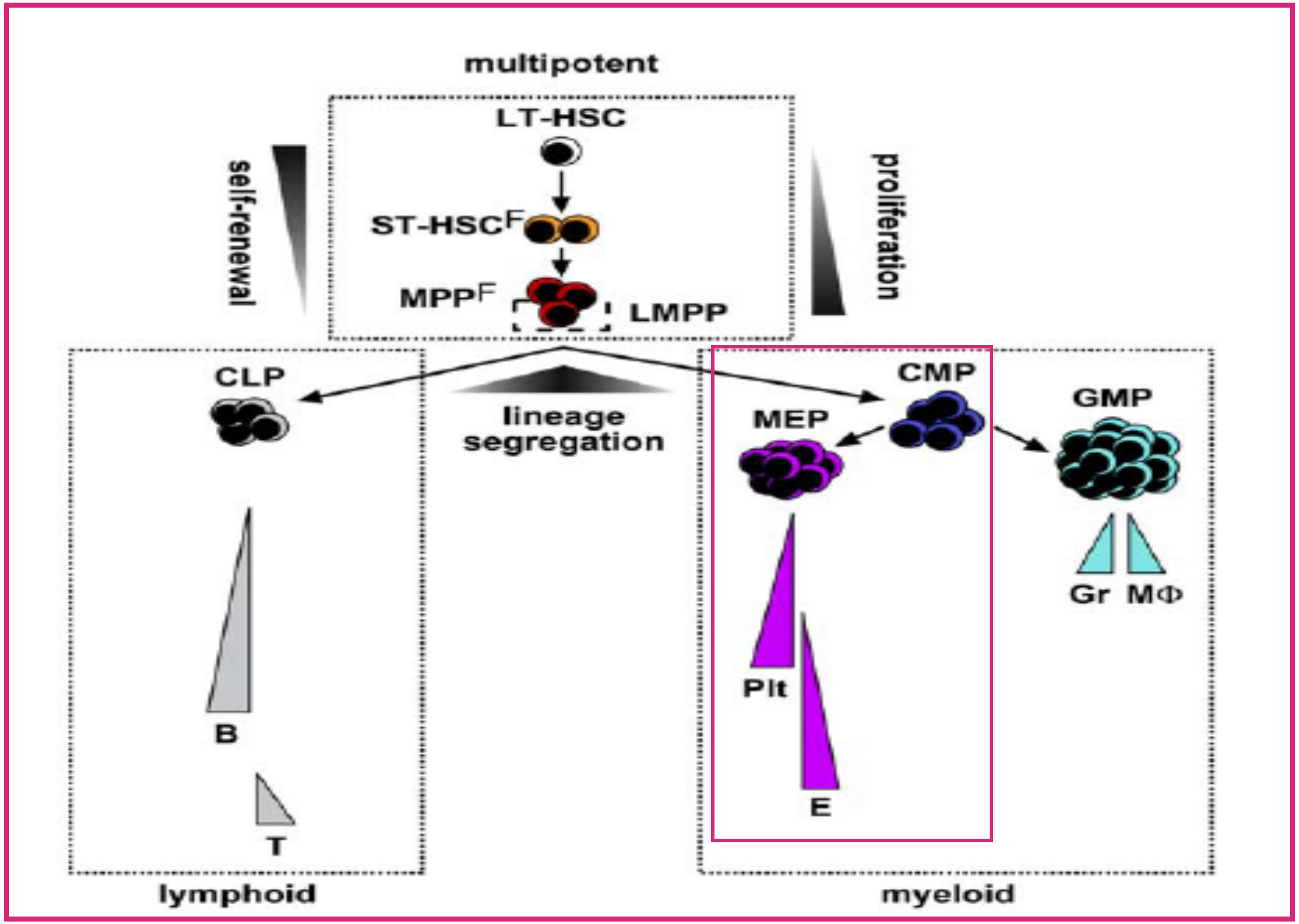
Sabati Ematologici della Romagna

Fisiologia della piastrinopoiesi

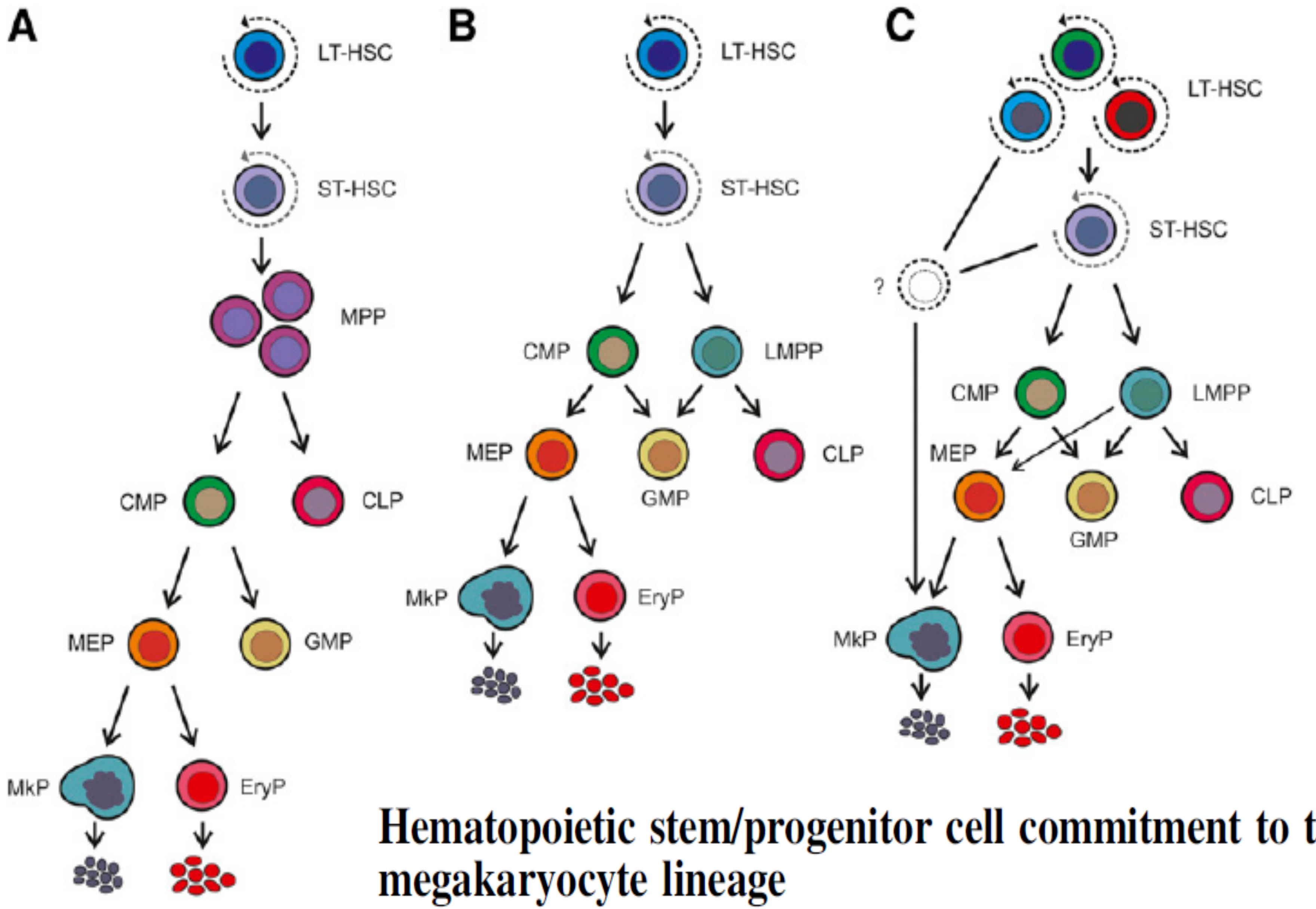
Lucia Catani

Istituto di Ematologia "L. & A. Seràgnoli"
Dipartimento Medicina Sperimentale, Diagnostica e Specialistica
Università di Bologna

EMOPOIESI



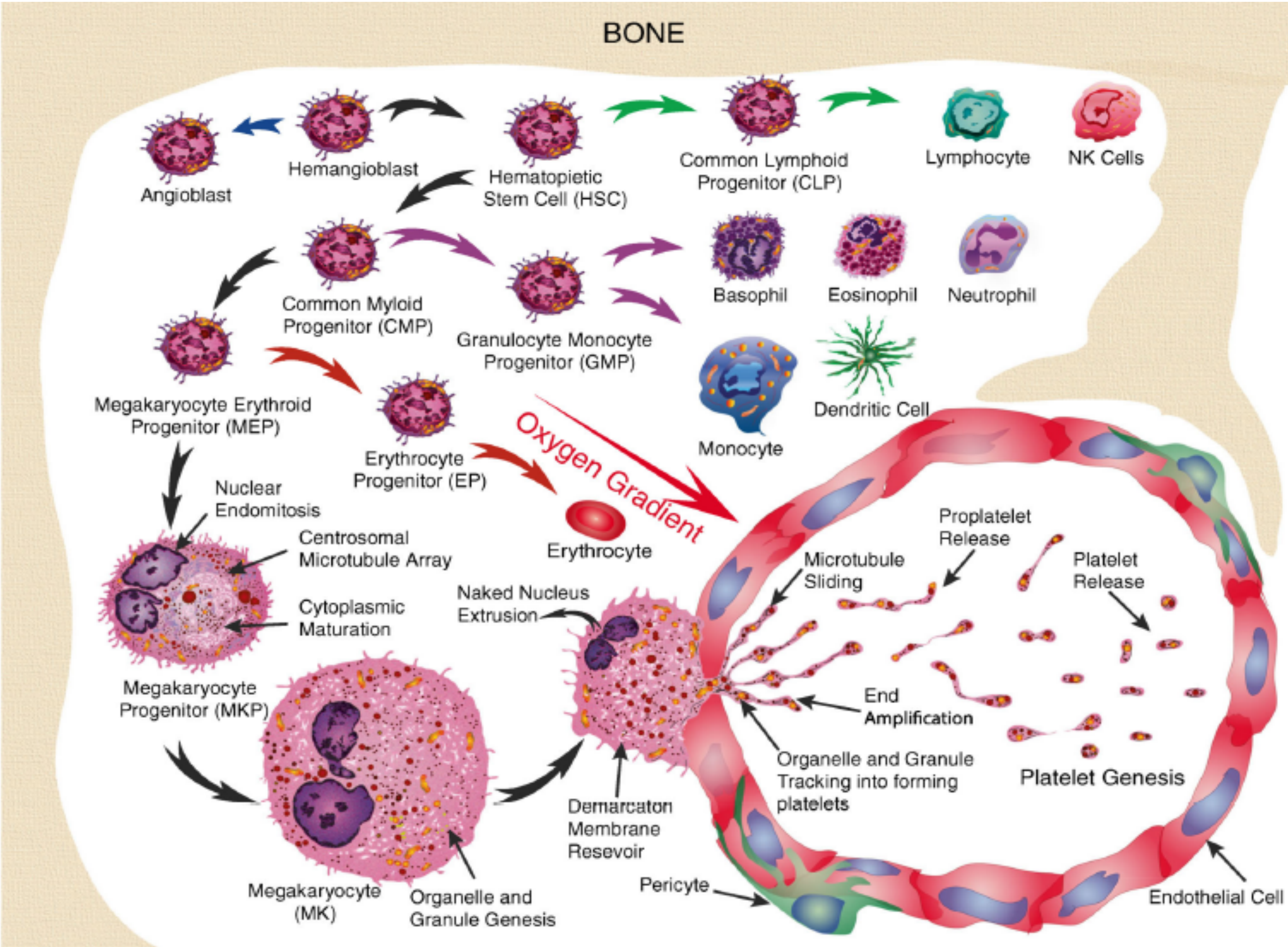
Forsberg EC Cell 2006



Hematopoietic stem/progenitor cell commitment to the megakaryocyte lineage

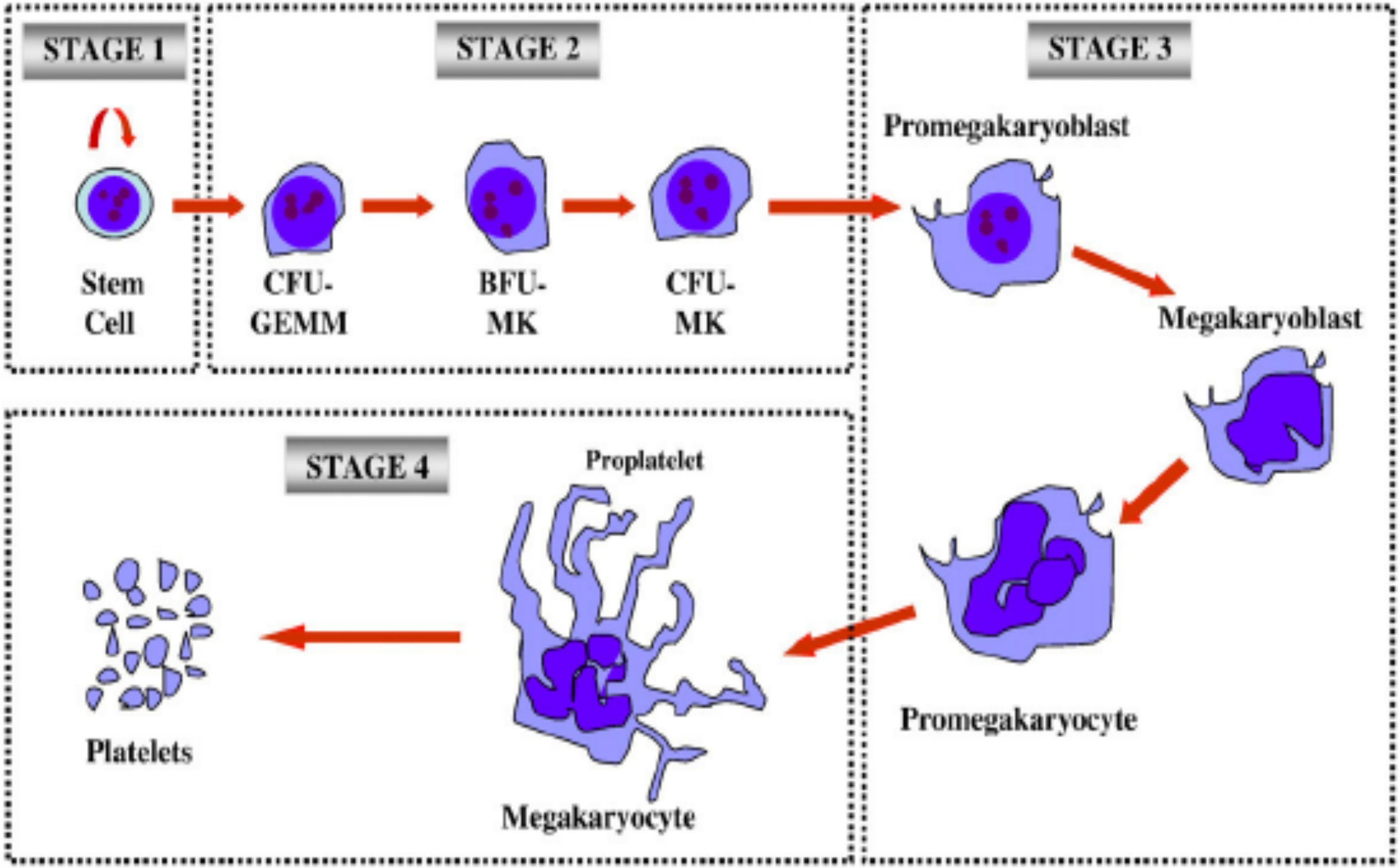
Carolien M. Woolthuis[1] and Christopher Y. Park[1,2]

(*Blood.* 2016;127(10): 1242-1248)



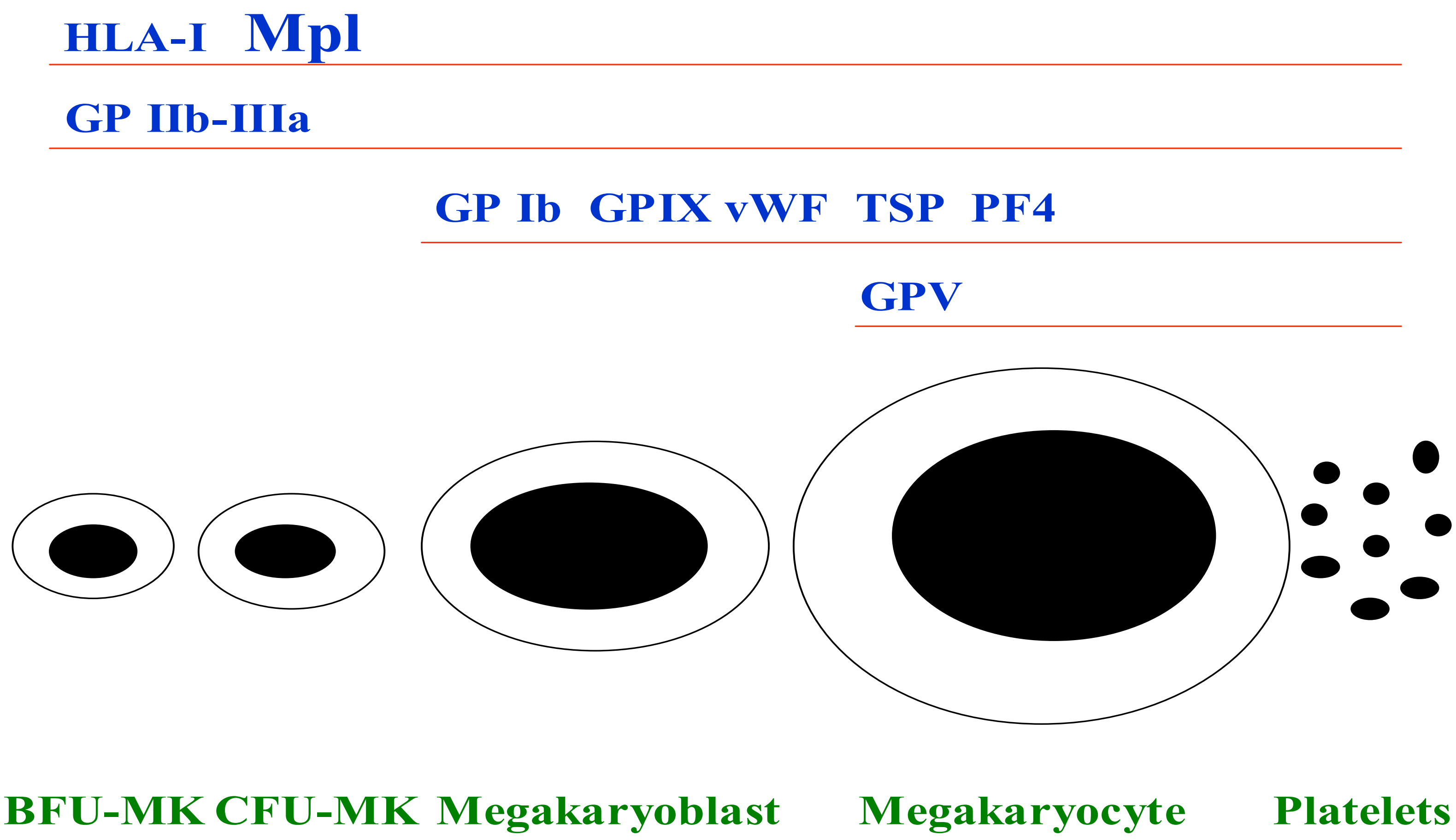
BONE
Angioblast
Hemangioblast
Hematopietic
Stem Cell (HSC)
Common Lymphoid
Progenitor (CLP)
Lymphocyte
NK Cells
Common Myloid
Progenitor (CMP)
Granulocyte Monocyte
Progenitor (GMP)
Basophil
Eosinophil
Neutrophil
Monocyte
Dendritic Cell
Megakaryocyte Erythroid
Progenitor (MEP)
Erythrocyte
Progenitor (EP)
Erythrocyte
Oxygen Gradient
Nuclear
Endomitosis
Centrosomal
Microtubule Array
Cytoplasmic
Maturation
Megakaryocyte
Progenitor (MKP)
Naked Nucleus
Extrusion
Megakaryocyte
(MK)
Organelle and
Granule Genesis
Demarcaton
Membrane
Resevoir
Microtubule
Sliding
Proplatelet
Release
Platelet
Release
End
Amplification
Organelle and Granule
Tracking into forming
platelets
Platelet Genesis
Pericyte
Endothelial Cell

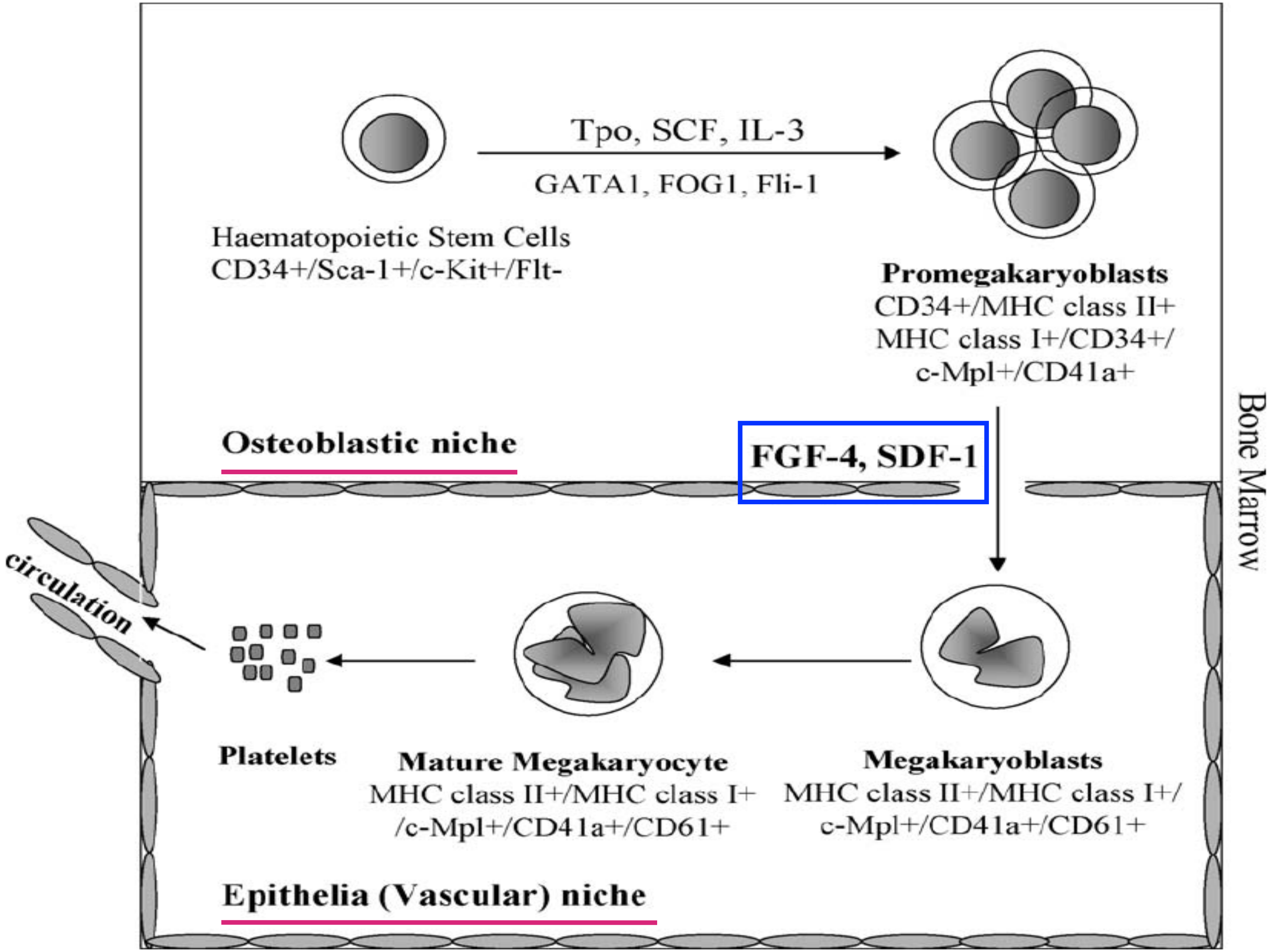
Megakaryocytopoiesis



Reems JA et al. Transfusion Med Rev 2010

SVILUPPO MEGACARIOCITARIO

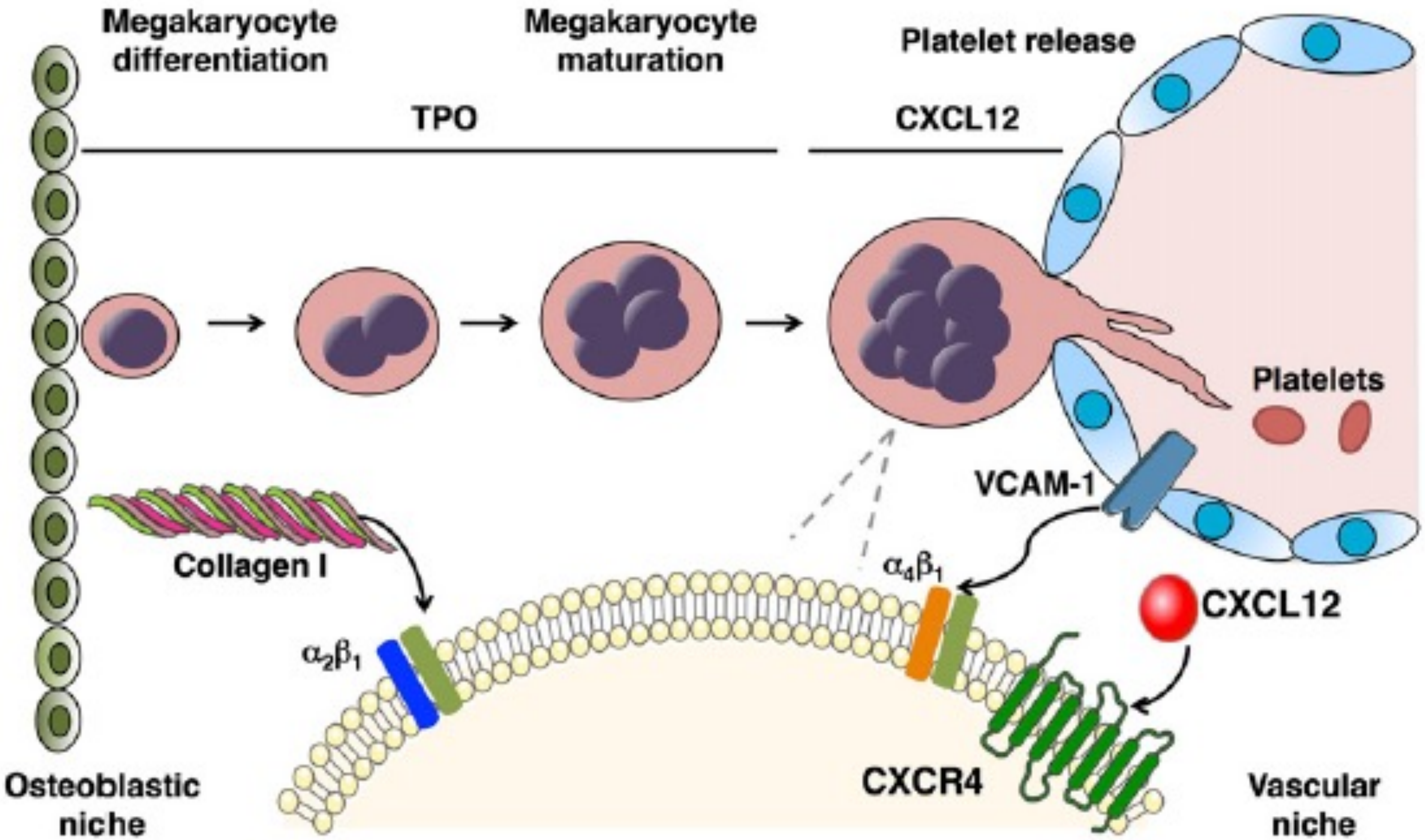




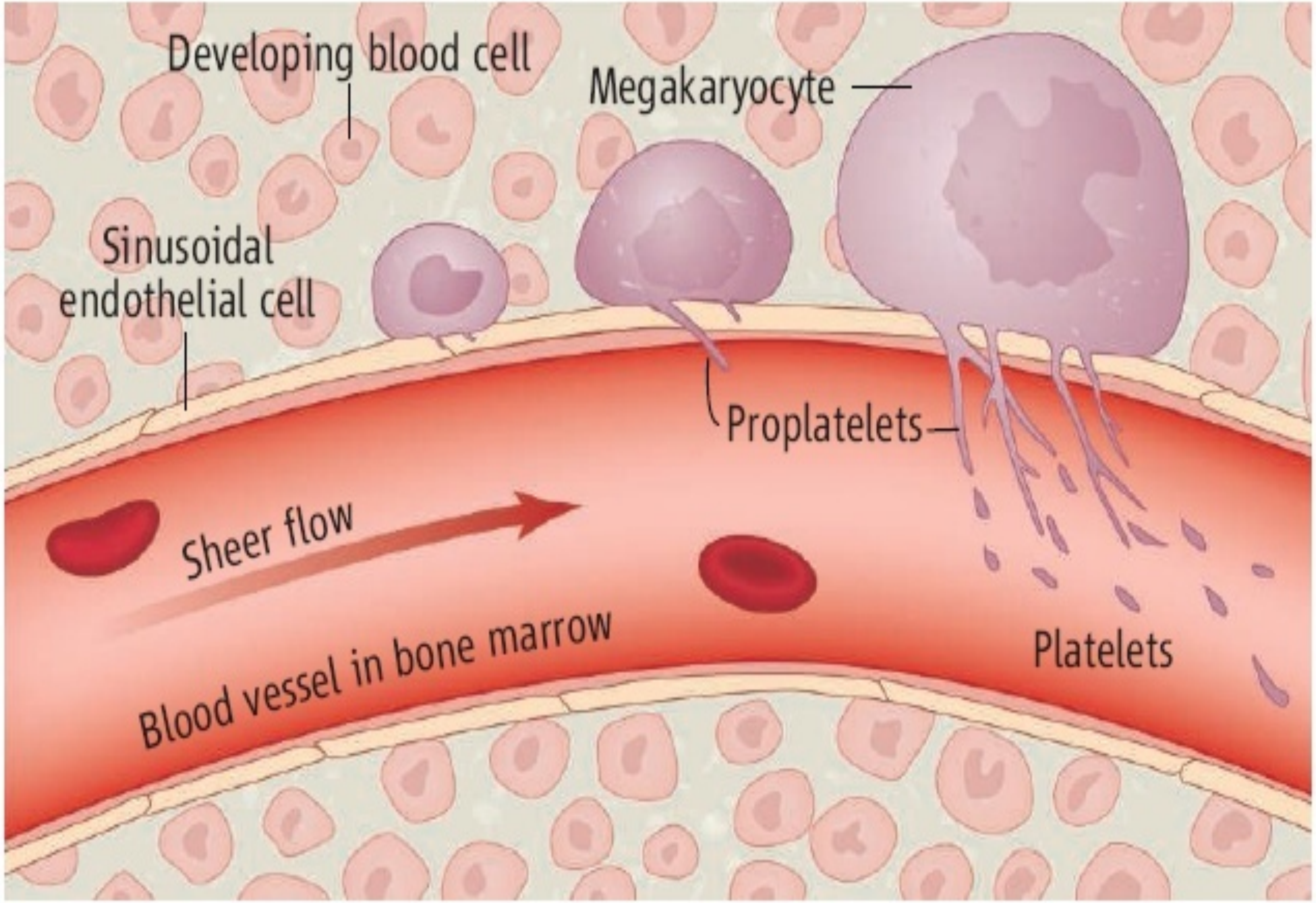
Pallotta et al. PLoS ONE 2009
Kacena et al. Bone 2006
Avecilla et al. Nature Medicine 2004

Int J Biochem Cell Biology 2006

Megakaryopoiesis and thrombopoiesis.

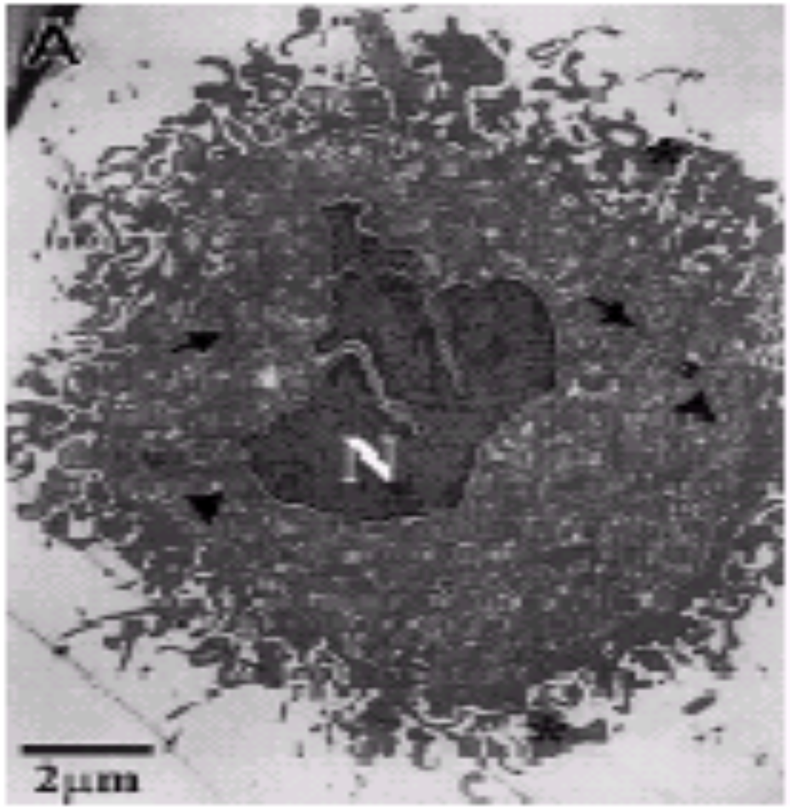


(*Blood*. 2015;126(16):1877-1884)



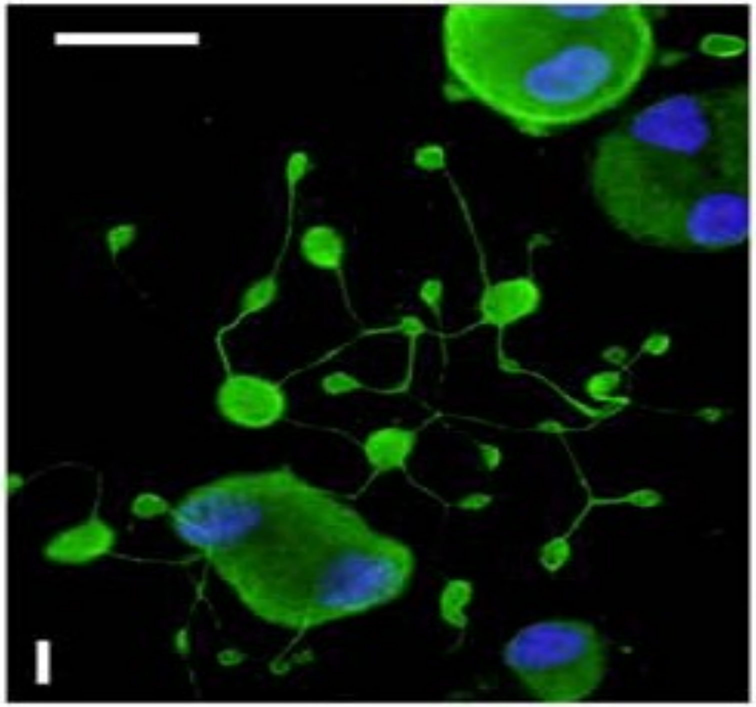
Geddis AE and Kaushansky K Science 2007

Proplatelets



Hitchcock et al. Blood 2003

PLoS ONE | June 2011 | Volume 6 | Issue 6 |

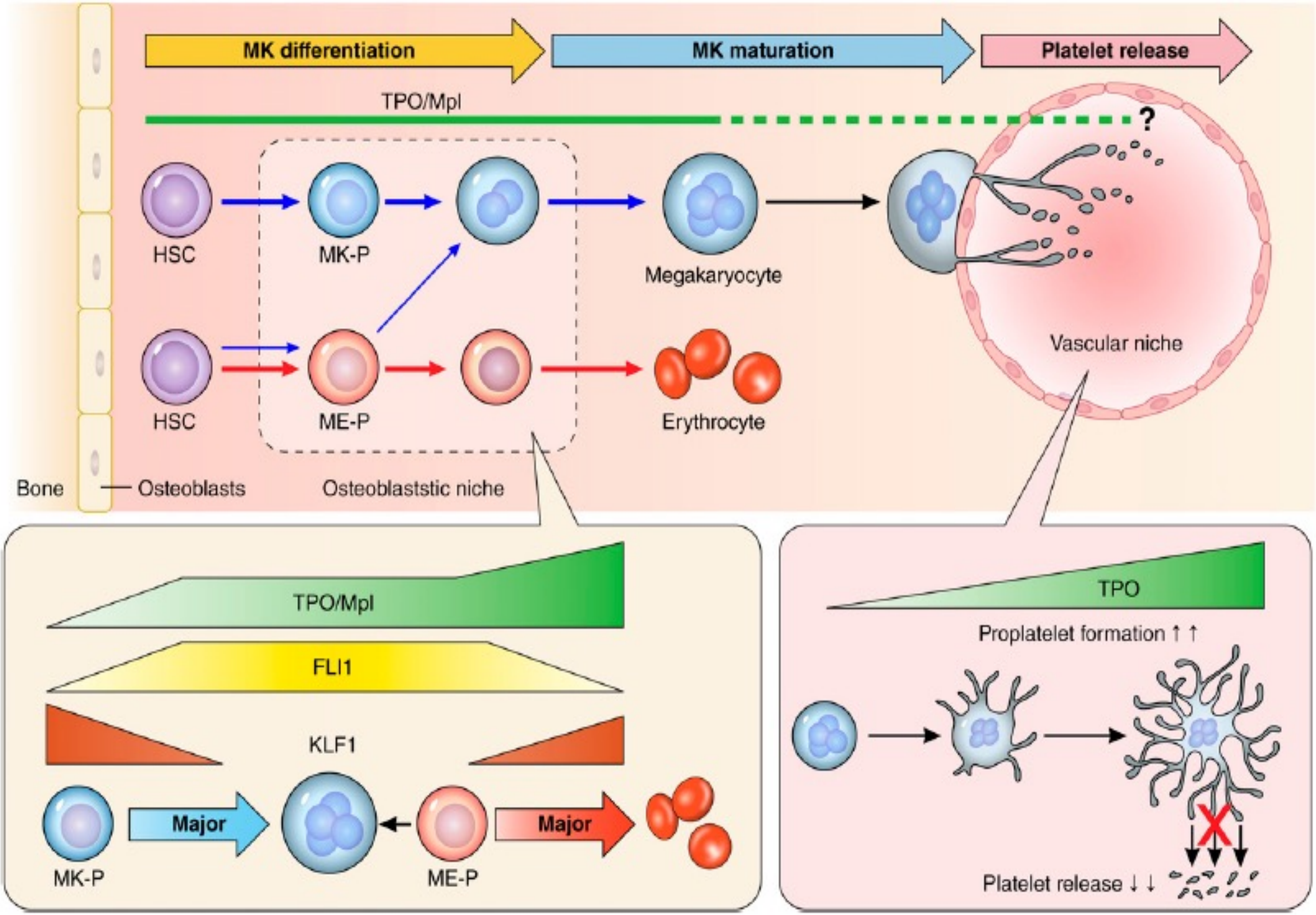


SVILUPPO MEGACARIOCITARIO

NICCHIA
CELLULA STAMINALE EMOPOIETICA

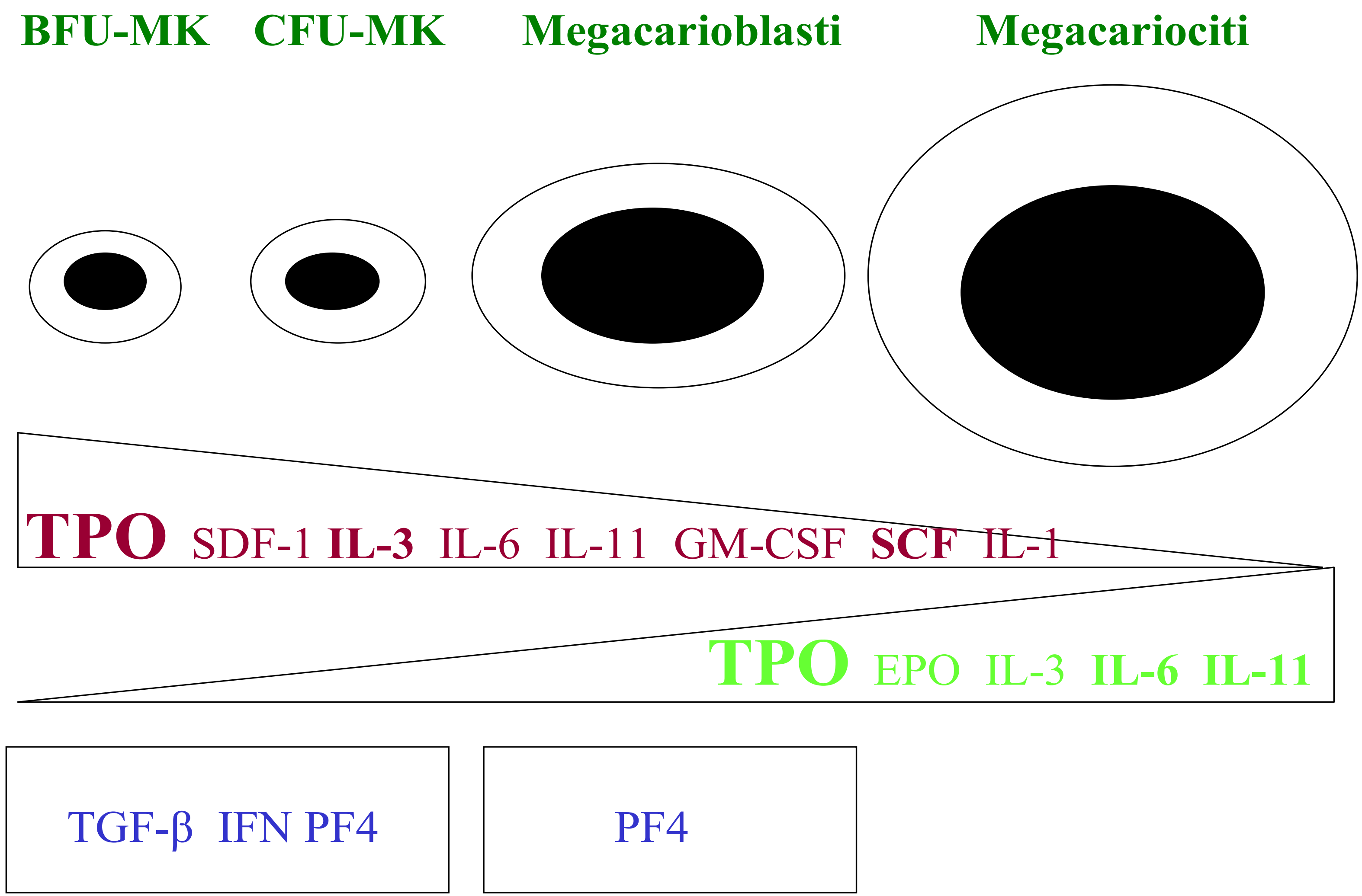
CITOCHINE
FATTORI DI CRESCITA

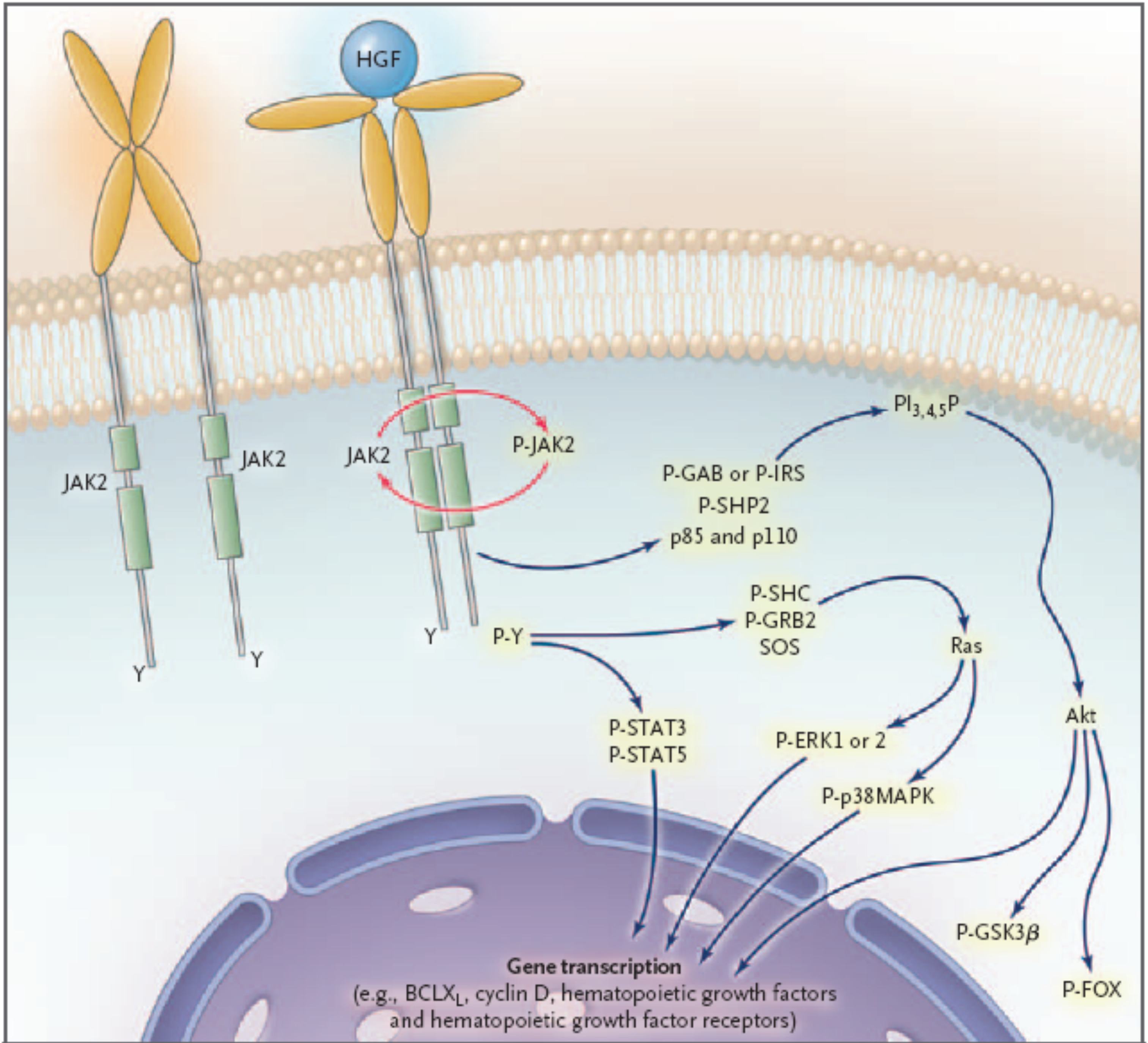
REGOLAZIONE
GENICA/TRASCRIZIONALE



(*Blood.* 2016;127(10):1234-1241)

PROLIFERAZIONE E DIFFERENZIAZIONE MEGACARIOCITARIA
CITOCHINE E FATTORI DI CRESCITA




HGF
JAK2
JAK2
JAK2
P-JAK2
Y
Y
Y
P-Y
PI$_{3,4,5}$P
P-GAB or P-IRS
P-SHP2
p85 and p110
P-SHC
P-GRB2
SOS
Ras
Akt
P-STAT3
P-STAT5
P-ERK1 or 2
P-p38MAPK
P-GSK3β
P-FOX
Gene transcription
(e.g., BCLX$_L$, cyclin D, hematopoietic growth factors
and hematopoietic growth factor receptors)

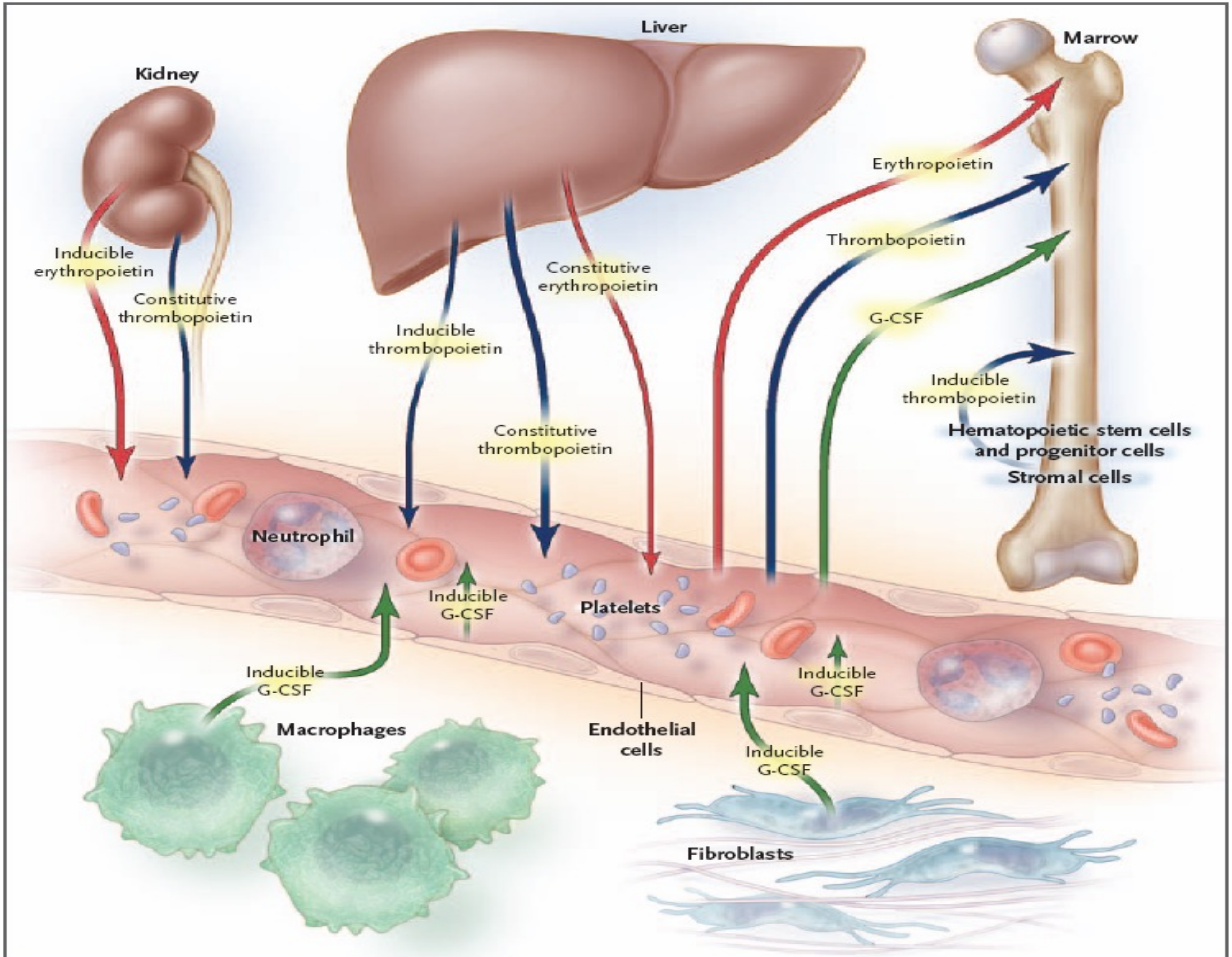


Figure 2. Regulation of the Production of Hematopoietic Growth Factors.

RECETTORE DELLA TROMBOPOIETINA

MPL

Cromosoma 1p34

CELLULE STAMINALI

CELLULE MEGACARIOCITARIE

PIASTRINE

TPO

- STIMOLA LA MATURAZIONE E PROLIFERAZIONE DELLE CELLULE MEGACARIOCITARIE

- TOPI KNOCK-OUT PER TPO O c-MPL HANNO UNA RIDUZIONE DEL NUMERO DELLE PIASTRINE DI 85%-95%

- AUMENTA LA REATTIVITA' DELLE PIASTRINE AD ALCUNI STIMOLI AGGREGANTI

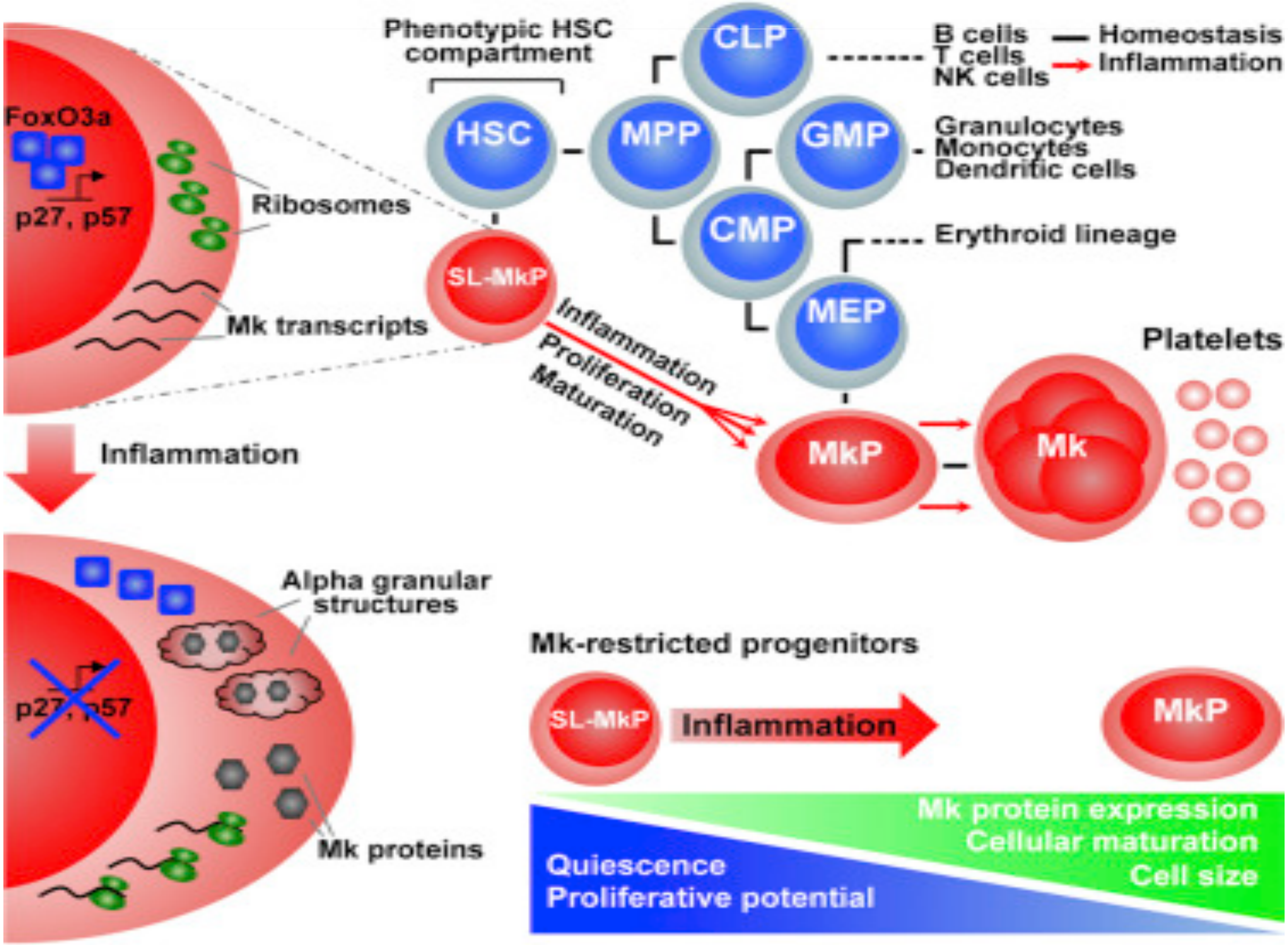
REGOLAZIONE LIVELLI CIRCOLANTI DI TROMBOPOIETINA

Recettore Mpl

Cellula staminale emopoietica

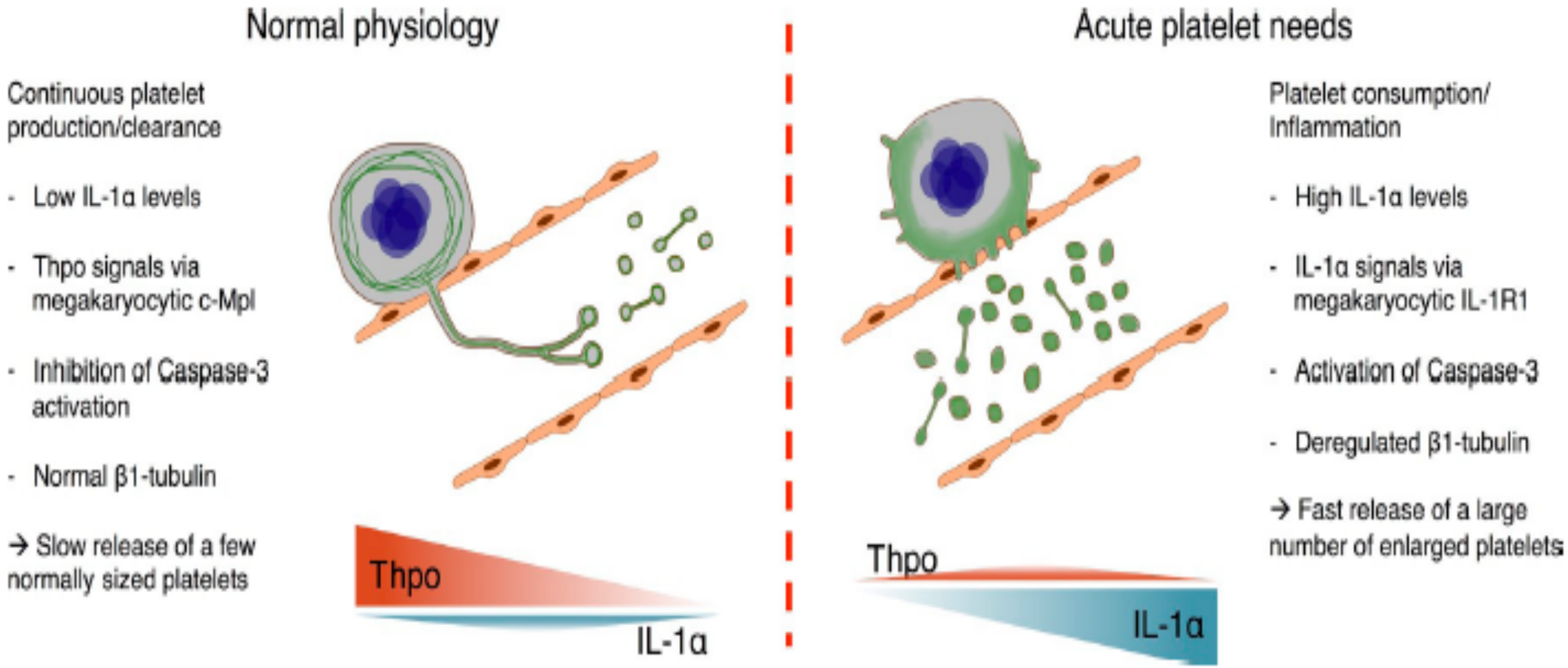
Cellule megacariocitarie

Piastrine



Cell Stem Cell.2015 Oct 1;17(4):422-34. doi: 10.1016/j.stem.2015.07.007.

Inflammation-Induced Emergency Megakaryopoiesis Driven by Hematopoietic Stem Cell-like Megakaryocyte Progenitors.



The Rockefeller University Press
J. Cell Biol. Vol. 209 No. 3 327–328
www.jcb.org/cgi/doi/10.1083/jcb.201504026

SVILUPPO MEGACARIOCITARIO

NICCHIA
CELLULA STAMINALE EMOPOIETICA

CITOCHINE
FATTORI DI CRESCITA

REGOLAZIONE
GENICA/TRASCRIZIONALE

ELSEVIER

Bone 39 (2006) 978–984

BONE

www.elsevier.com/locate/bone

Review

A reciprocal regulatory interaction between megakaryocytes, bone cells, and hematopoietic stem cells

Melissa A. Kacena *, Caren M. Gundberg, Mark C. Horowitz

ARTICLE

Journal of Cellular Biochemistry 109:774–781 (2010)

Journal of Cellular Biochemistry

Immature and Mature Megakaryocytes Enhance Osteoblast Proliferation and Inhibit Osteoclast Formation

Wendy A. Ciovacco,[1] Ying-Hua Cheng,[2] Mark C. Horowitz,[1] and Melissa A. Kacena[2*]

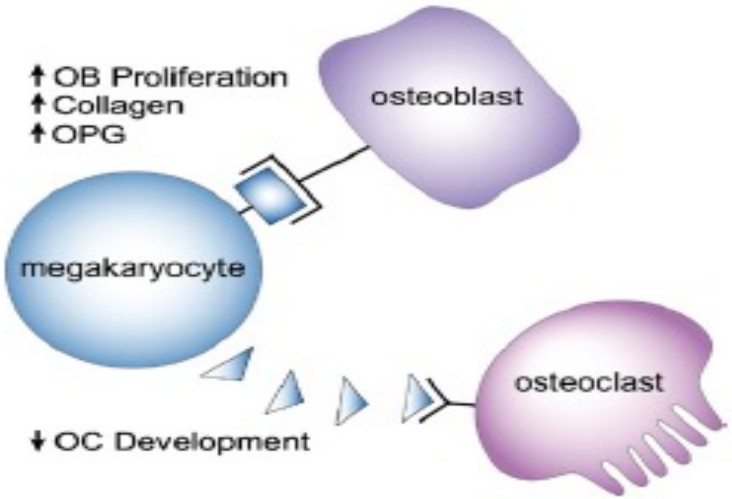


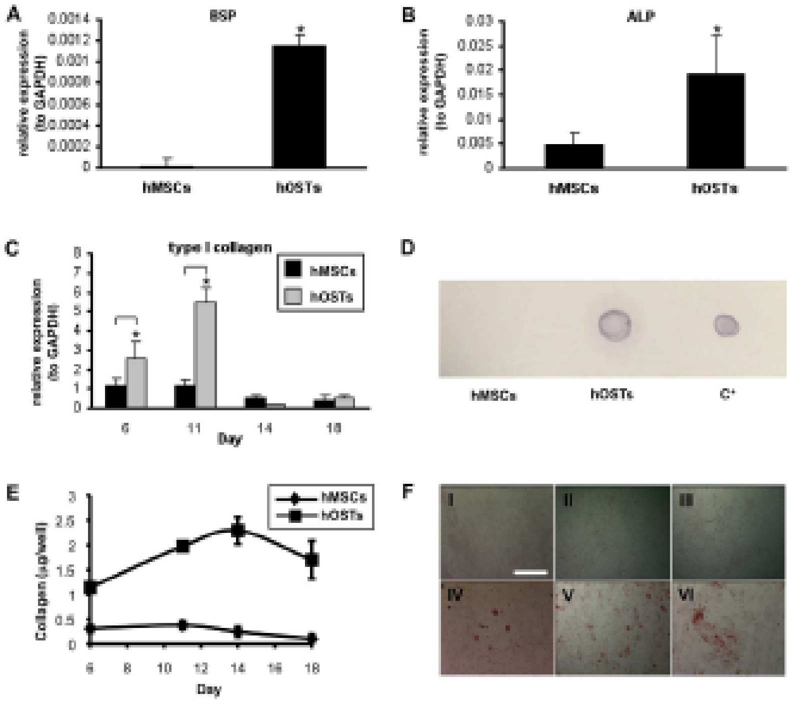
Fig. 2. Model illustrating that MK stimulate OB proliferation and differentiation and simultaneously inhibit OC formation, both of which lead to an increase in bone mass.

Bone Marrow Osteoblastic Niche: A New Model to Study Physiological Regulation of Megakaryopoiesis

Isabella Pallotta[1,2], Michael Lovett[1], William Rice[1], David L. Kaplan[1*], Alessandra Balduini[1,2*]

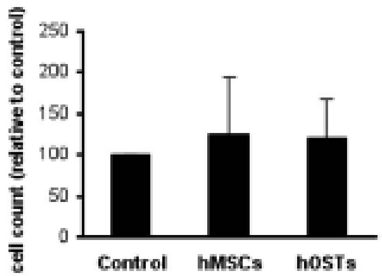
PLoS ONE | www.plosone.org December 2009 | Volume 4 | Issue 12 |

Characterization of the osteoblastic niche.



Role of the osteoblastic niche in megakaryocyte differentiation and proplatelet formation.

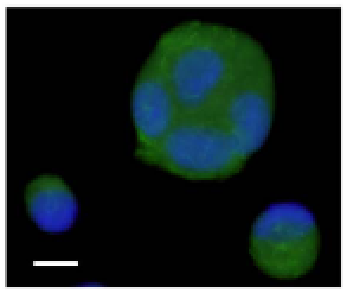
A



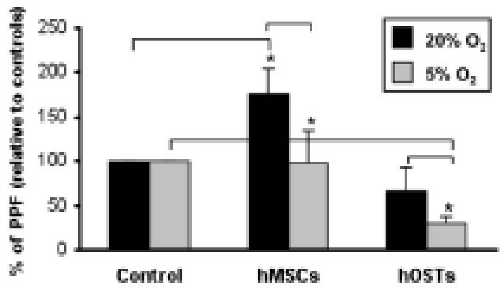
B

	CD61+cells/ total cells,%	stage I	stage II	stage III
Control	65.7 ± 3.4	43.3 ± 24.6	50.8 ± 26.7	5.8 ± 2.1
hMSCs	66 ± 4.8	6.2 ± 1.2	72.1 ± 7.8	21.7 ± 9.1
hOSTs	47 ± 6.3	55.9 ± 8.1	40.7 ± 9.5	3.3 ± 1.4

C



D

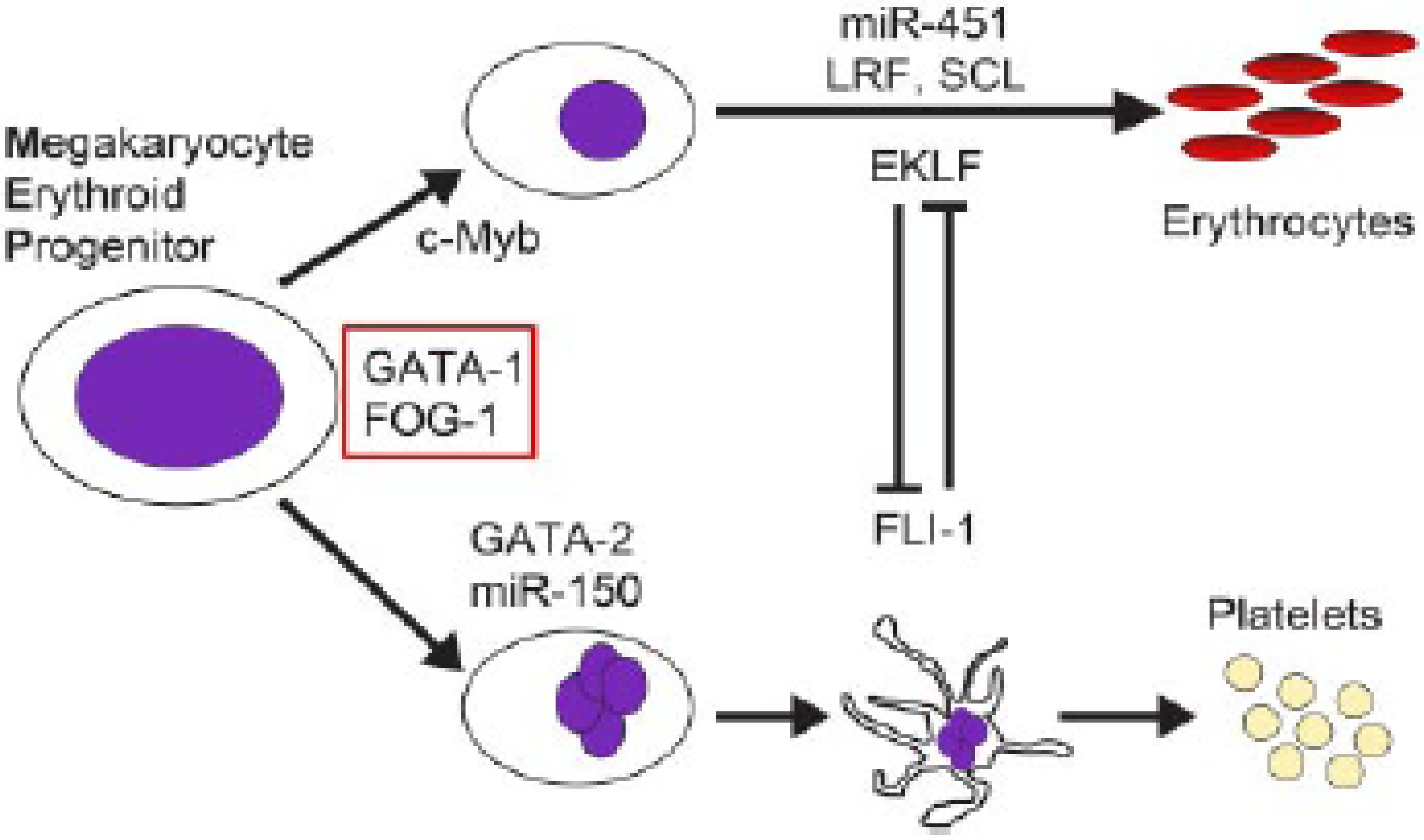


SVILUPPO MEGACARIOCITARIO

NICCHIA
CELLULA STAMINALE EMOPOIETICA

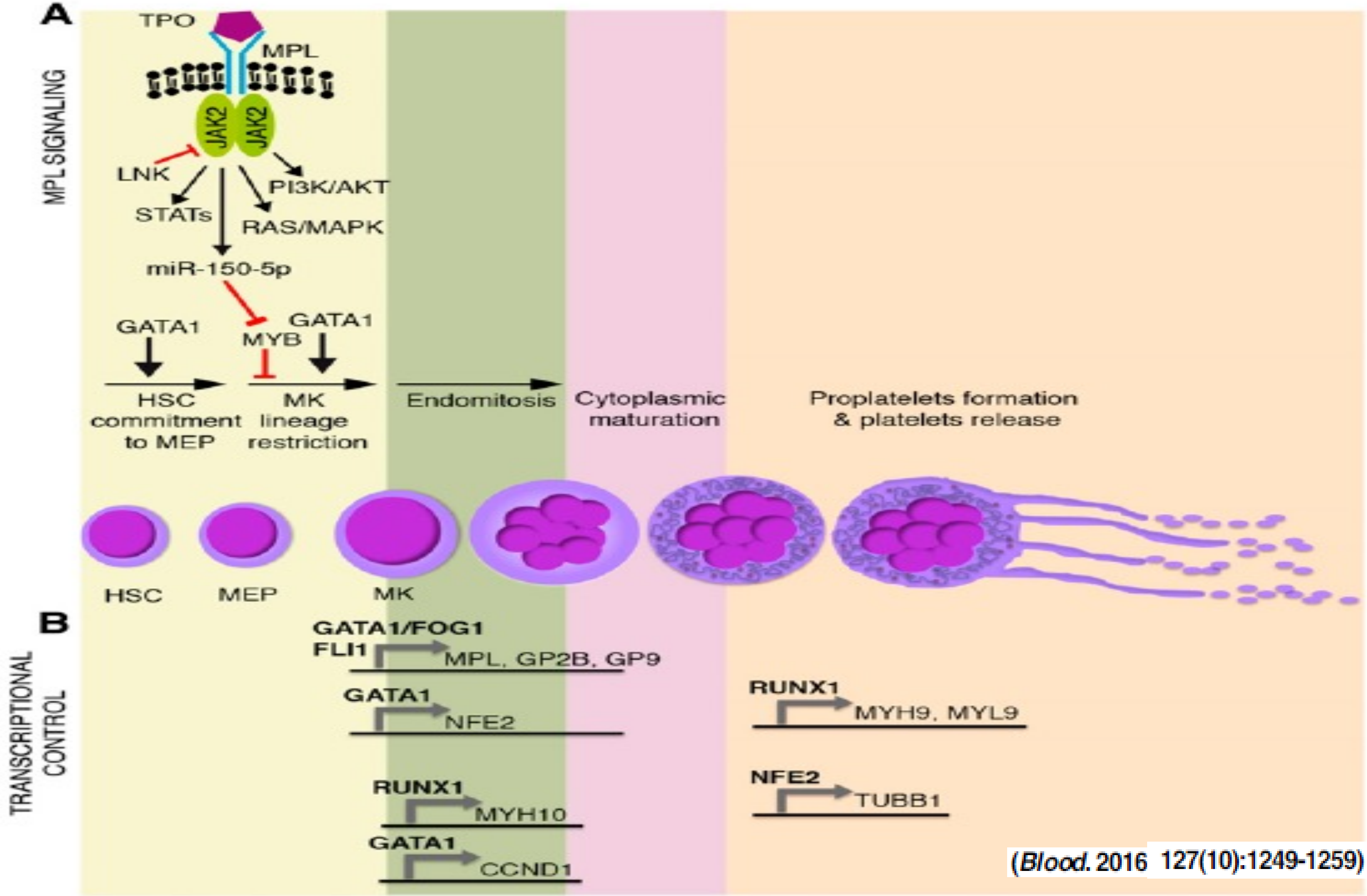
CITOCHINE
FATTORI DI CRESCITA

REGOLAZIONE GENICA/TRASCRIZIONALE

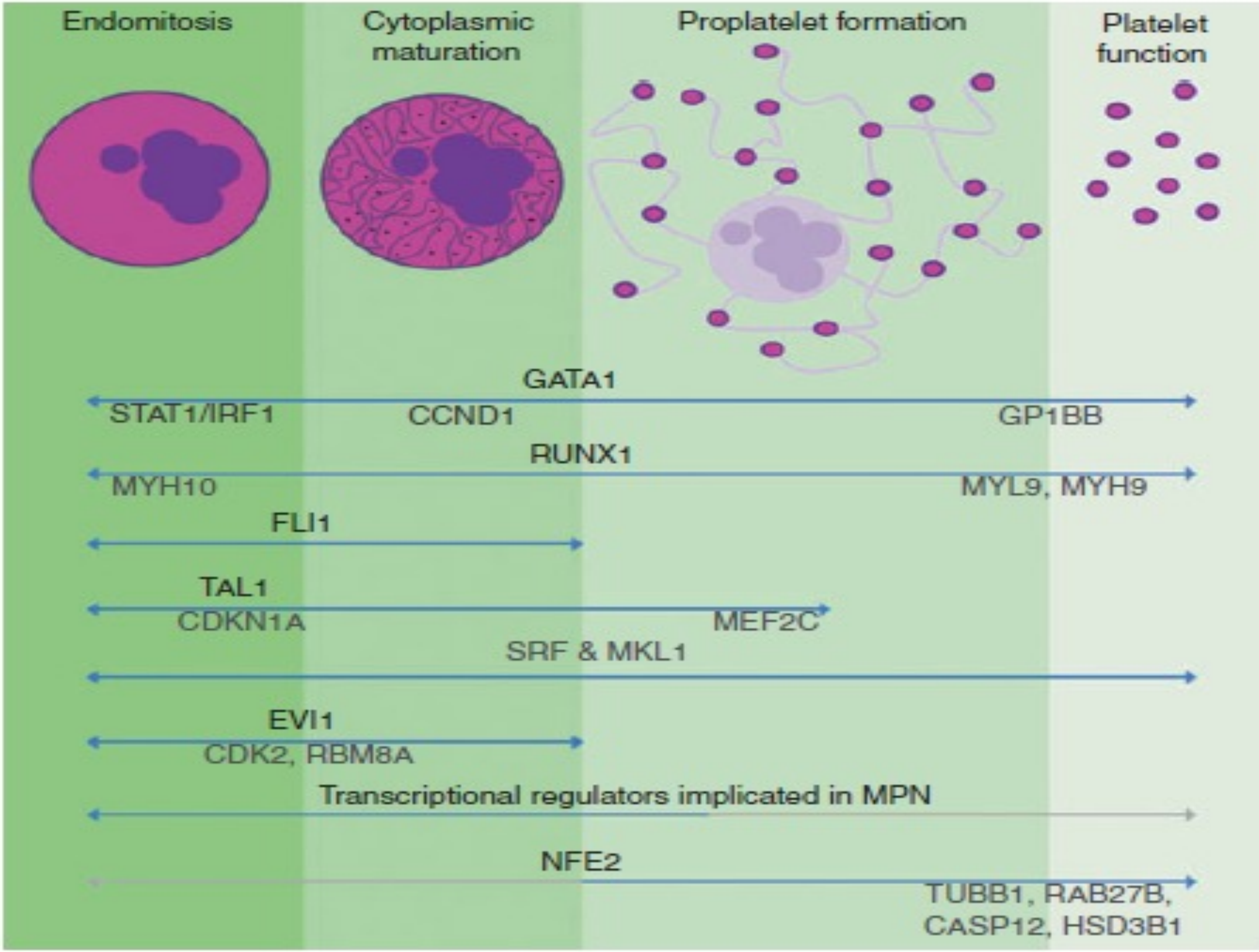


(*Blood.* 2011; 118(2):231-239)

TRANSCRIPTIONAL REGULATION



(*Blood*. 2016 127(10):1249-1259)



Endomitosis
Cytoplasmic maturation
Proplatelet formation
Platelet function
GATA1
STAT1/IRF1
CCND1
GP1BB
RUNX1
MYH10
MYL9, MYH9
FLI1
TAL1
CDKN1A
MEF2C
SRF & MKL1
EVI1
CDK2, RBM8A
Transcriptional regulators implicated in MPN
NFE2
TUBB1, RAB27B, CASP12, HSD3B1

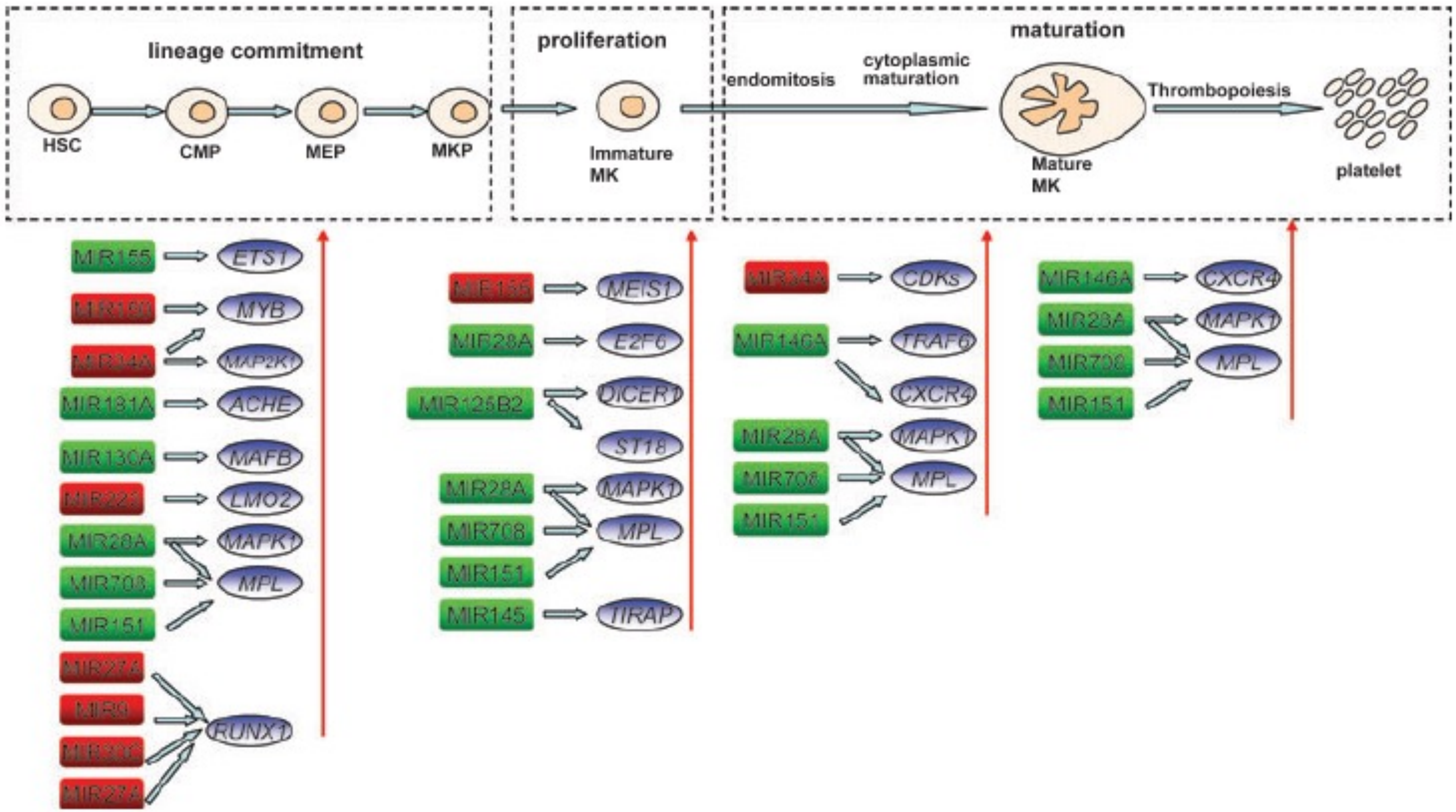
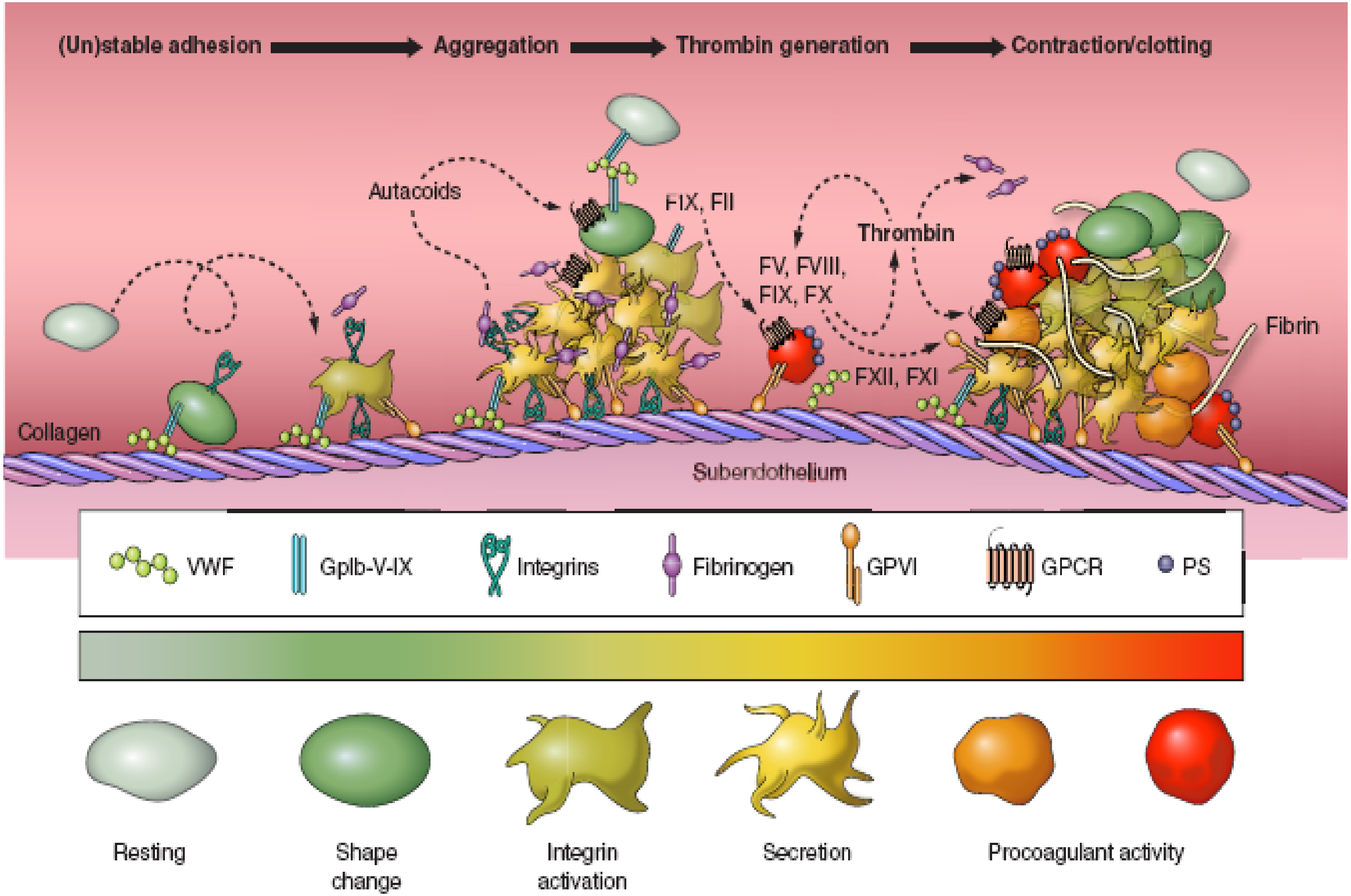


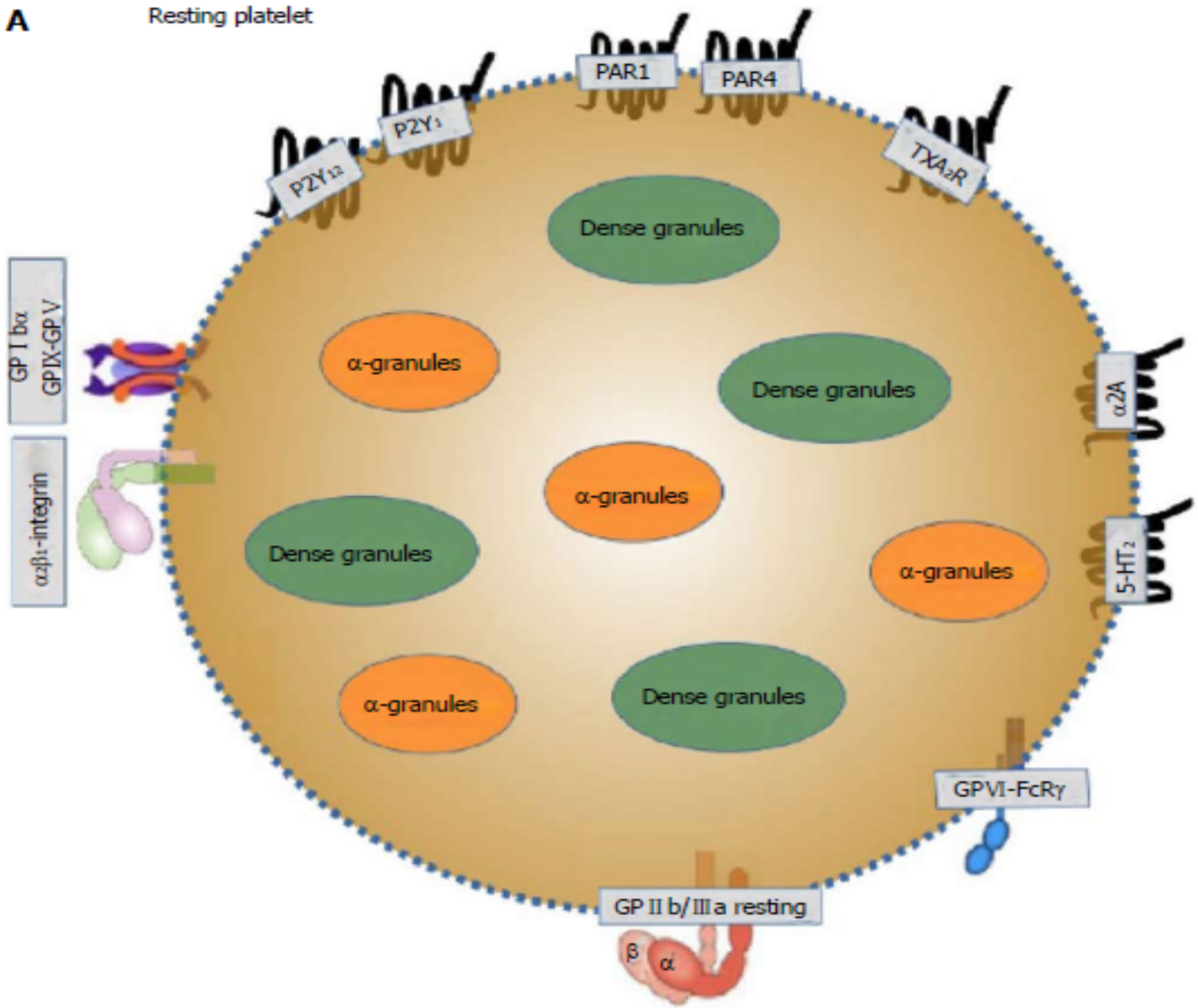
Fig 2. The regulation network of miRNA in megakaryocytopoiesis.

NEW FUNDAMENTALS IN HEMOSTASIS



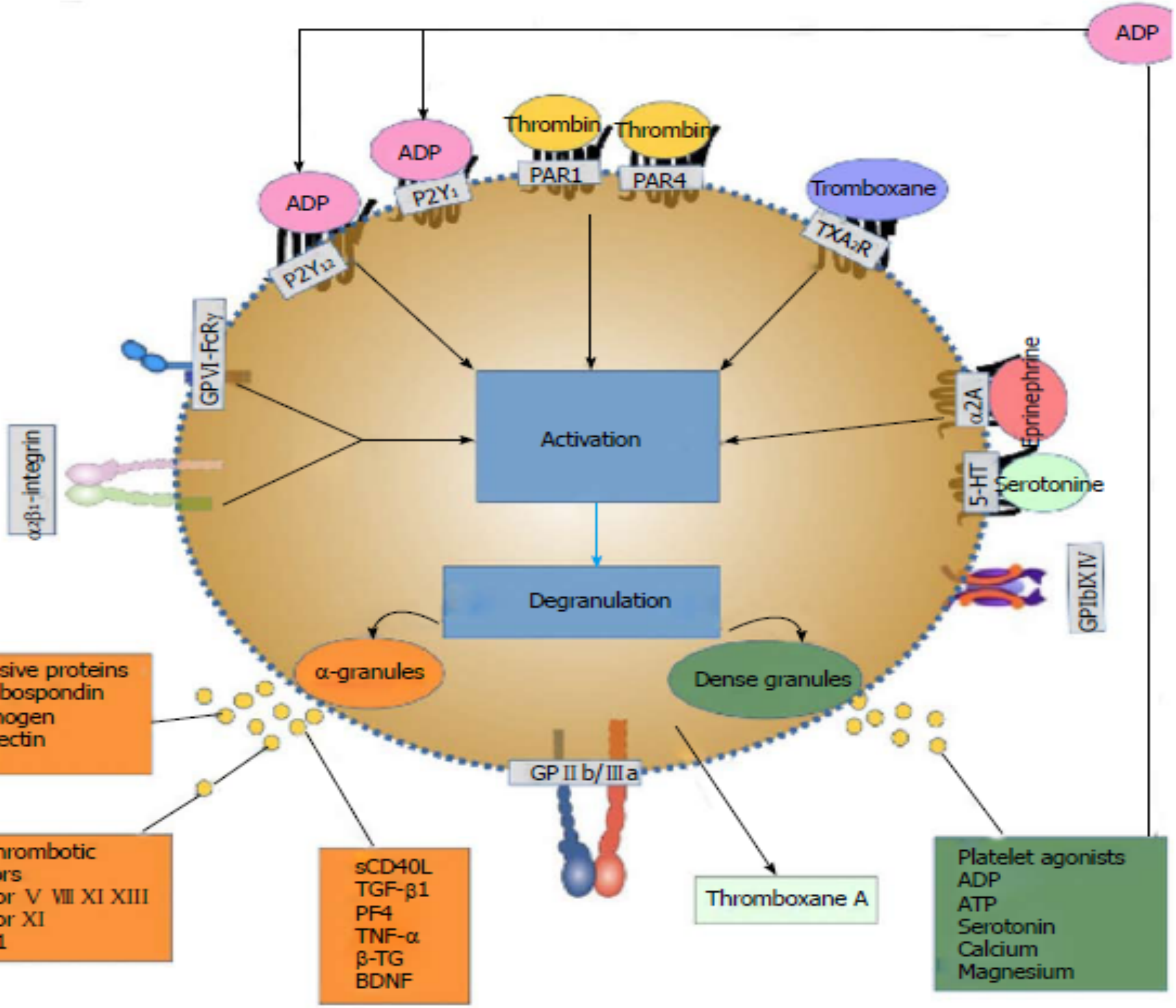
Physiol Rev 93: 327–358, 2013

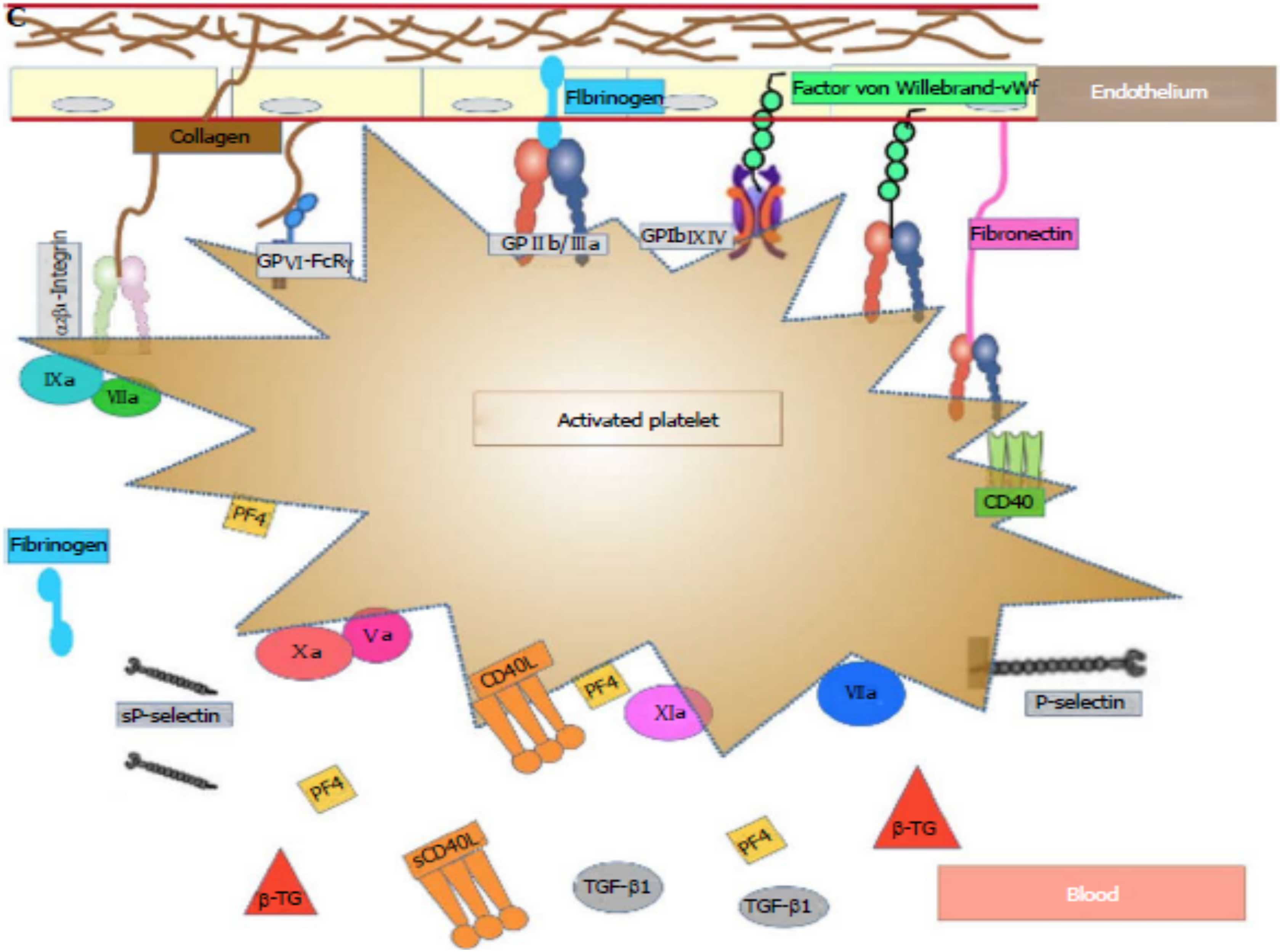
Henri H. Versteeg, Johan W. M. Heemskerk, Marcel Levi, and Pieter H. Reitsma



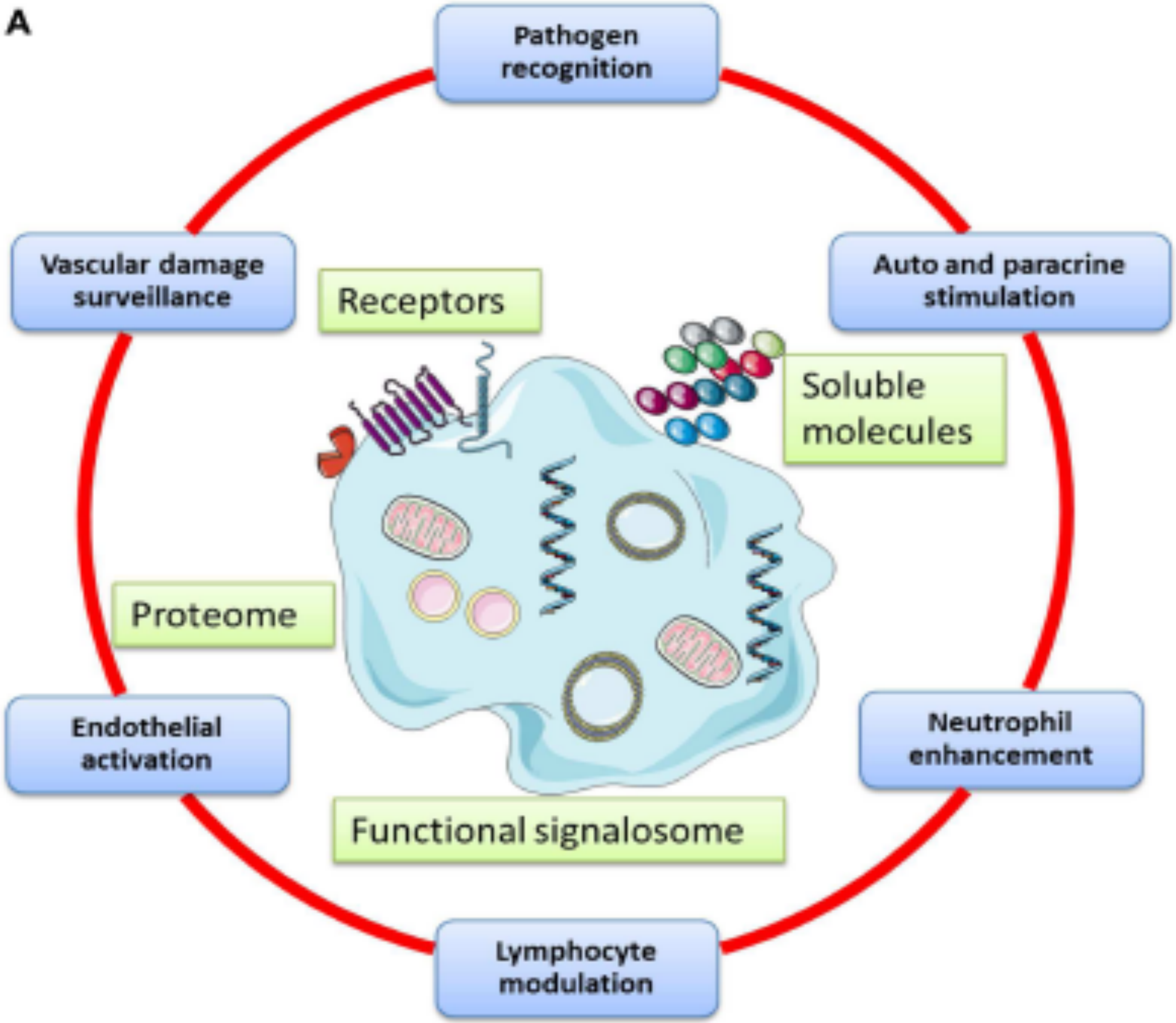
World J Psychiatr 2016 March 22; 6(1): 84-101

B


ADP
ADP
ADP
Thrombin
Thrombin
P2Y1
PAR1
PAR4
Tromboxane
TXA2R
P2Y12
GPVI-FcRγ
α2β1-integrin
Activation
α2A
Eprinephrine
5-HT
Serotonine
GPIbIX IV
Degranulation
α-granules
Dense granules
Adhesive proteins
Trombospondin
Fibrinogen
P-selectin
VWF
GP II b/III a
Prothrombotic
factors
Factor V VIII XI XIII
Factor XI
PAI-1
sCD40L
TGF-β1
PF4
TNF-α
β-TG
BDNF
Thromboxane A
Platelet agonists
ADP
ATP
Serotonin
Calcium
Magnesium


C
Endothelium
Fibrinogen
Factor von Willebrand-vWf
Collagen
GPVI-FcRγ
GP II b/ III a
GPIbIX IV
Fibronectin
α2β1-Integrin
IXa
VIIa
Activated platelet
CD40
PF4
Fibrinogen
Xa
Va
CD40L
PF4
XIa
VIIa
P-selectin
sP-selectin
PF4
β-TG
sCD40L
TGF-β1
PF4
TGF-β1
β-TG
Blood

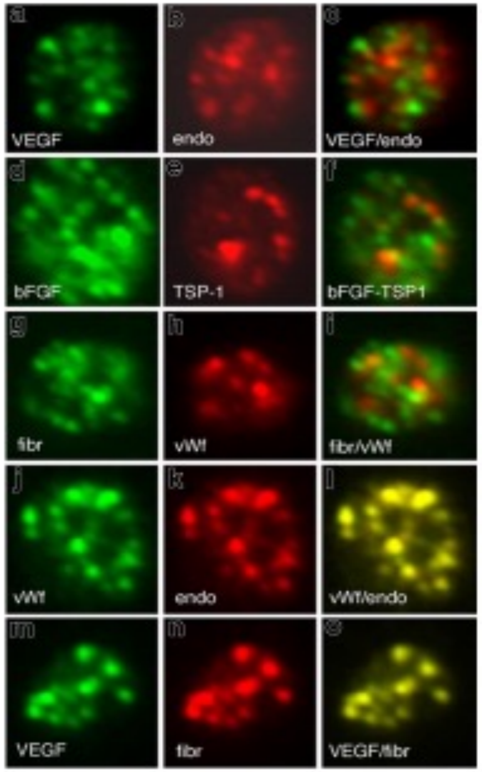
A

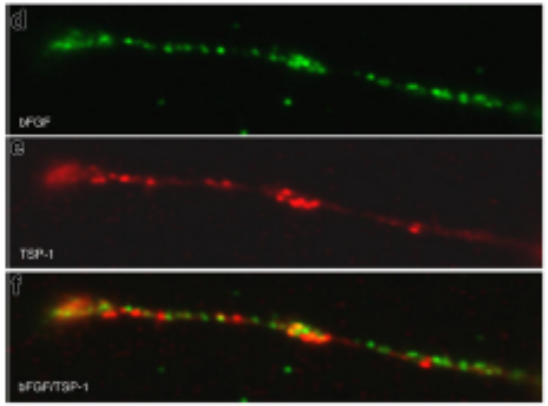

Pathogen recognition
Auto and paracrine stimulation
Neutrophil enhancement
Lymphocyte modulation
Endothelial activation
Vascular damage surveillance
Receptors
Soluble molecules
Proteome
Functional signalosome

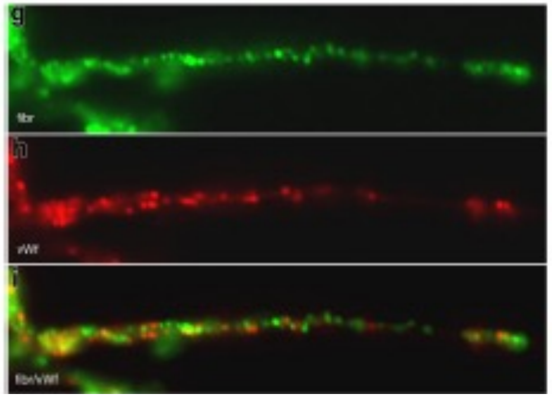
Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet α granules and differentially released

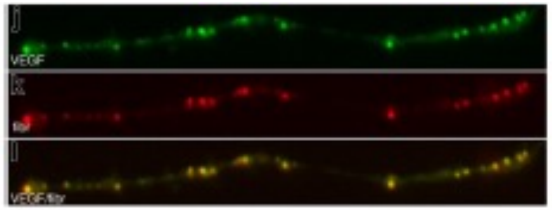
Joseph E. Italiano Jr,[1,2] Jennifer L. Richardson,[1] Sunita Patel-Hett,[1,2] Elisabeth Battinelli,[1,3] Alexander Zaslavsky,[2] Sarah Short,[2] Sandra Ryeom,[2] Judah Folkman,[2] and Giannoula L. Klement[2,4]

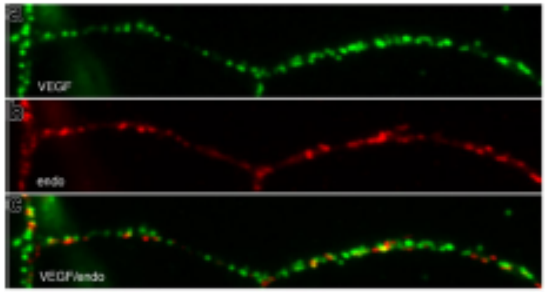
BLOOD, 1 FEBRUARY 2008 · VOLUME 111, NUMBER 3

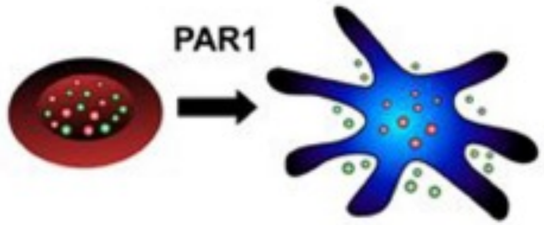


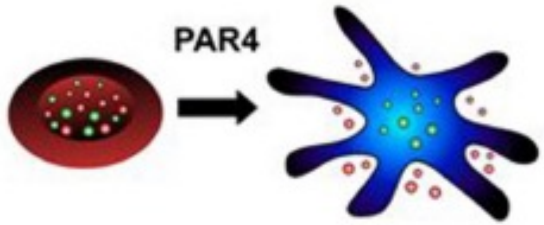








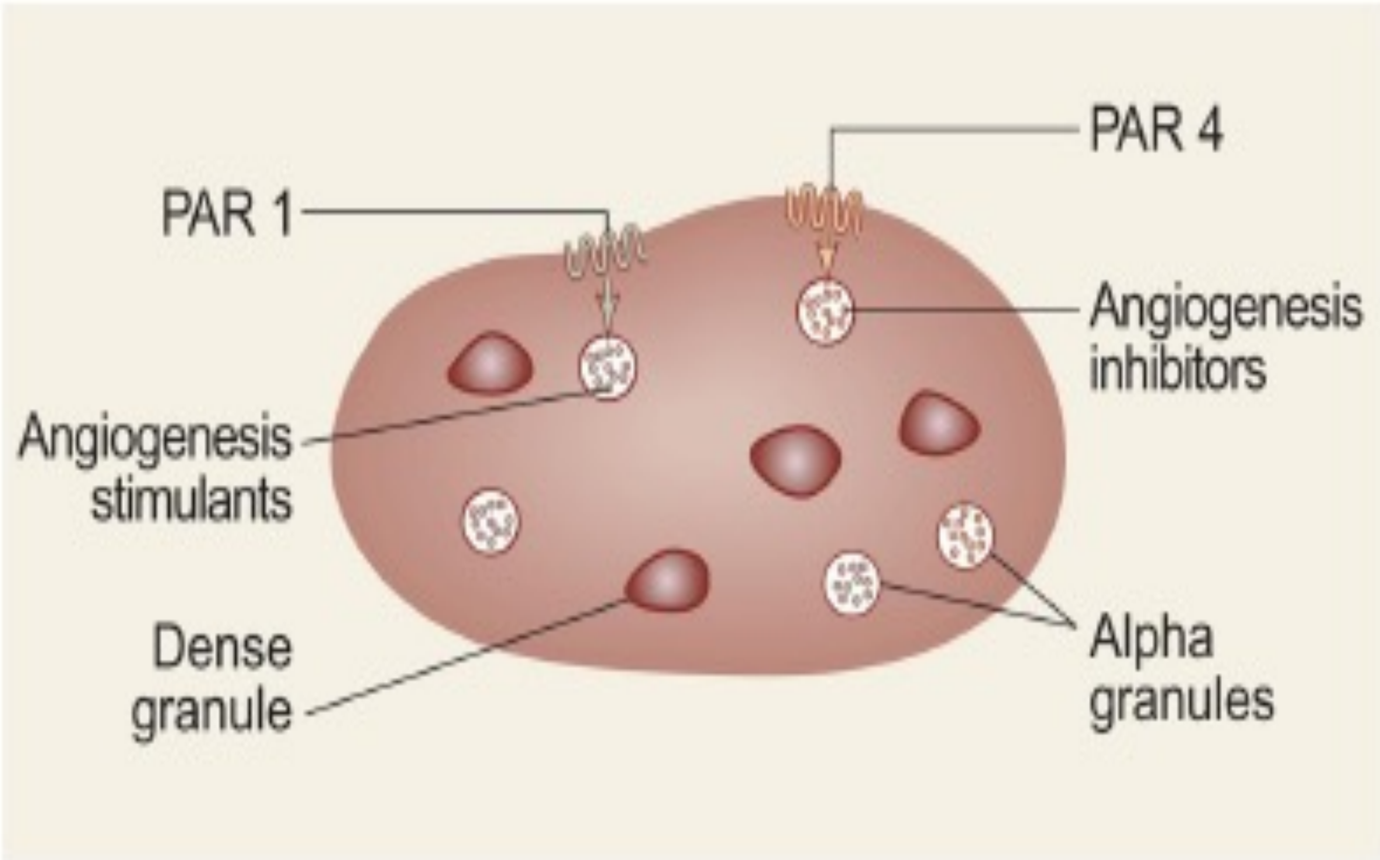




The yin-yang of platelet granules

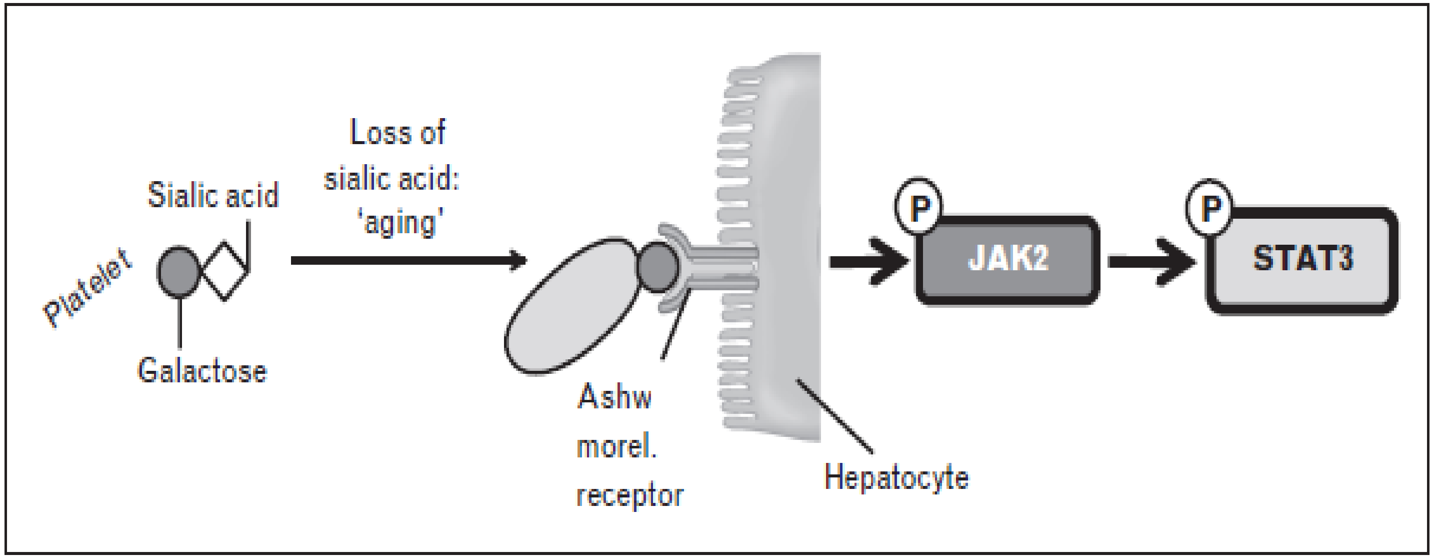
Charles S. Abrams UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

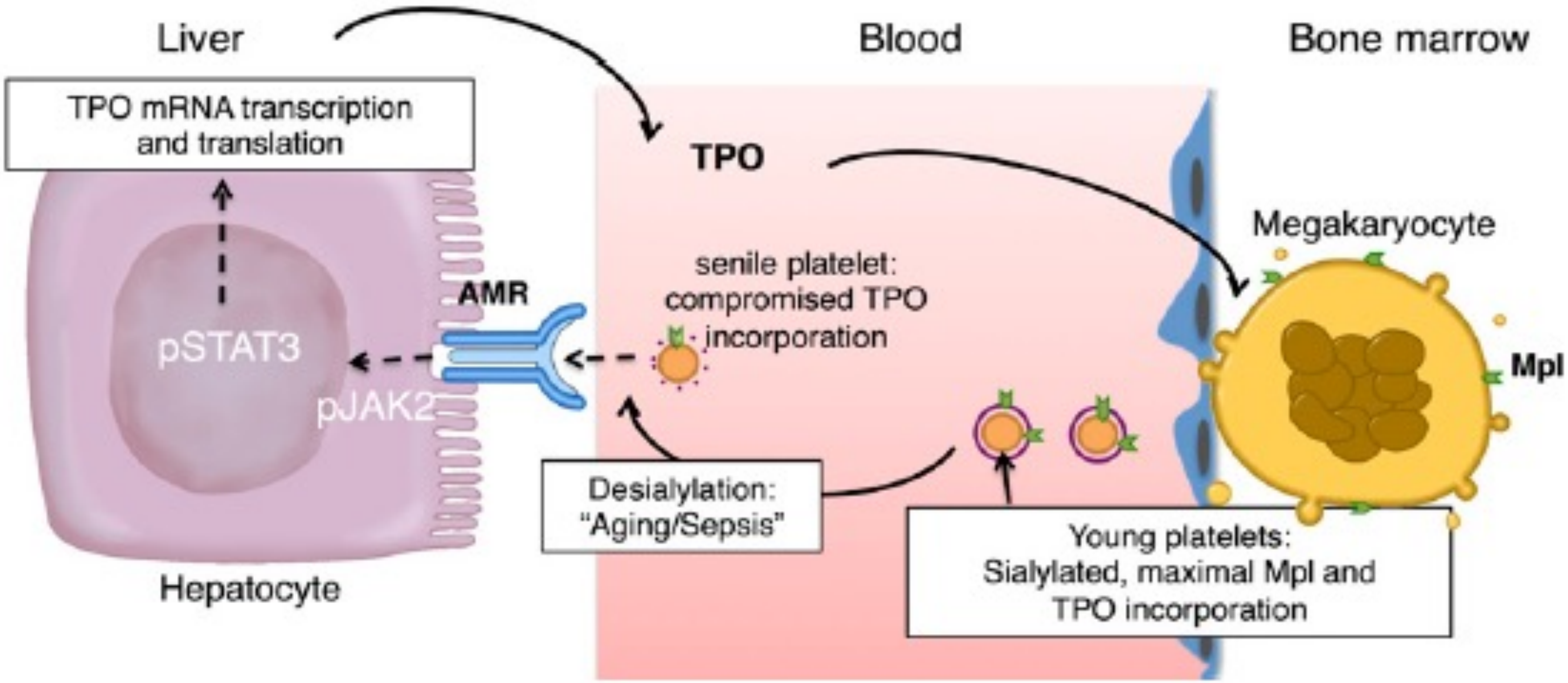
blood 1 FEBRUARY 2008 | VOLUME 111, NUMBER 3



KEY POINTS

- The Ashwell–Morrell receptor (AMR) recognizes senescent, desialylated platelets under steady state conditions.
- Desialylated platelets and the AMR are the physiological ligand–receptor pair regulating hepatic thrombopoietin (TPO) mRNA production.
- The AMR-mediated removal of desialylated platelets regulates TPO synthesis in the liver by recruiting JAK2 and STAT3 to increase thrombopoiesis.





(*Blood*. 2015;126(16):1877-1884)

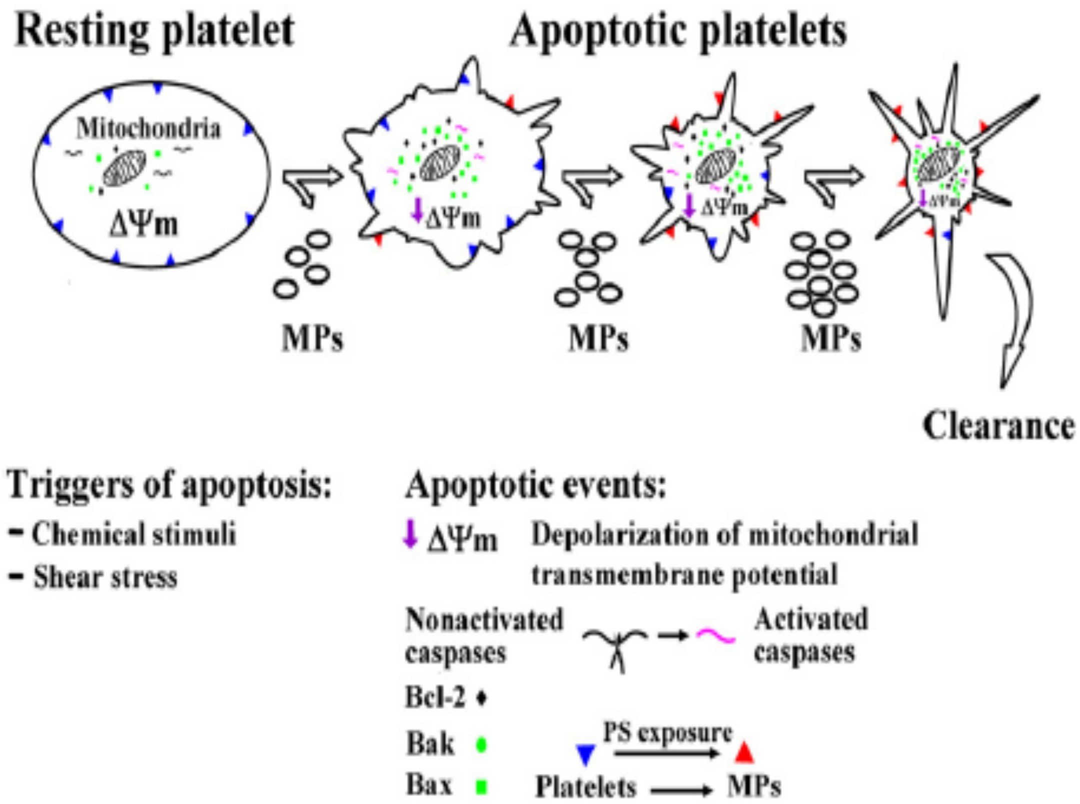
Cell *128*, 1173–1186, March 23, 2007

Programmed Anuclear Cell Death Delimits Platelet Life Span

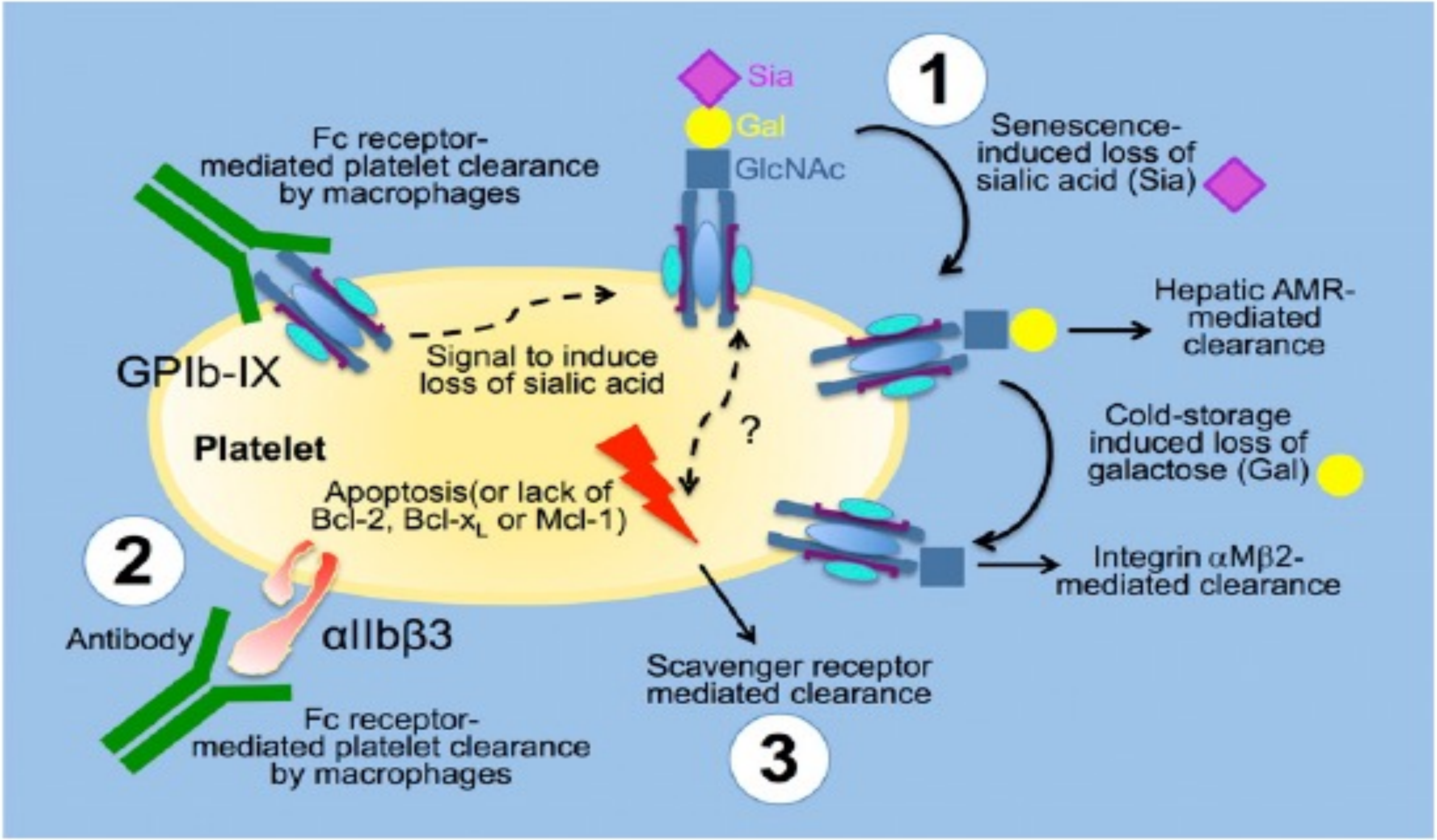
Kylie D. Mason,[2,4] Marina R. Carpinelli,[1] Jamie I. Fletcher,[2] Janelle E. Collinge,[1] Adrienne A. Hilton,[1] Sarah Ellis,[5] Priscilla N. Kelly,[2] Paul G. Ekert,[6] Donald Metcalf,[3] Andrew W. Roberts,[3] David C.S. Huang,[2,7,*] and Benjamin T. Kile[1,4,7,*]

BCL-xl **BAK**

sopravvivenza delle piastrine



Platelet clearance mechanisms.



(*Blood*. 2015;126(16):1877-1884)

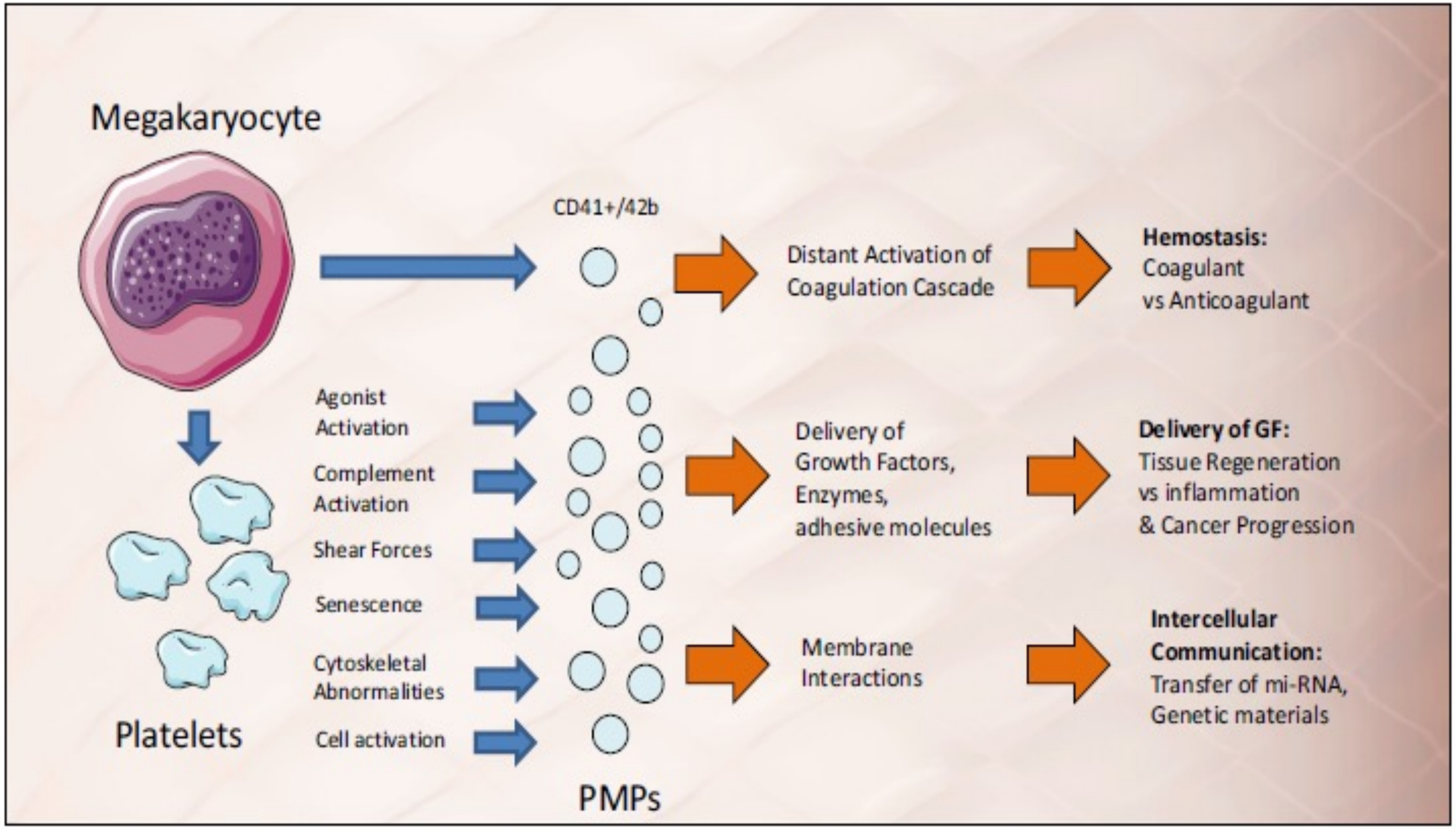
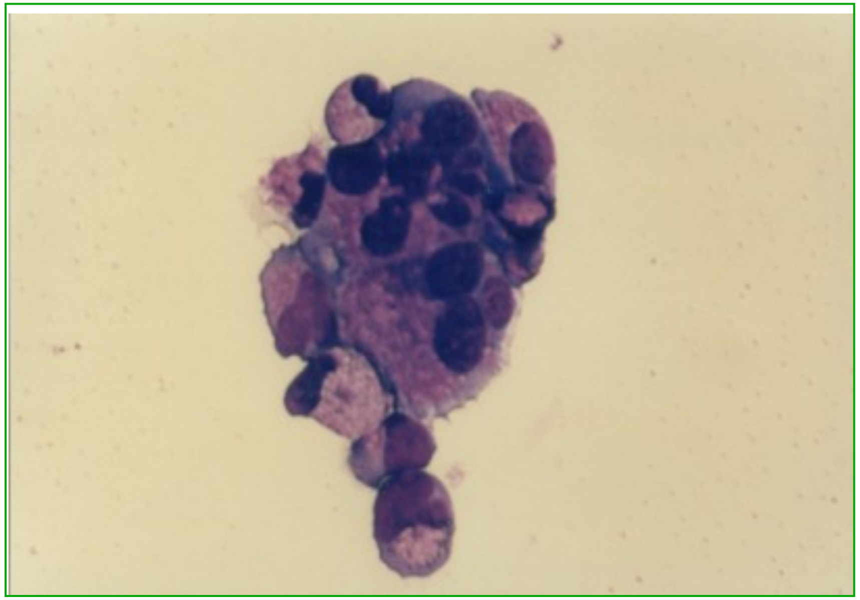


Fig. 1. Mechanisms of generation of PMPs from platelets and megakaryocytes and their mechanism of action.

H.A. Goubran et al./Transfusion and Apheresis Science 52 (2015) 12–18



………the enigmatic megakaryocyte gradually reveals its secrets

K. Kaushansky