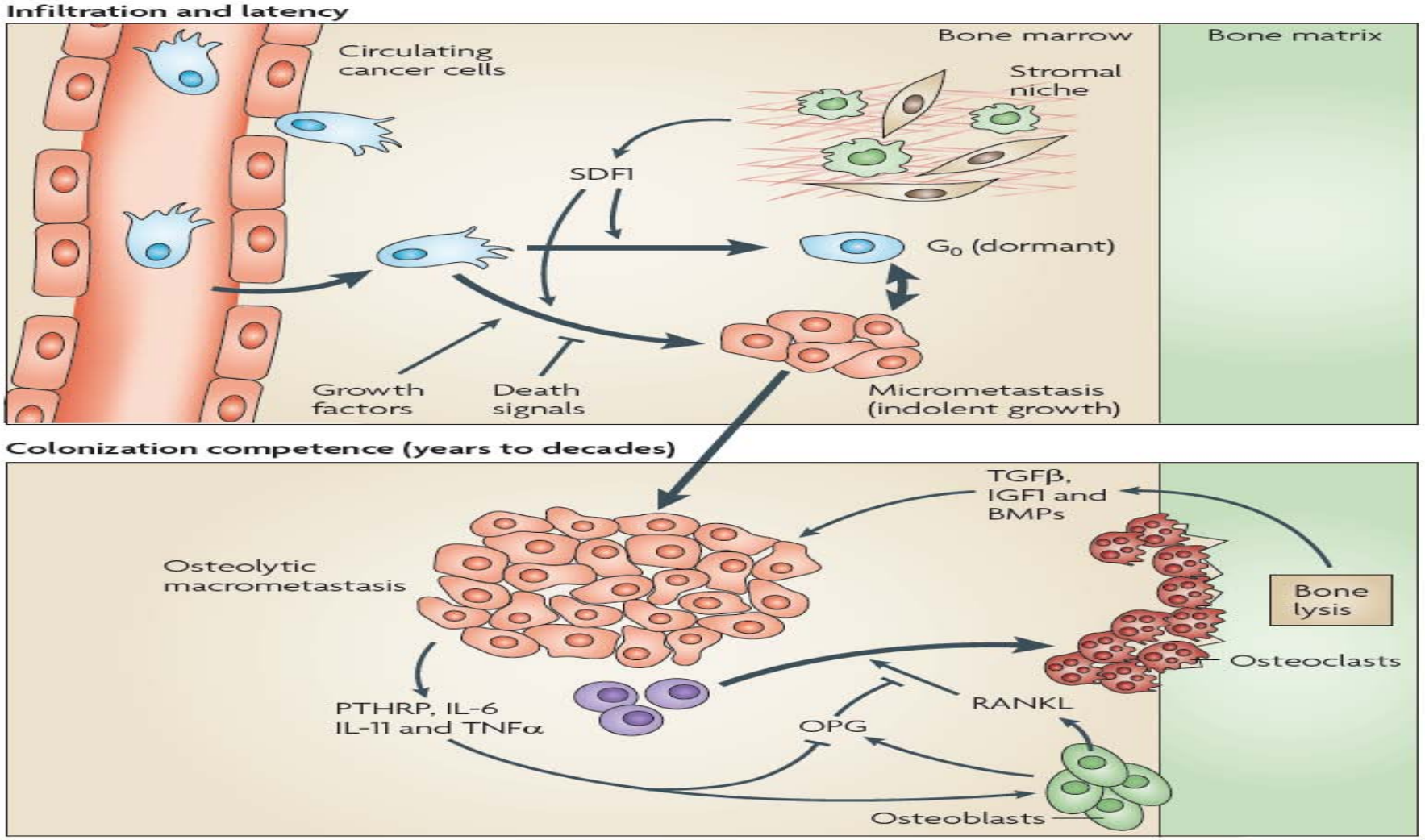
(Nguyen DX, *Nat Rev Cancer* 2009)

DI CĂN PHỔI



Epiregulin (*EREG), prostaglandin G/H synthase 2 (PTGS2)*
Lysyl oxidase (*LOX)*, angiopoietin-like 4 (ANGPTL4), transforming growth factor-β (TGFβ)

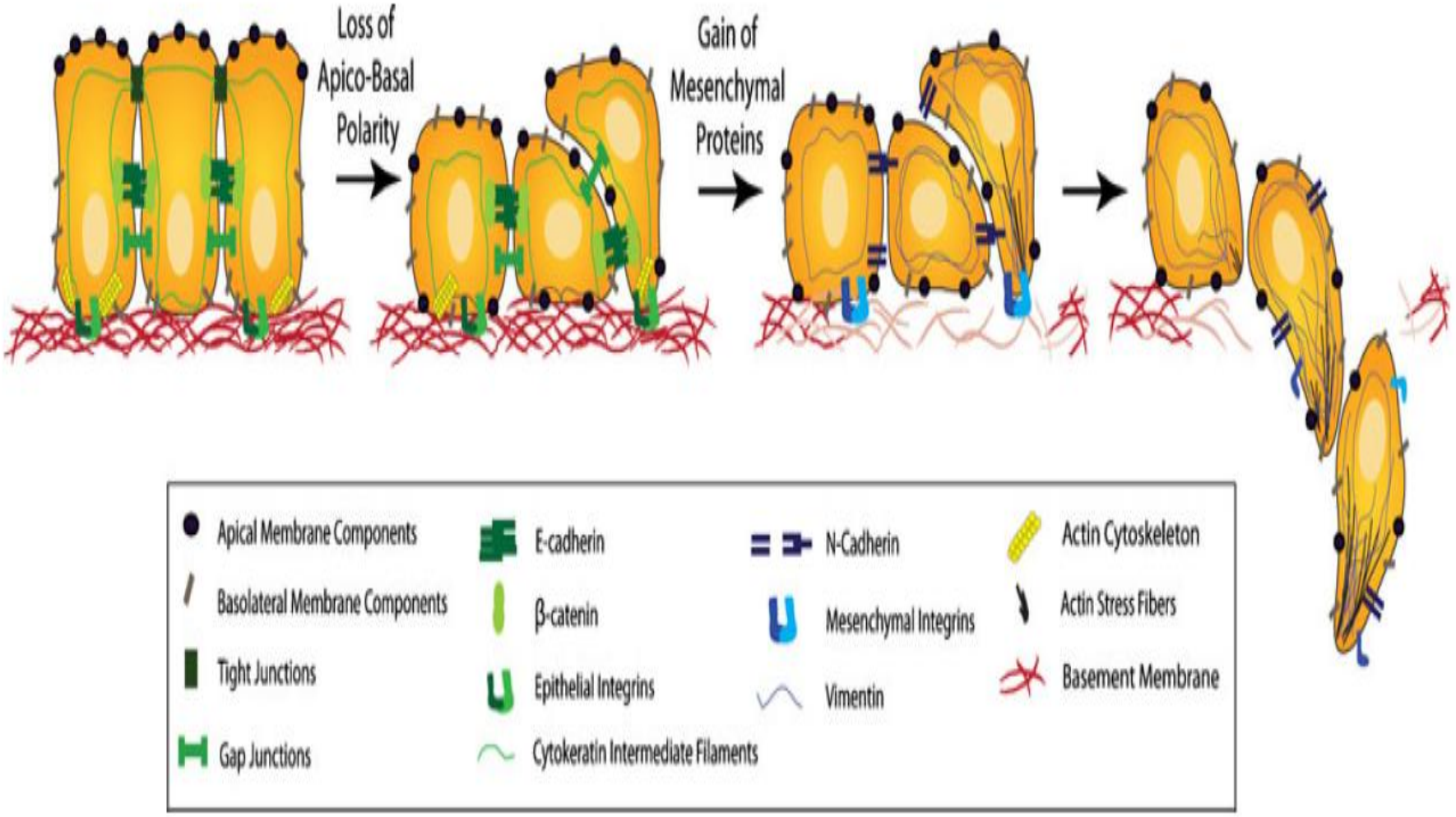
DI CĂN XƯƠNG



SDF1: stromal cell-derived factor 1, **PTHRP**: parathyroid hormone-related protein, **RANKL**: receptor activator of nuclear factor-κB ligand , **OPG**: osteoprotegerin, **TGFβ**: transforming growth factor-β, **BMPs**: bone morphogenetic proteins, **IGFs**: insulin-like growth factors.

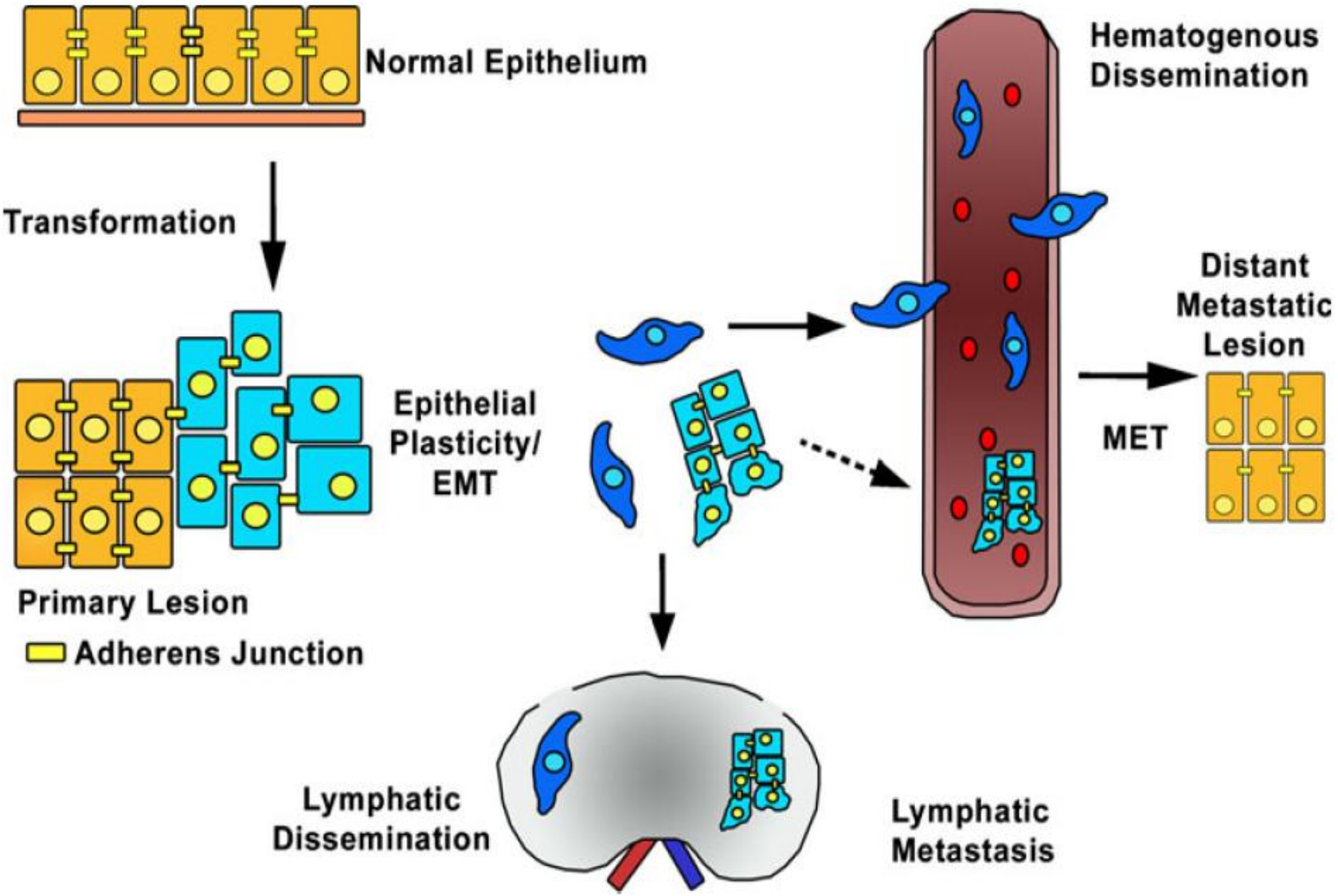
Epithelial – Mesenchymal Transition

CÁC THAY ĐỔI CHÍNH TRONG EMT



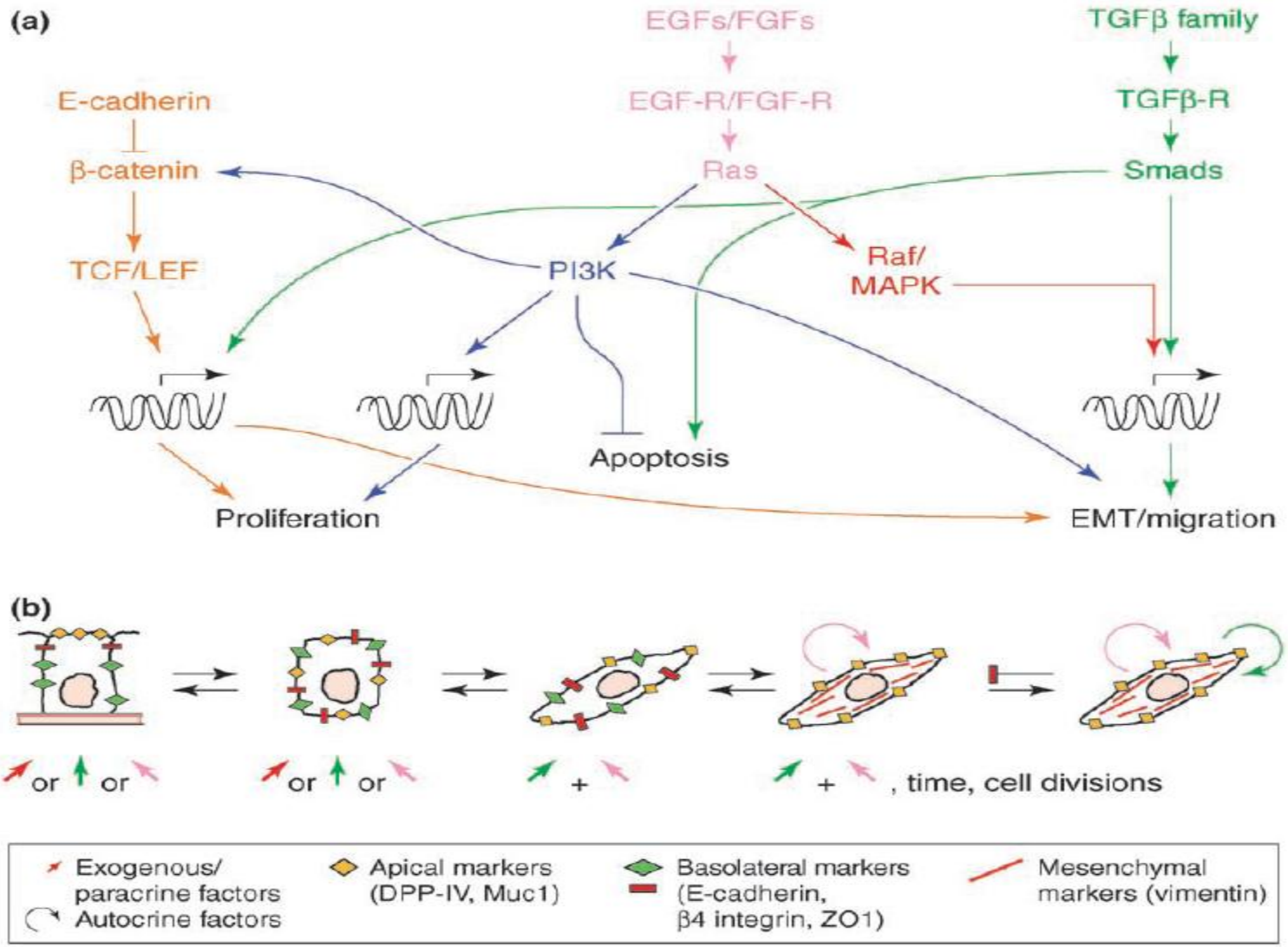
(Micalizzi DS, J Mammary Gland Biol Neoplasia 2010)

EMT THÚC ĐẨY DI CĂN

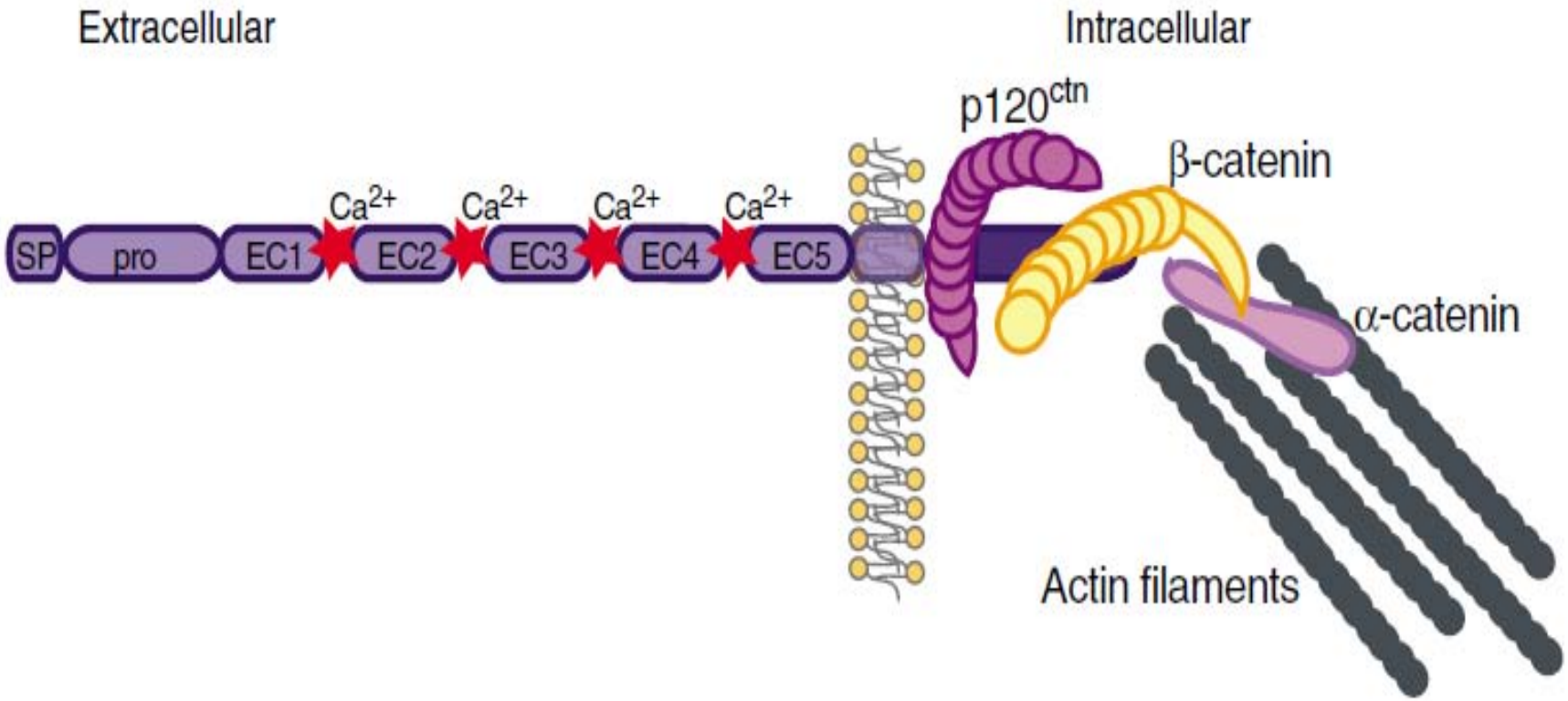


(Micalizzi DS, J Mammary Gland Biol Neoplasia 2010)

CƠ CHẾ PHÂN TỬ CỦA EMT



CẤU TRÚC CỦA CADHERIN



signal peptide (SP), pro-region (pro), extracellular domain (EC1-EC5)

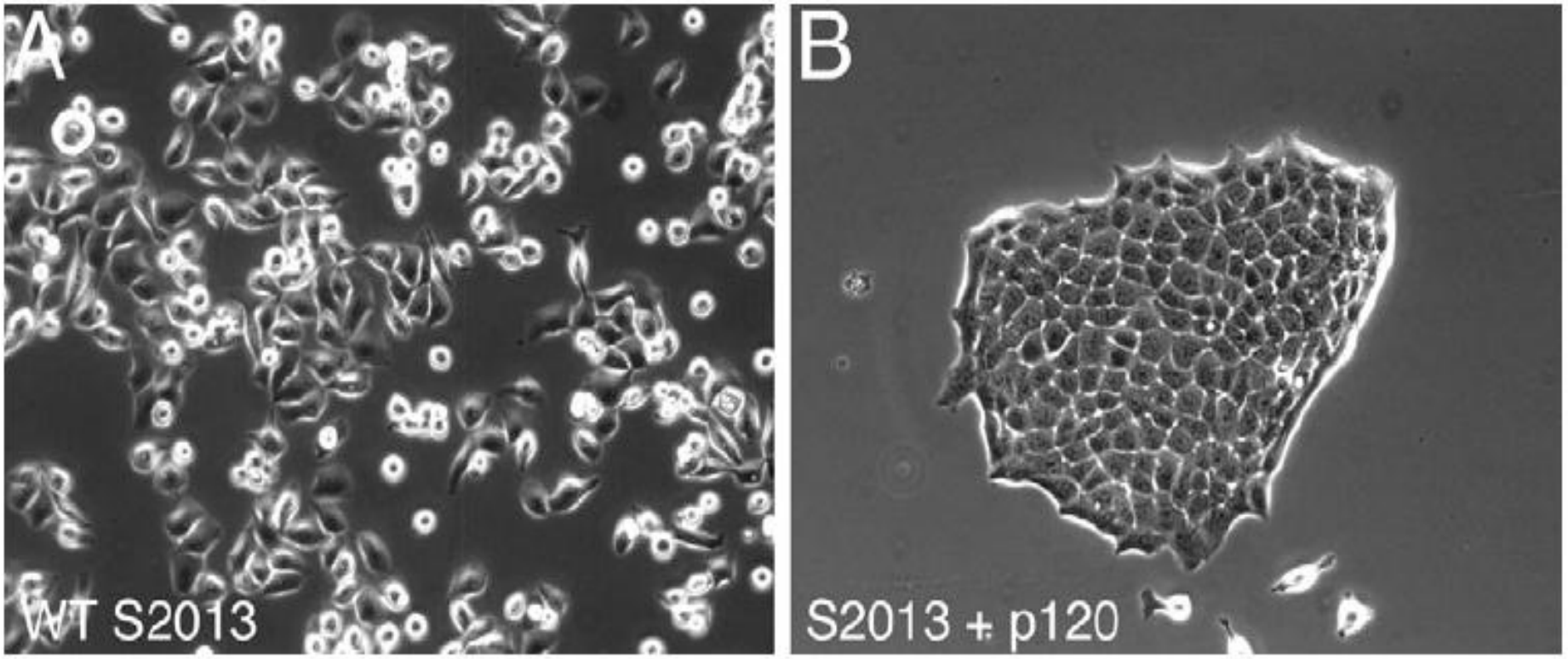
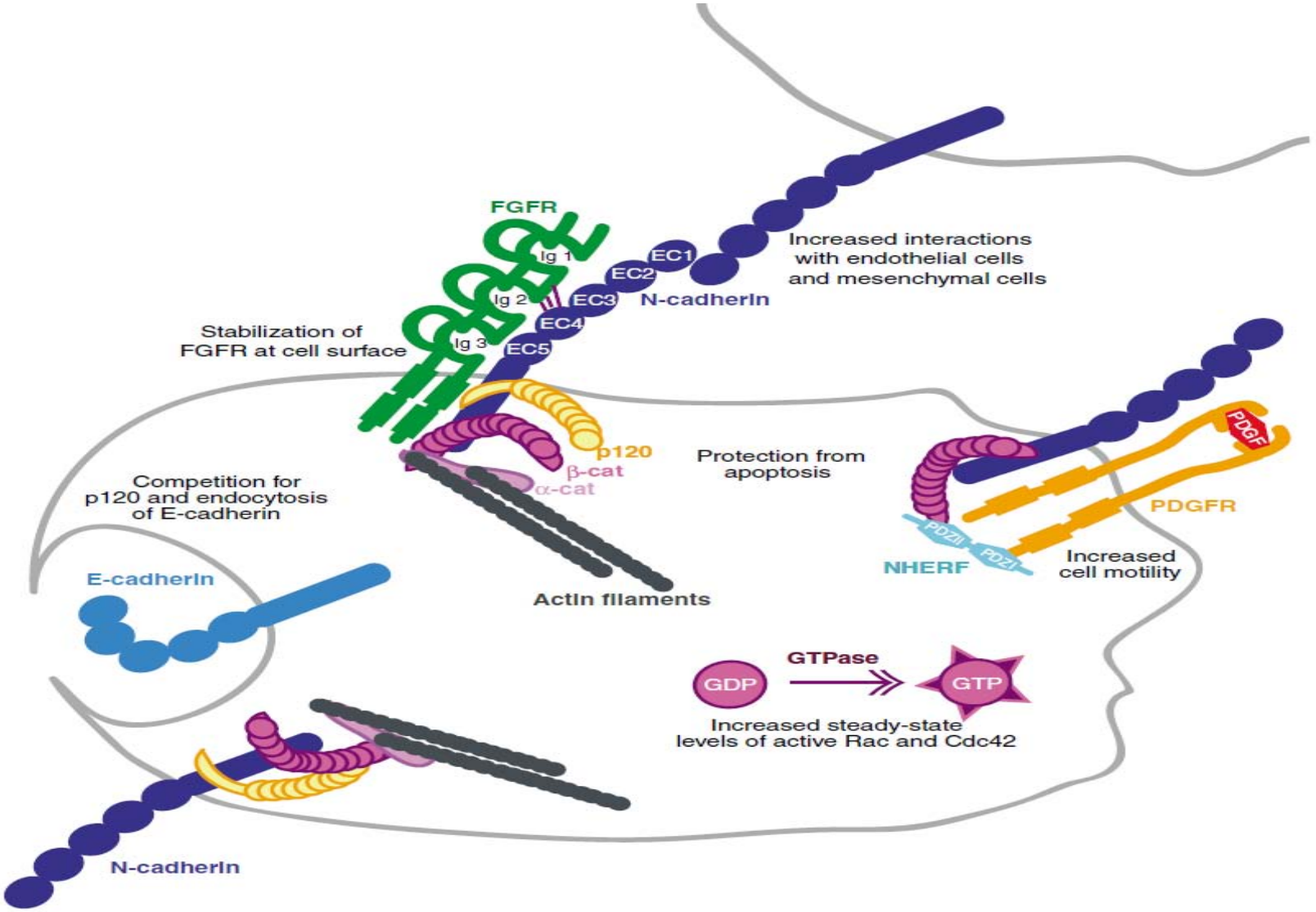


Fig. 3. p120-catenin promotes epithelial morphology in p120-deficient S2013 pancreatic cancer cells. Parental S2013 cells (wild type; WT) are scattered (A), whereas cells expressing p120-catenin form compact colonies of cobblestone-like cells (B).

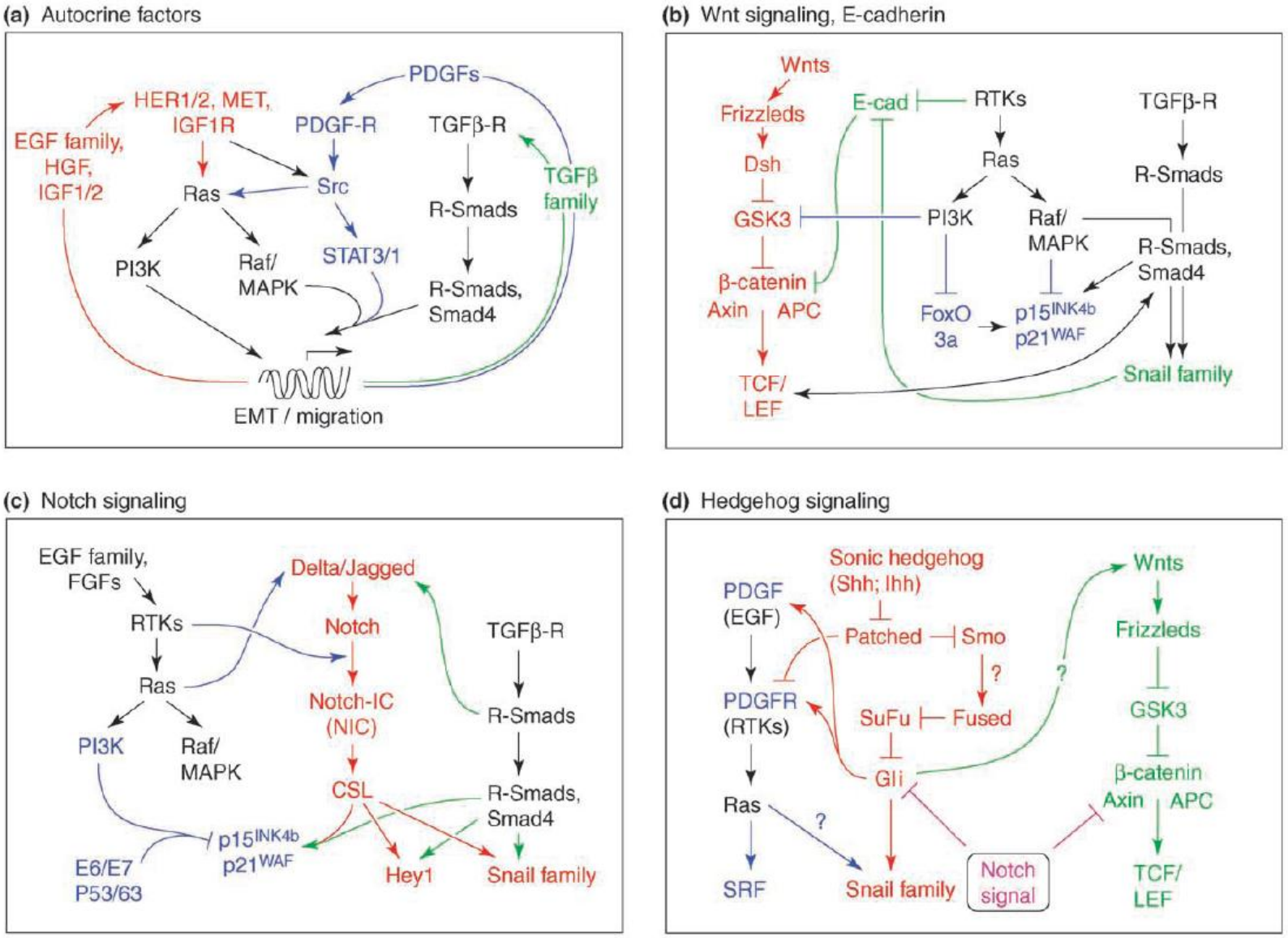
(Wheelock MJ, Journal of Cell Science 2008)

E-CADHERIN VÀ N-CADHERIN

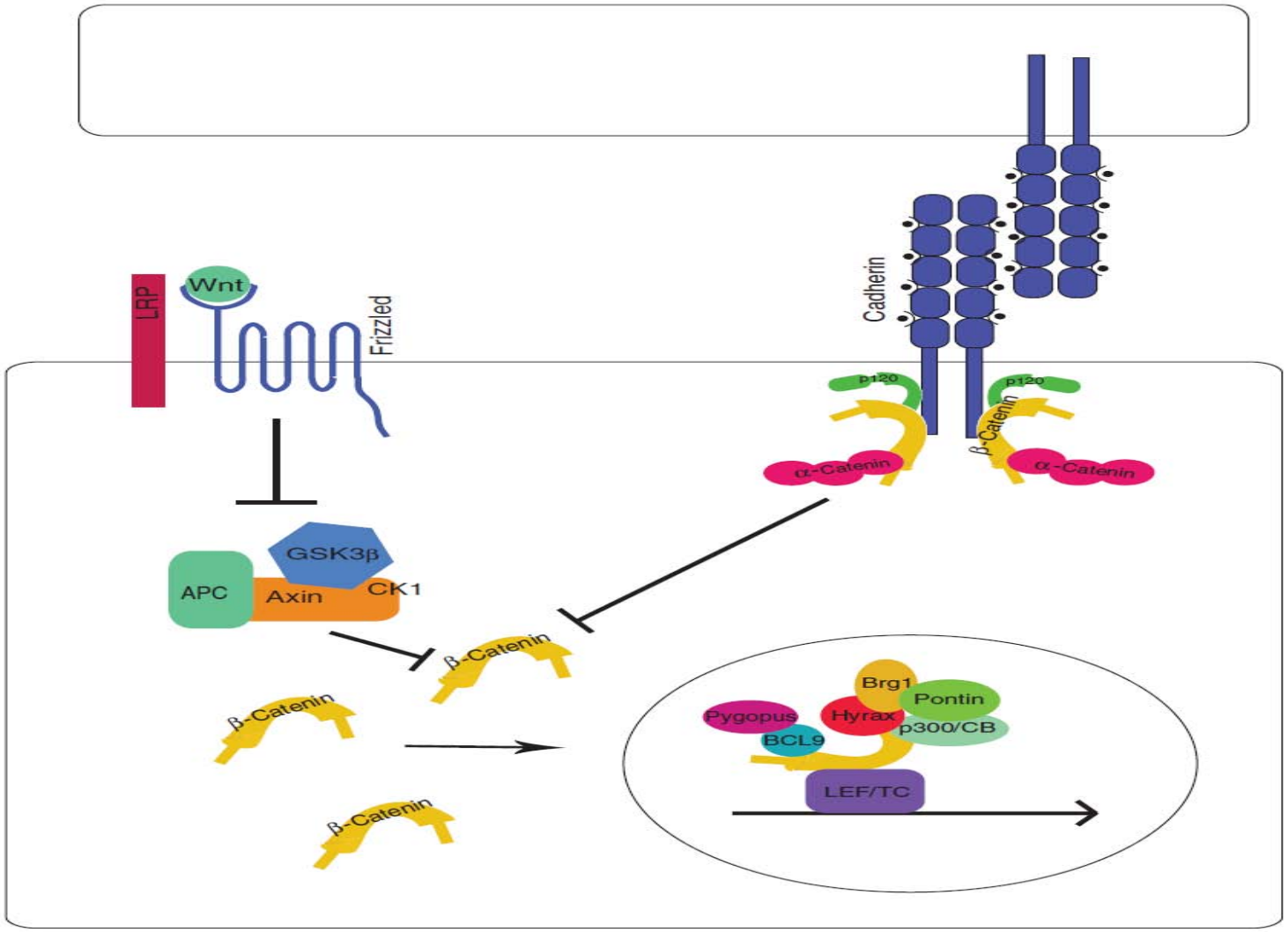


(Wheelock MJ, Journal of Cell Science 2008)

MỘT SỐ TÍN HIỆU ẢNH HƯỞNG TRÊN EMT

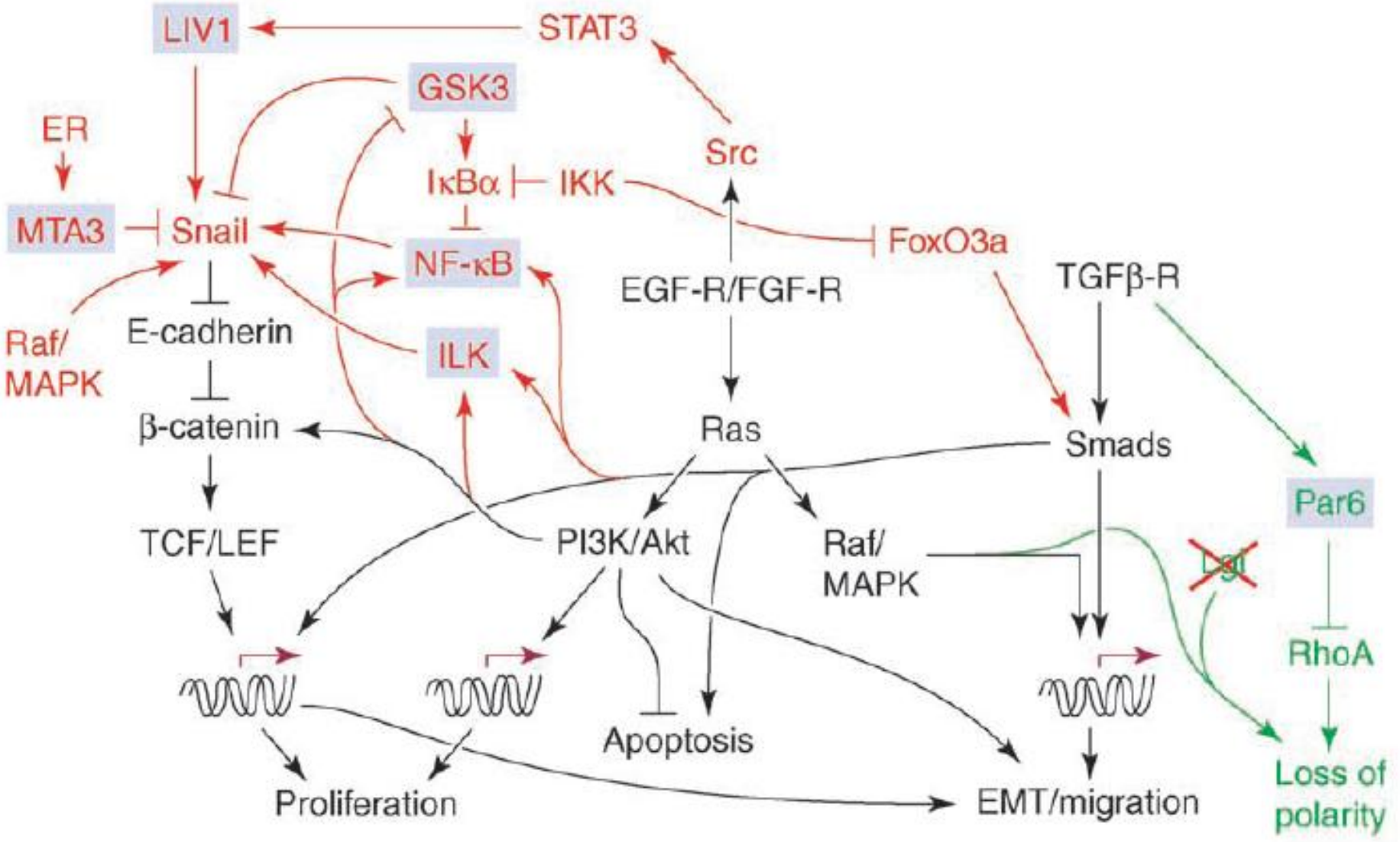


ĐIỀU HÒA BETA-CATENIN

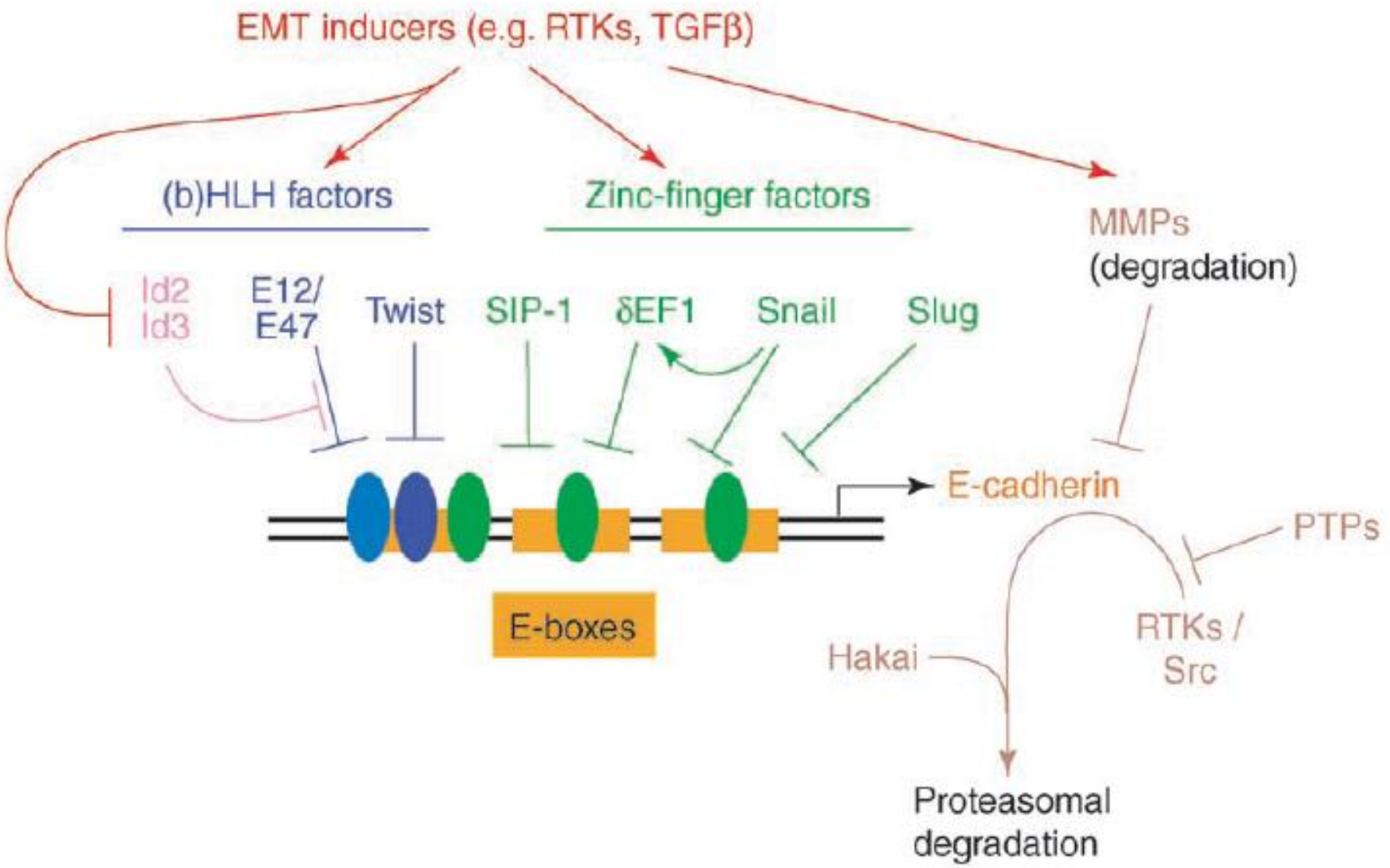


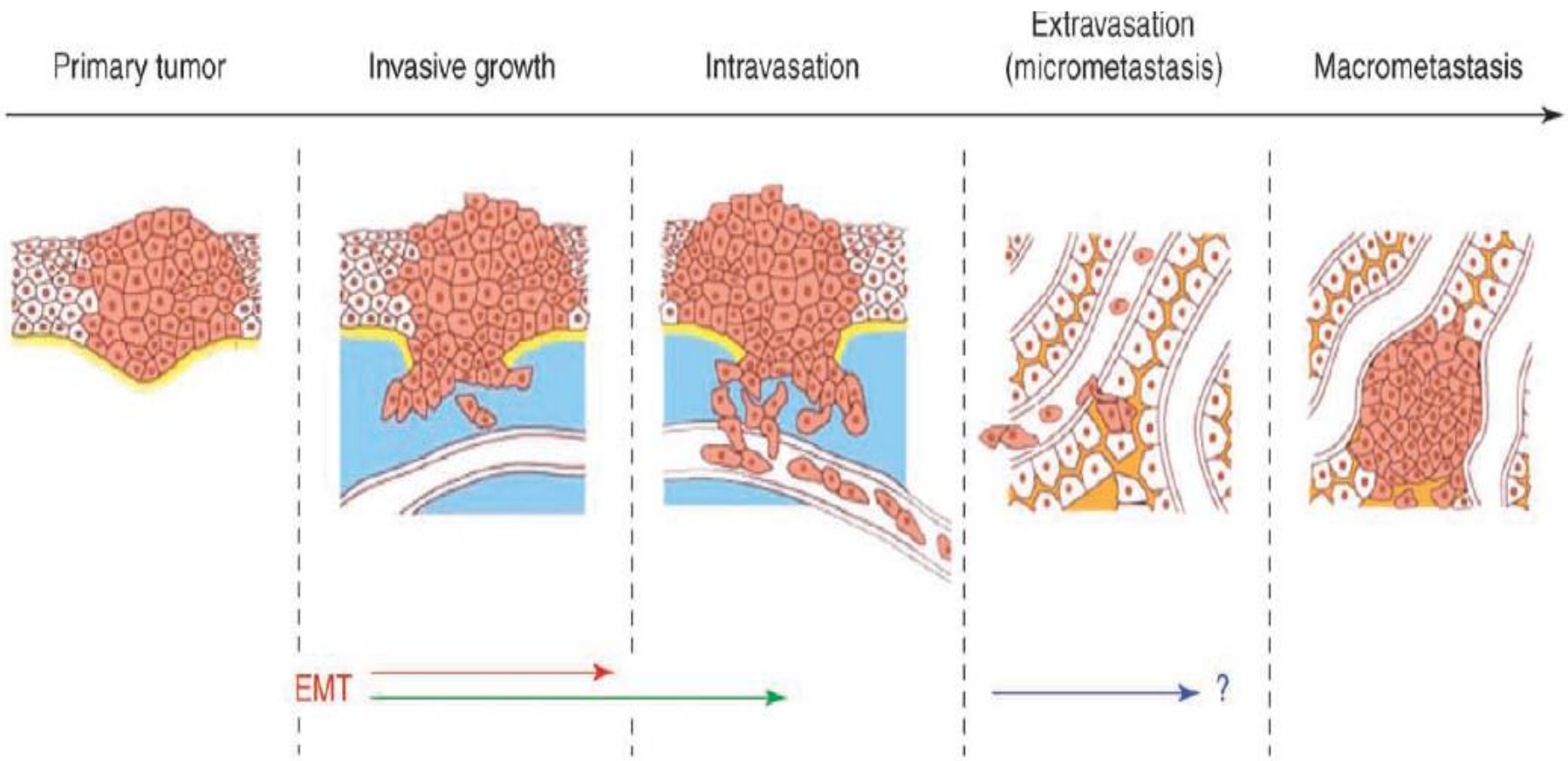
(Jeanes A, Oncogene 2008)

MẠNG LƯỚI ĐIỀU HÒA EMT



ĐIỀU HÒA BIỂU HIỆN E-CADHERIN




Primary tumor
Invasive growth
Intravasation
Extravasation
(micrometastasis)
Macrometastasis
EMT
?

FAK và SRC

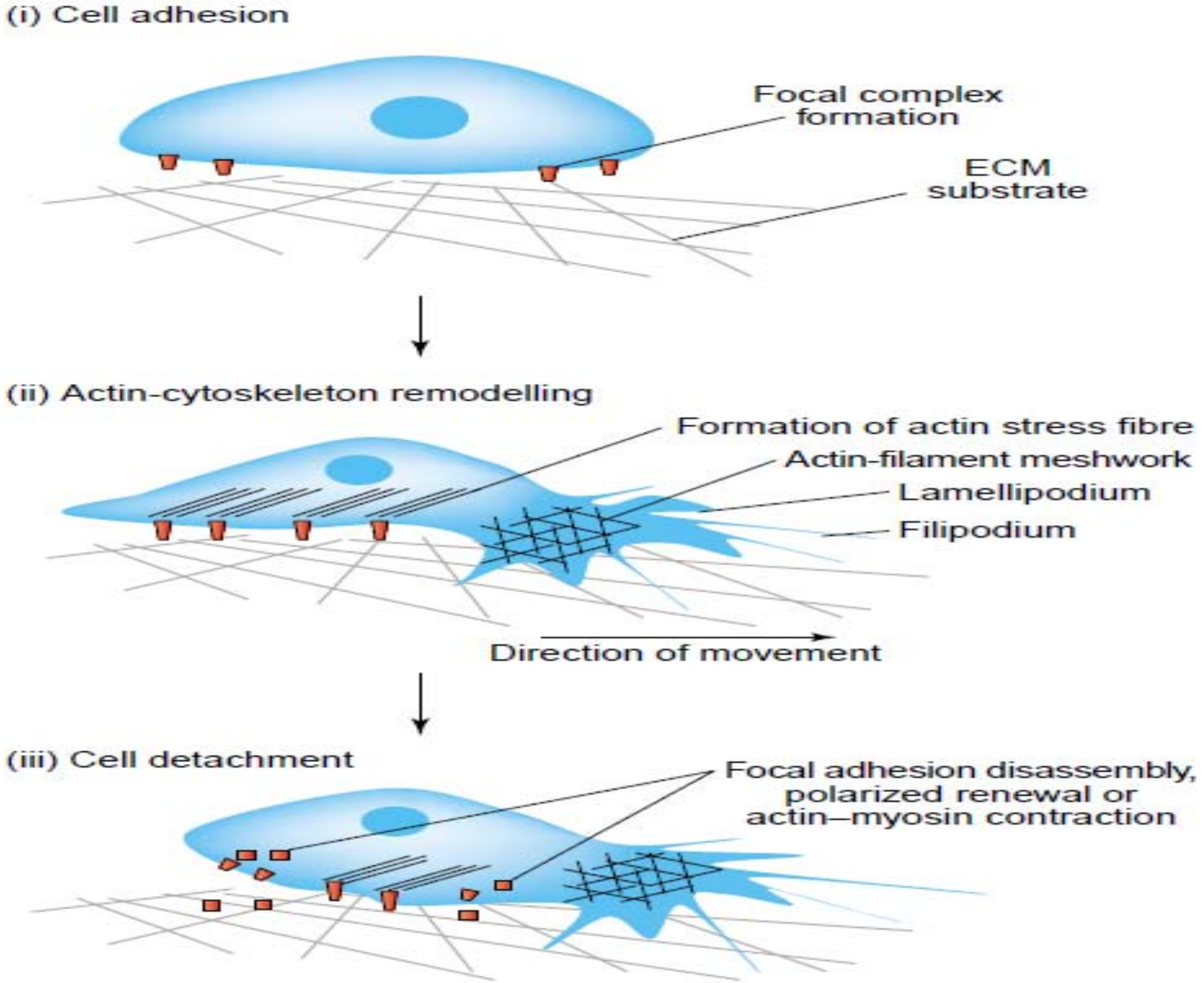

(i) Cell adhesion
Focal complex formation
ECM substrate
(ii) Actin-cytoskeleton remodelling
Formation of actin stress fibre
Actin-filament meshwork
Lamellipodium
Filipodium
Direction of movement
(iii) Cell detachment
Focal adhesion disassembly, polarized renewal or actin–myosin contraction

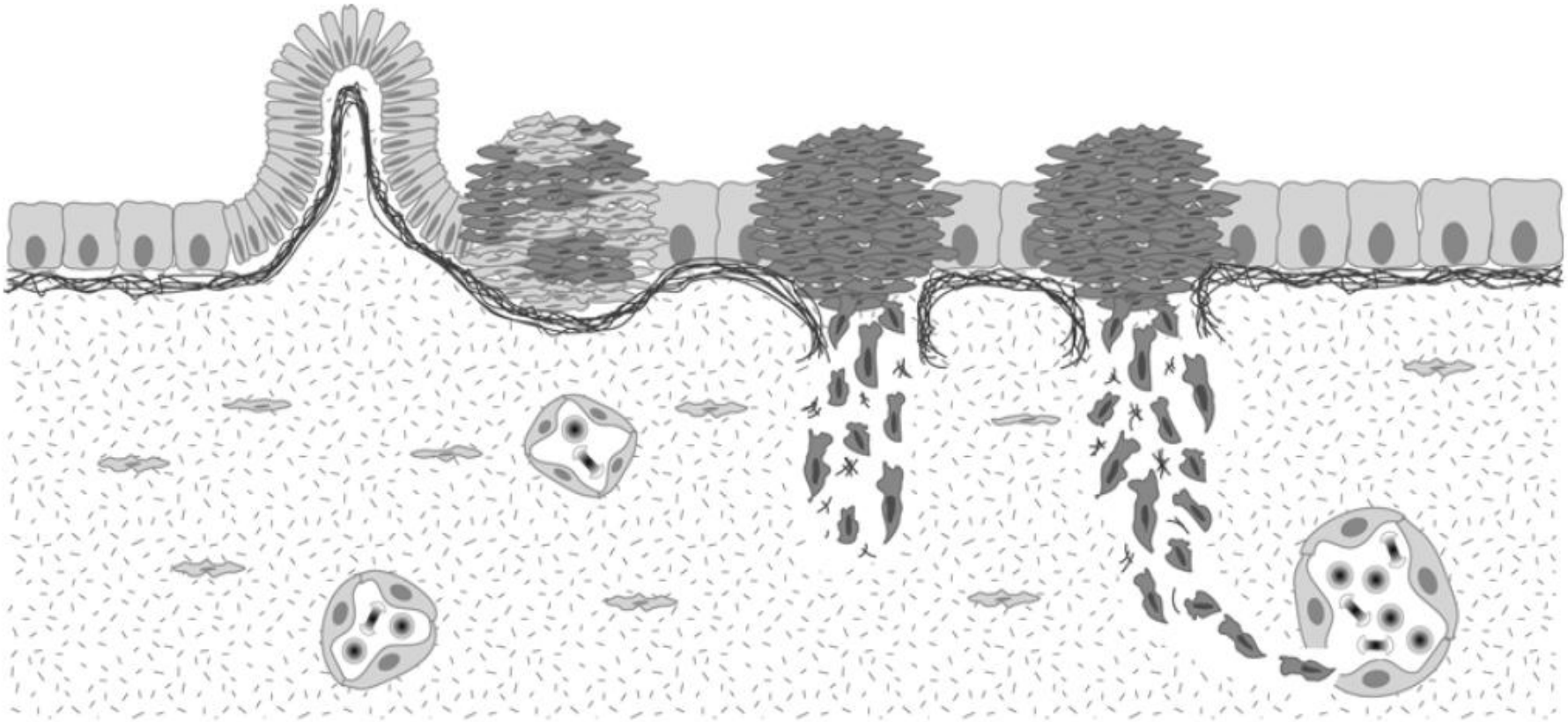
Table 1. FAK expression in tumors

Tissue	N	B	PI	I	M	Method
Breast		–		+ + +	+ + + +	Northern
	+/–			+ + +	+ + + +	Western
		+	+ + +	+ + +		IHC
	+/–			+/+ + +		IHC
Colon	–	+		+ + + +	+ + + + +	Northern
	+	–	+ + +	+ + +	+ + +	Western
	+				+ + +	Western
		+	+ + +	+ + +		IHC
	+			+ + +	+	Western, IHC
	+/–			+ +/+ + +		IHC
Thyroid	+	+		+/+ + +***	+ + + +	Western
Prostate	+/–	+		+	+ + +	RT-PCR, Western
	+/+ + +	+/+ + +	+ + +	+ + +	+ + +	IHC
Oral cavity**	–/+ +		+/+ + +	+/+ + + +		IHC
Liver	–			+ + +		Western
	+			+ + + + +		RT-PCR
	+/–			+ +/+ + +		IHC
Stomach	+/–			+ +/+ + +		IHC
Ovary	+			+ + + +		Western
Sarcoma**	+ +	+/–		+ + + +		Western
Brain/astrocytes	–	–	+	–	+ + + + +	Western
	–		–	+	+ +	IHC
		–	+ +	+ +	+ +	IHC
	+			+ + +		Western
Head neck				>2 copies		FISH

(N, normal; B, benign; PI, preinvasive; M, metastatic; IHC, immunohistochemistry)

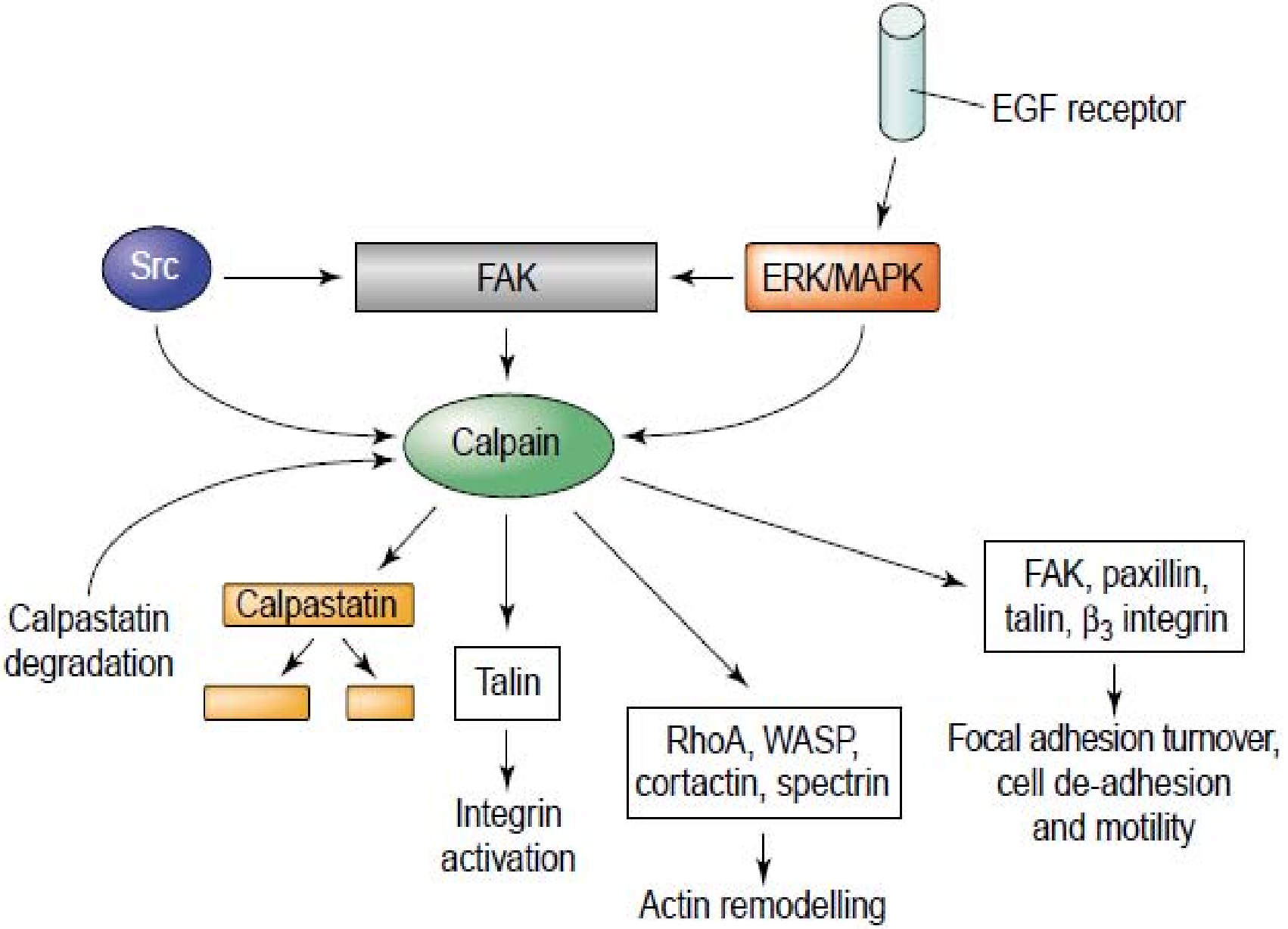
(Gabarra-Niecko V, *Cancer and Metastasis Reviews* 2003)

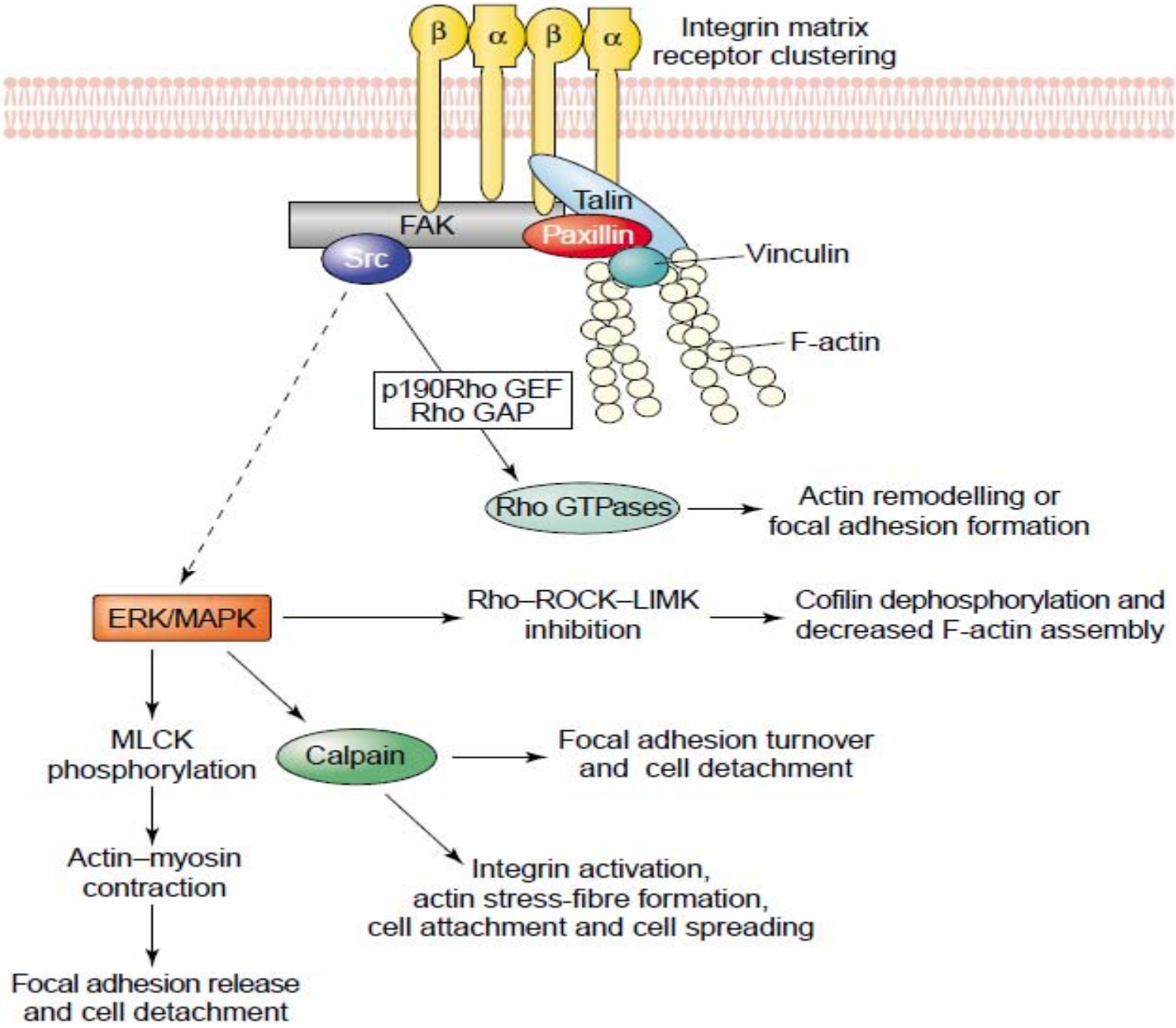
FAK VÀ DIỄN TIẾN UNG THƯ

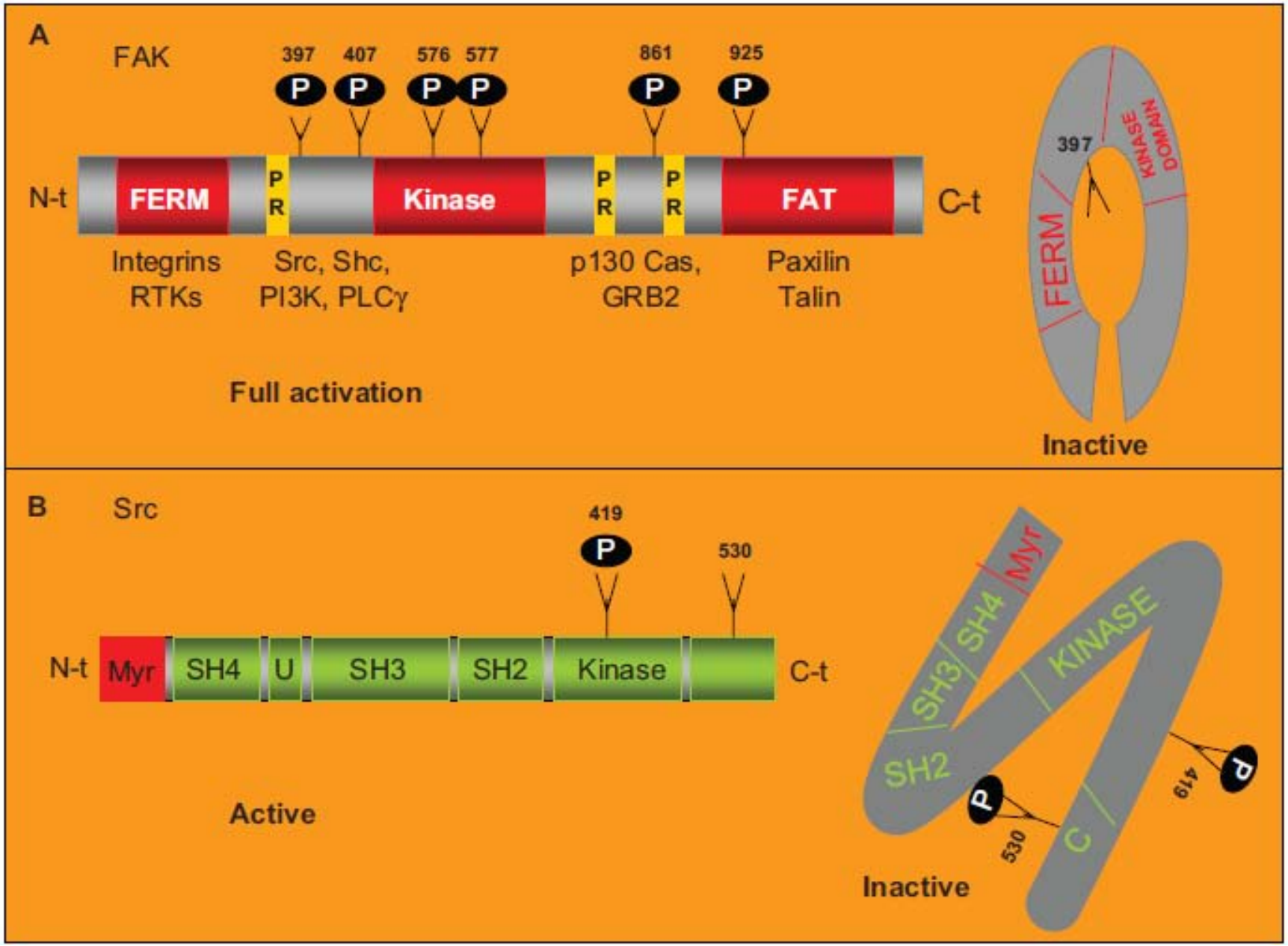


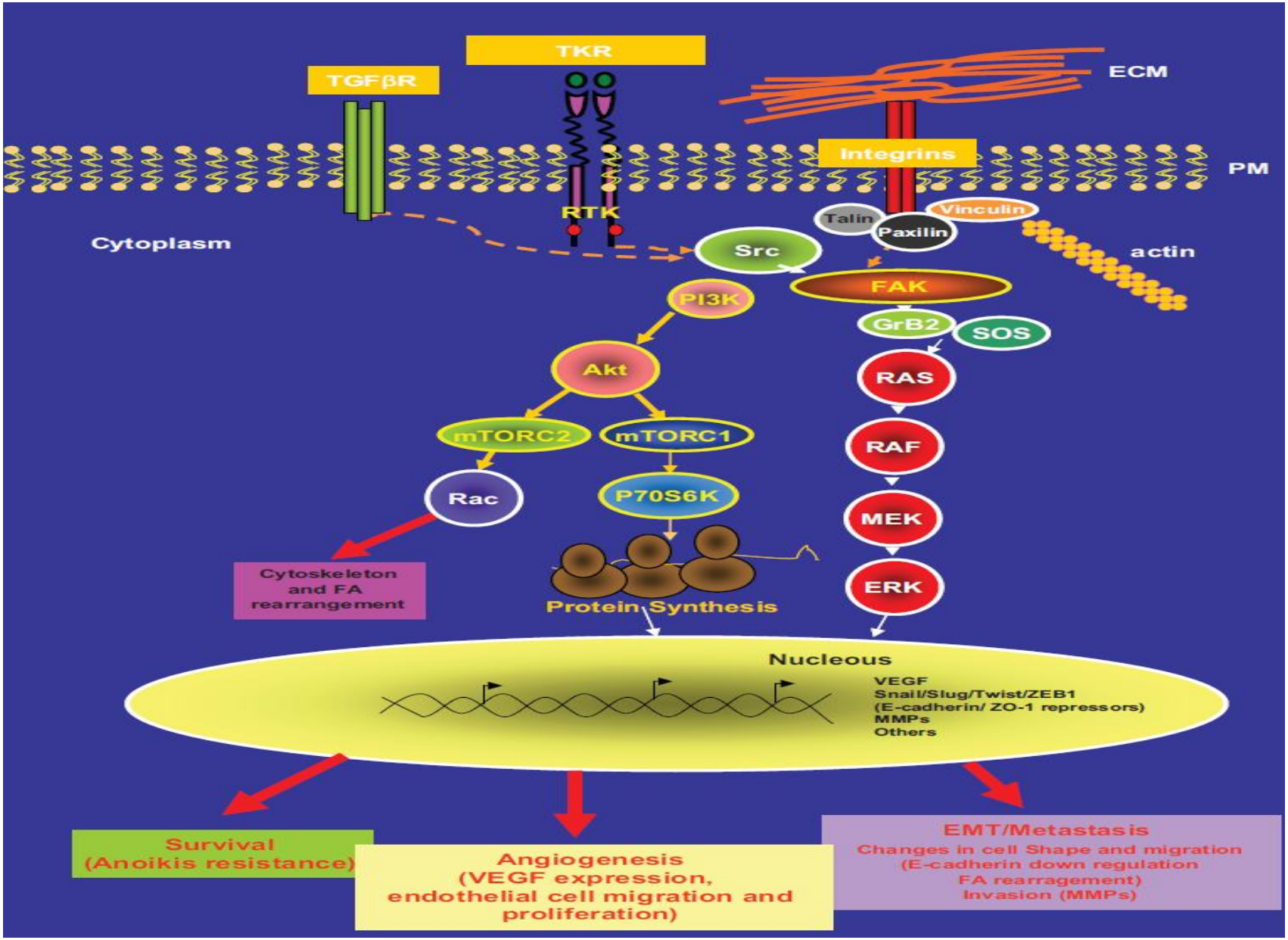
In normal epithelium and benign hyperplasias, FAK is expressed at low levels. In preinvasive, invasive and metastatic lesions, FAK is overexpressed (dark cells). Through its ability to regulate cell survival, growth, migration and invasion, FAK may influence tumor cell behavior and therefore promote malignancy

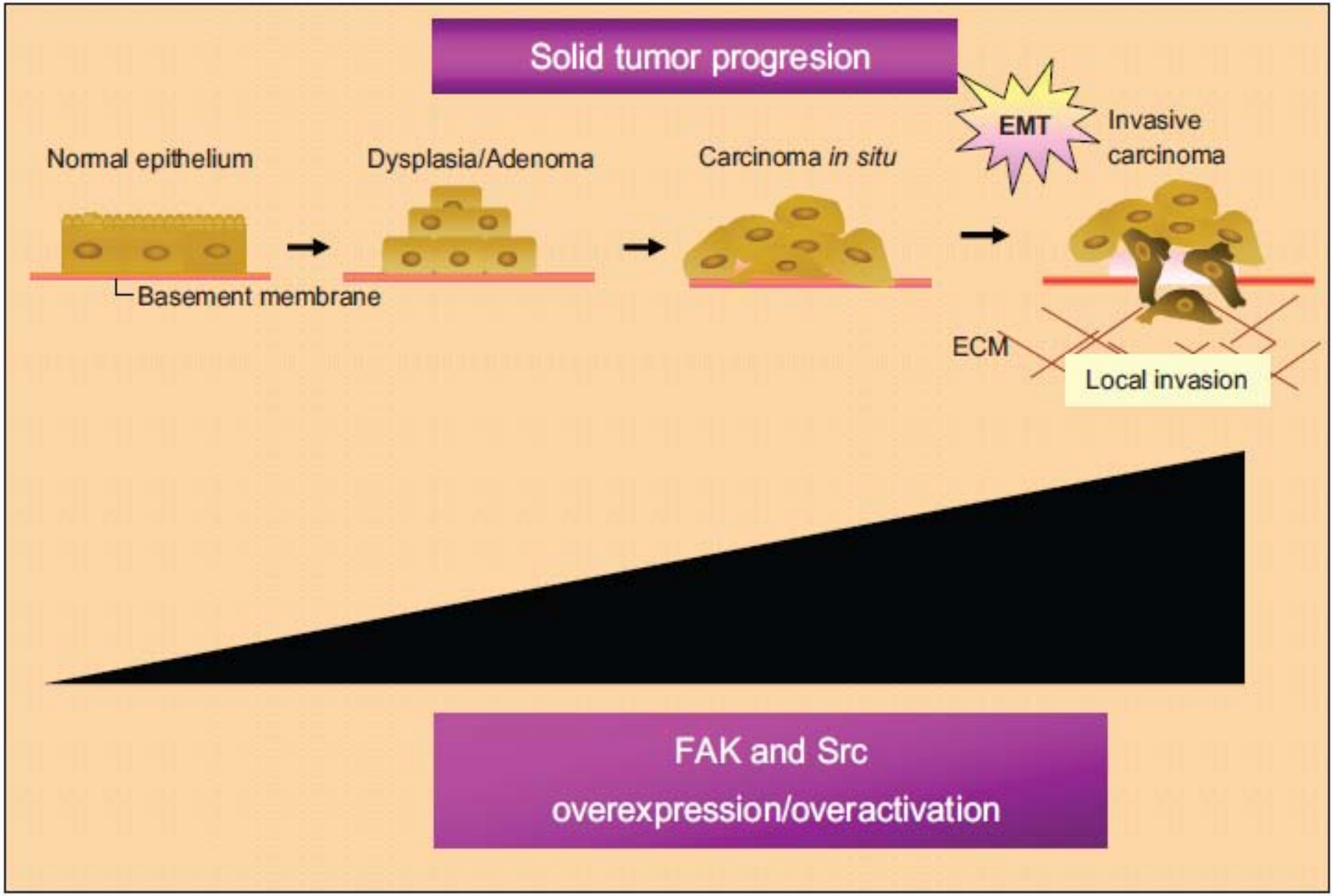
TƯƠNG TÁC FAK-SRC



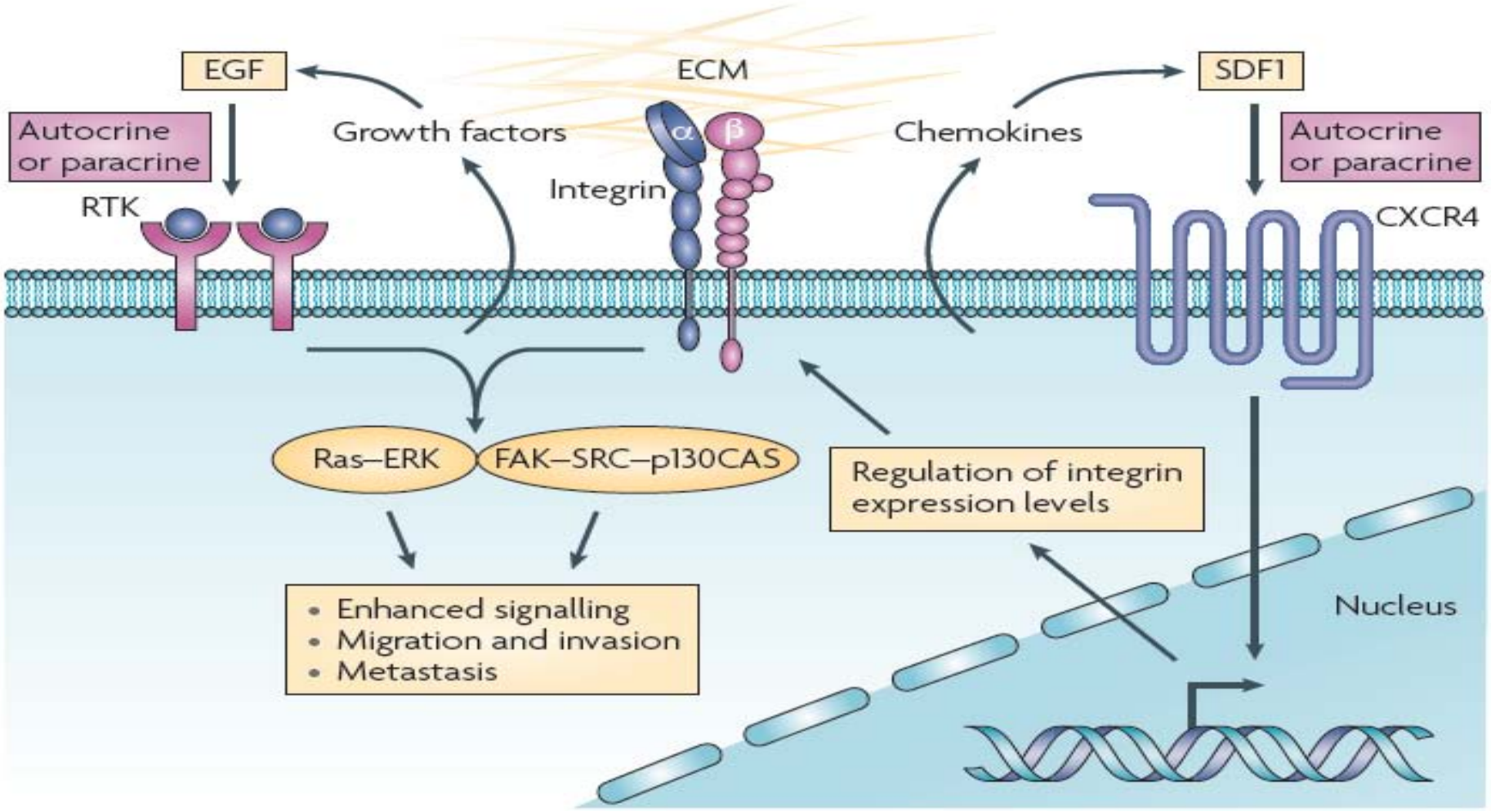

β
α
β
α
Integrin matrix
receptor clustering
Talin
FAK
Paxillin
Src
Vinculin
F-actin
p190Rho GEF
Rho GAP
Rho GTPases
Actin remodelling or
focal adhesion formation
ERK/MAPK
Rho–ROCK–LIMK
inhibition
Cofilin dephosphorylation and
decreased F-actin assembly
MLCK
phosphorylation
Calpain
Focal adhesion turnover
and cell detachment
Actin–myosin
contraction
Integrin activation,
actin stress-fibre formation,
cell attachment and cell spreading
Focal adhesion release
and cell detachment


A
FAK
397
407
576
577
861
925
P
N-t
FERM
PR
Kinase
PR
PR
FAT
C-t
Integrins
RTKs
Src, Shc,
PI3K, PLCγ
p130 Cas,
GRB2
Paxilin
Talin
Full activation
397
KINASE DOMAIN
FERM
Inactive
B
Src
419
530
N-t
Myr
SH4
U
SH3
SH2
Kinase
C-t
Active
Myr
SH4
SH3
KINASE
SH2
C
419
530
Inactive


TKR
TGFβR
ECM
Integrins
PM
RTK
Talin
Vinculin
Paxilin
Cytoplasm
actin
Src
FAK
PI3K
GrB2
SOS
Akt
RAS
mTORC2
mTORC1
RAF
Rac
P70S6K
MEK
Cytoskeleton and FA rearrangement
Protein Synthesis
ERK
Nucleous
VEGF
Snail/Slug/Twist/ZEB1
(E-cadherin/ ZO-1 repressors)
MMPs
Others
Survival
(Anoikis resistance)
Angiogenesis
(VEGF expression, endothelial cell migration and proliferation)
EMT/Metastasis
Changes in cell Shape and migration
(E-cadherin down regulation
FA rearragement)
Invasion (MMPs)


Solid tumor progresion
EMT
Invasive carcinoma
Normal epithelium
Dysplasia/Adenoma
Carcinoma *in situ*
Basement membrane
ECM
Local invasion
FAK and Src overexpression/overactivation

TƯƠNG TÁC INTEGRIN-GROWTH FACTOR VÀ INTEGRIN-CYTOKINE RECEPTOR



THUỐC ỨC CHẾ FAK VÀ SRC

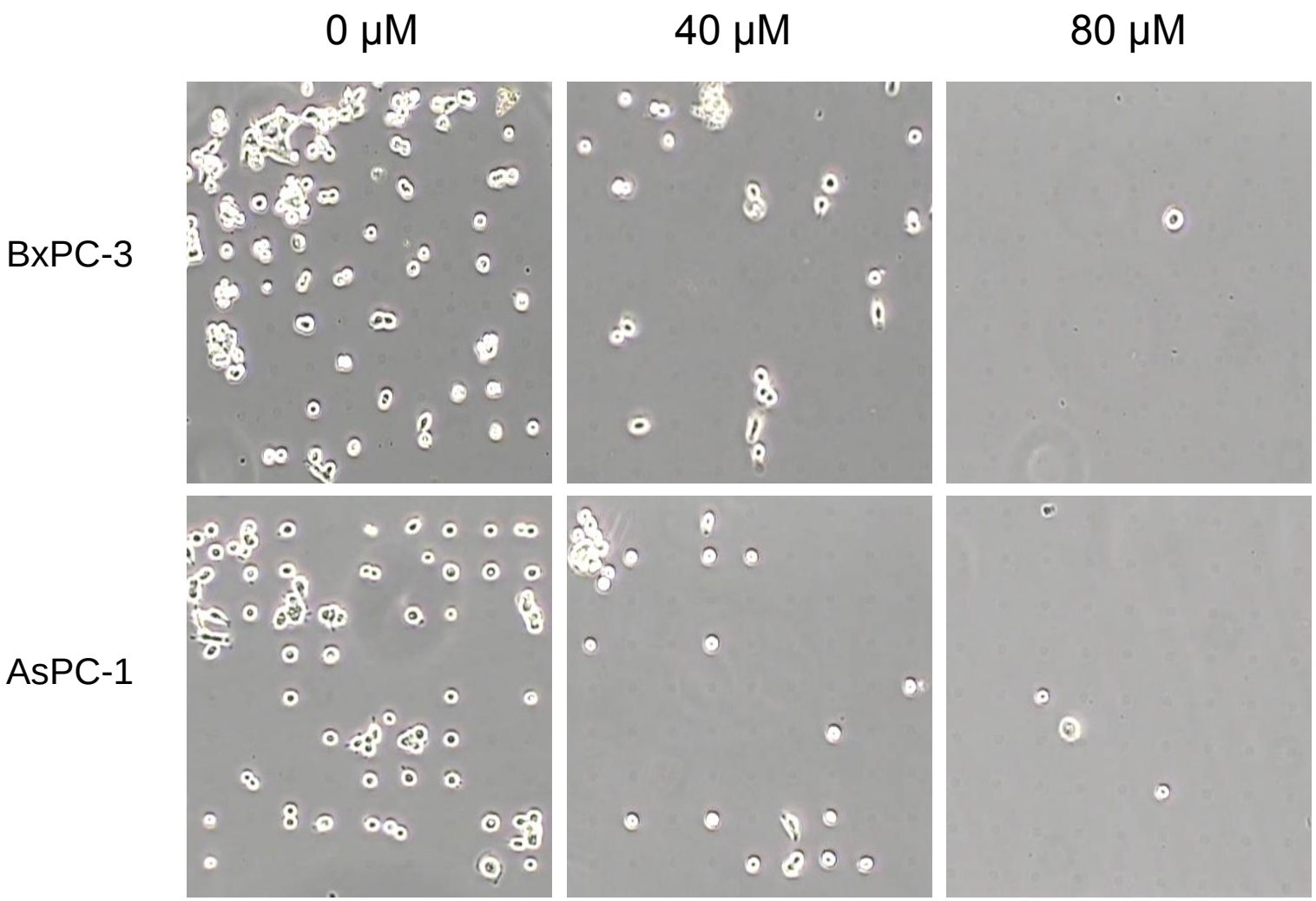
Table 1 Summary of FAK and Src inhibitors under clinical and preclinical development

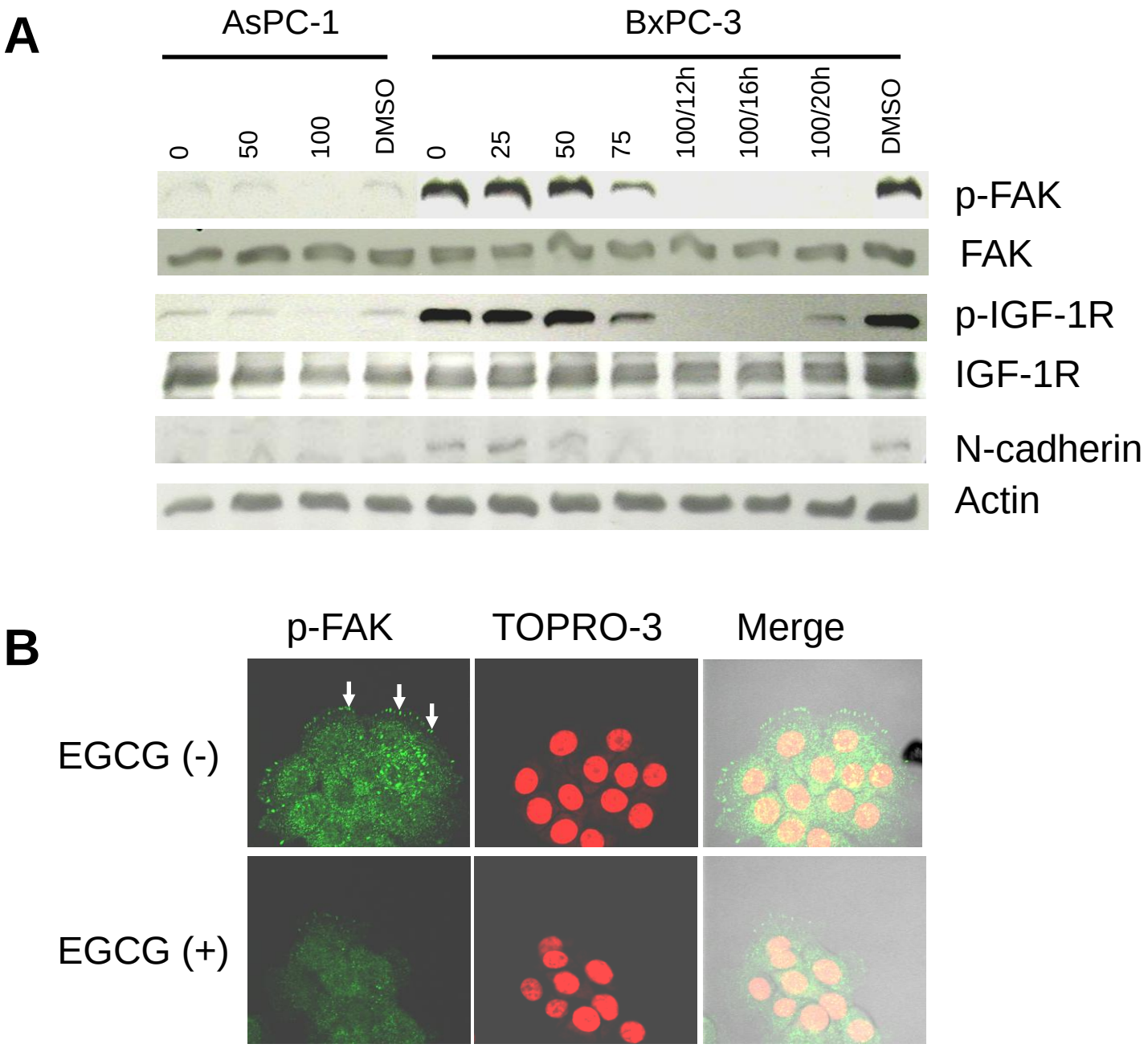
Drug	Target (IC50)	IC50	IC50	IC50	Preclinical activity	Clinical activity
	Src	FAK	Abl	IGF1R		
BMS-354825 (Dasatinib)	0.55 nM		3.0 nM		Solid and hematological tumor models	Approved in Imatinib refractory CML and Philadelphia chromosome + ALL, Phase 1–2 clinical trials in solid and hematological tumors are underway
PF-562,271	797 nM	1.5 nM (0.7 ng/mL)		>500 nM	Colon, breast, prostate, pancreatic and lung tumor models	Phase 1 clinical trial in solid tumors has been already communicated
TAE-226		100 nM/L = 100 nM		300 nM/L = 300 nM	Glioma and human pancreatic tumor cell lines	Not yet
AZD0530	≤4 nM 27 nM				Skin, prostate, breast and pancreatic tumor models	Phase 1–2 clinical trial underway
SKI-606 (Bosutinib)	3.8 nM				CML, colon and breast models	Phase 1 clinical trial has been already communicated, Ph II clinical trial in CML patients after imatinib failure under development

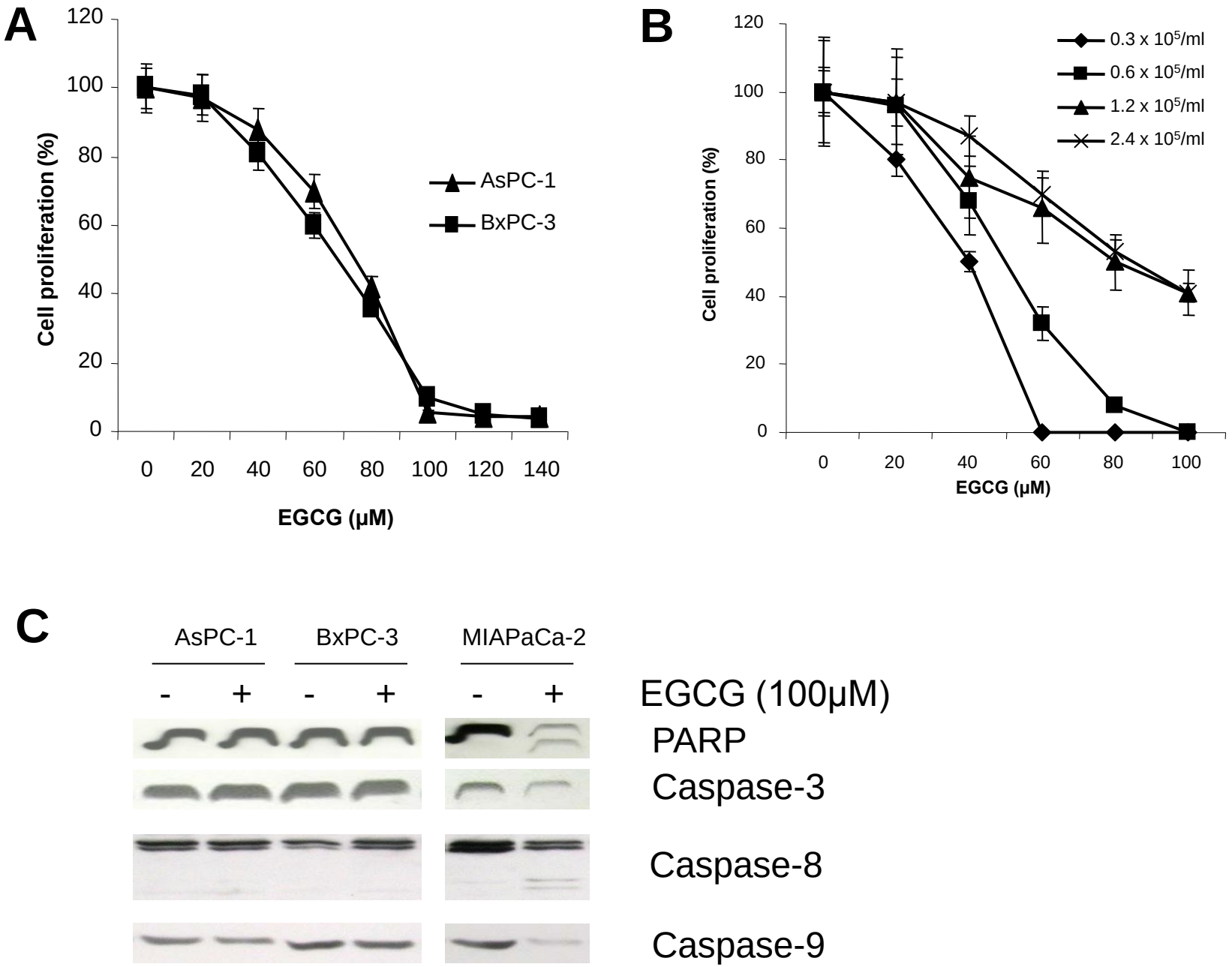
Abbreviations: FAK, focal adhesion kinase; CML, chronic myelogenous leukemia; IGF, insulin-like growth factor; IC, inhibitory concentration.

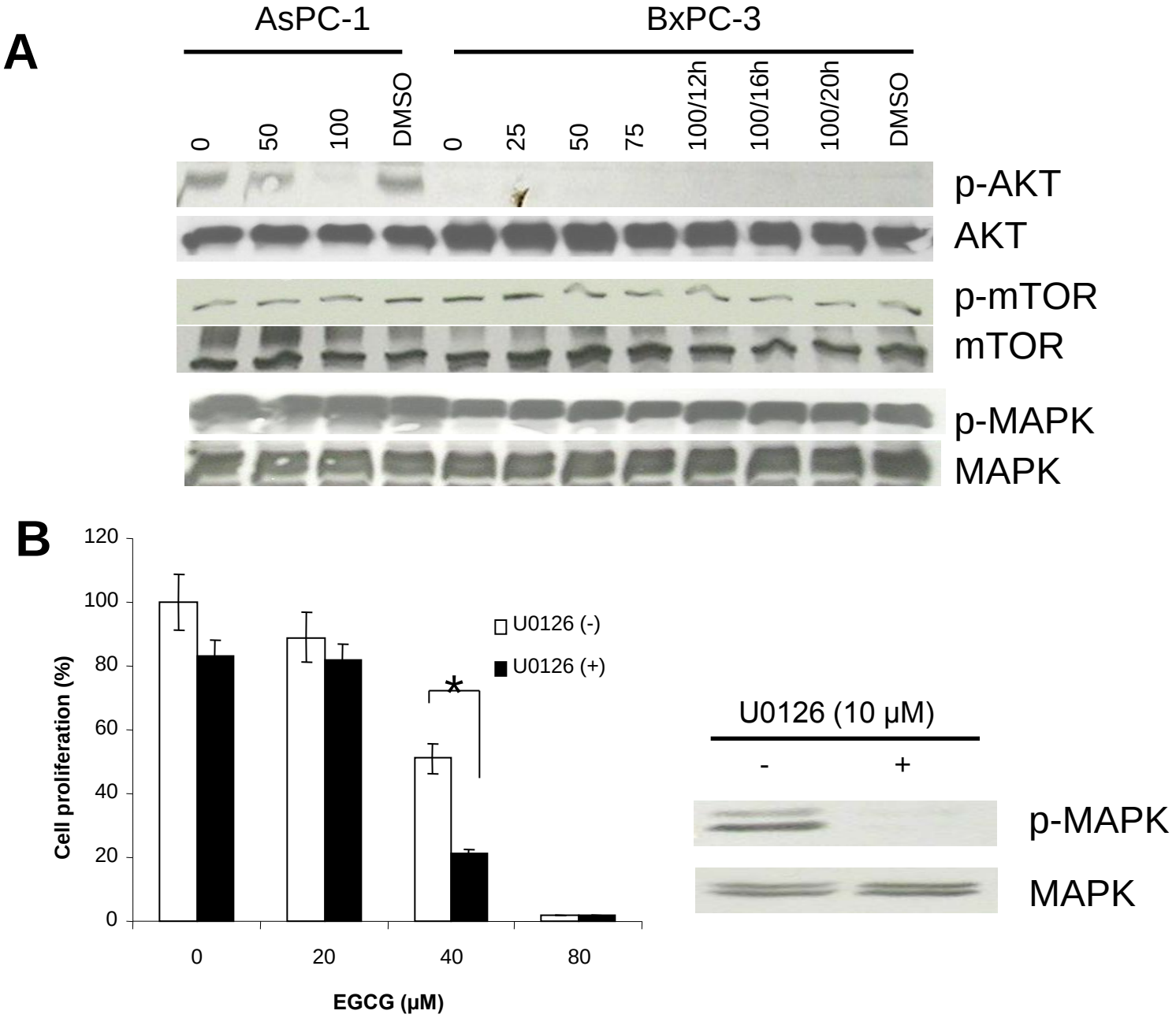
(Bolos V, *OncoTargets and Therapy* 2010)

Green Tea Epigalocatechin gallate (EGCG) Exhibits anticancer effect in Human Pancreatic Carcinoma Cells via Inhibition of both Focal Adhesion Kinase and Insulin-like Growth Factor-I Receptor

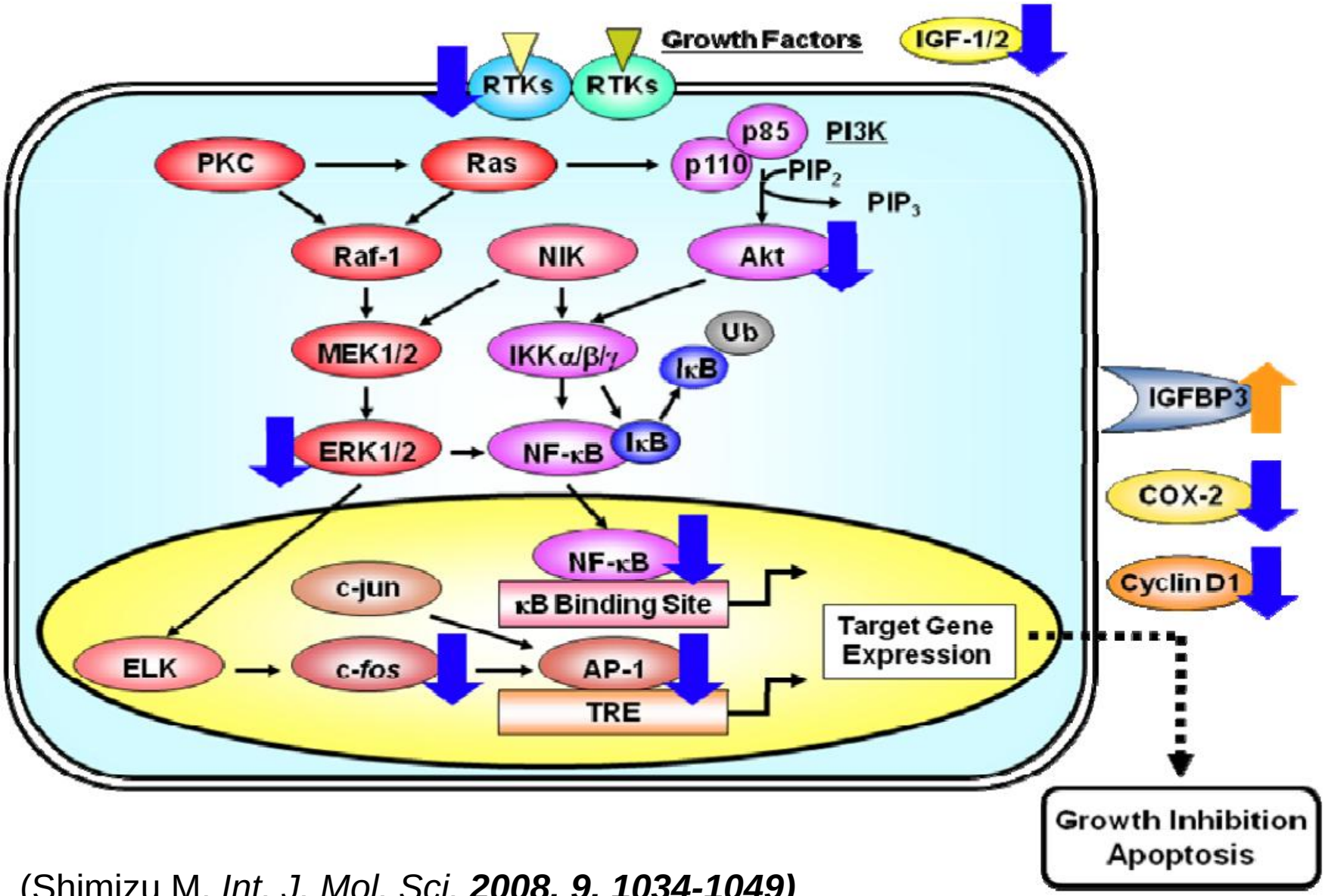



A
AsPC-1
BxPC-3
0
50
100
DMSO
0
25
50
75
100/12h
100/16h
100/20h
DMSO
p-FAK
FAK
p-IGF-1R
IGF-1R
N-cadherin
Actin
B
p-FAK
TOPRO-3
Merge
EGCG (-)
EGCG (+)


A
120
100
80
60
40
20
0
Cell proliferation (%)
0
20
40
60
80
100
120
140
EGCG (μM)
AsPC-1
BxPC-3
B
120
100
80
60
40
20
0
Cell proliferation (%)
0
20
40
60
80
100
EGCG (μM)
0.3 x 10^5/ml
0.6 x 10^5/ml
1.2 x 10^5/ml
2.4 x 10^5/ml
C
AsPC-1
BxPC-3
MIAPaCa-2
- + - + - +
EGCG (100μM)
PARP
Caspase-3
Caspase-8
Caspase-9


A
AsPC-1
BxPC-3
0
50
100
DMSO
0
25
50
75
100/12h
100/16h
100/20h
DMSO
p-AKT
AKT
p-mTOR
mTOR
p-MAPK
MAPK
B
120
100
80
60
40
20
0
Cell proliferation (%)
U0126 (-)
U0126 (+)
*
0
20
40
80
EGCG (μM)
U0126 (10 μM)
-
+
p-MAPK
MAPK

TÁC ĐỘNG CỦA EGCG TRÊN TẾ BÀO UNG THƯ



(Shimizu M, *Int. J. Mol. Sci.* ***2008, 9, 1034-1049)***