LIENS PHYSIOPATHOLOGIQUES ENTRE THROMBOSE & CANCER

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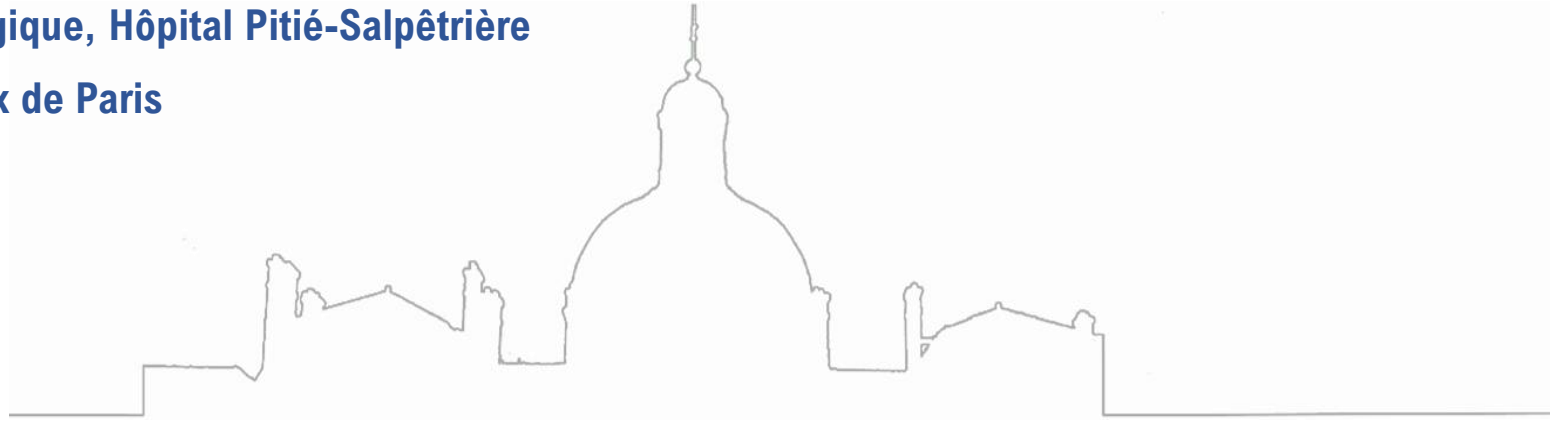
Assistance Publique Hôpitaux de Paris

Sorbonne Université



MÉDECINE SORBONNE UNIVERSITÉ

ICAN Institute of Cardiometabolism And Nutrition TOGETHER

UNICO AP-HP.6

UMR CAN Unité Mixte de Recherche UMRS 1166

HÔPITAUX UNIVERSITAIRES PITIÉ SALPÊTRIÈRE CHARLES FOIX

Association Cancer & Thrombose

Etude de population (1997-2017)
- **499 092 patients avec diagnostic de cancer**
- **1 497 276 témoins sans cancer**

blood
RESEARCH ARTICLE | NOVEMBER 10, 2020

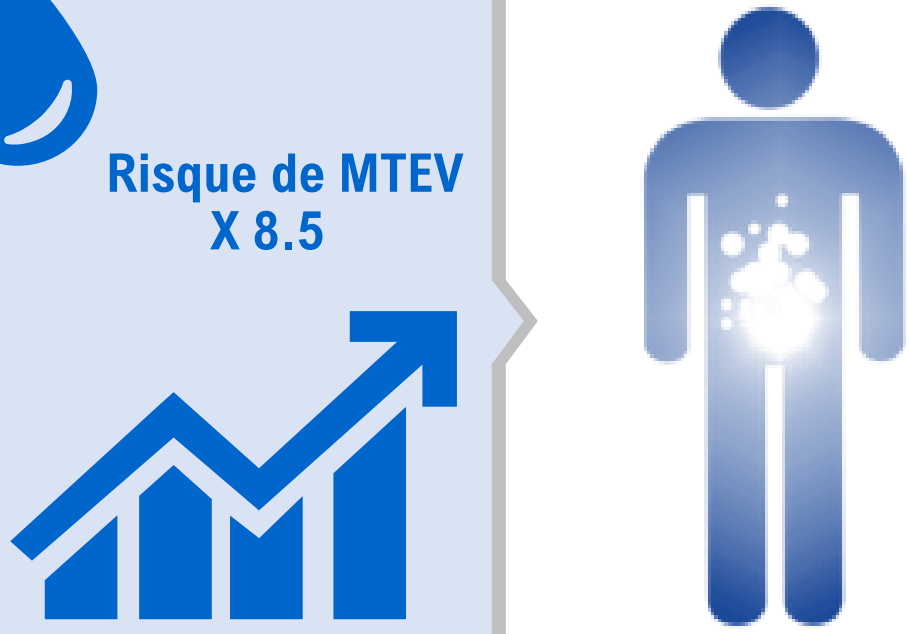
Venous thromboembolism in cancer patients: a population-based cohort study

Frits I. Mulder ✉, Erzsébet Horvàth-Puhó, Nick van Es, Hanneke van Laarhoven, Lars Pedersen, Florian Moik, Cihan Ay, Harry R Buller, Henrik Toft Sørensen

- **Incidence cumulée de MTEV à 12 mois : 3% *vs* 0.6%**
- **Hazard ratio : 8.5 (95% CI 8.2-8.8)**

Thrombose et

Risque de MTEV X 8.5



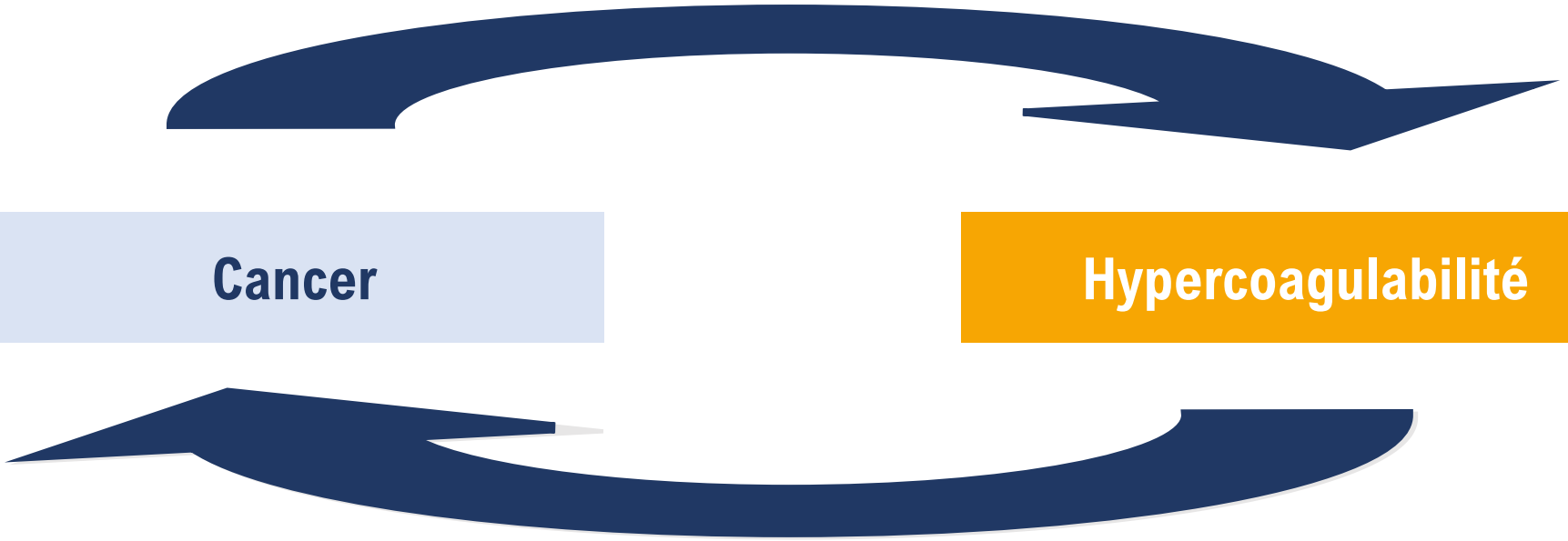
Facteurs de Risque de MTEV

Type de Cancer	Cancer du pancreas, de l'ovaire, du poumon, tumeurs cérébrales, lymphomes
Stade du Cancer	Stades avancé et métastatiques
Délai après le diagnostic	3 mois suivant le diagnostic
Traitements	Chimiothérapie, chirurgie, radiothérapie, thérapies ciblées

Mulder et al. Blood. 2020 Nov 10 [Epub ahead of print].

Hémostase & Thrombose : une relation bidirectionnelle

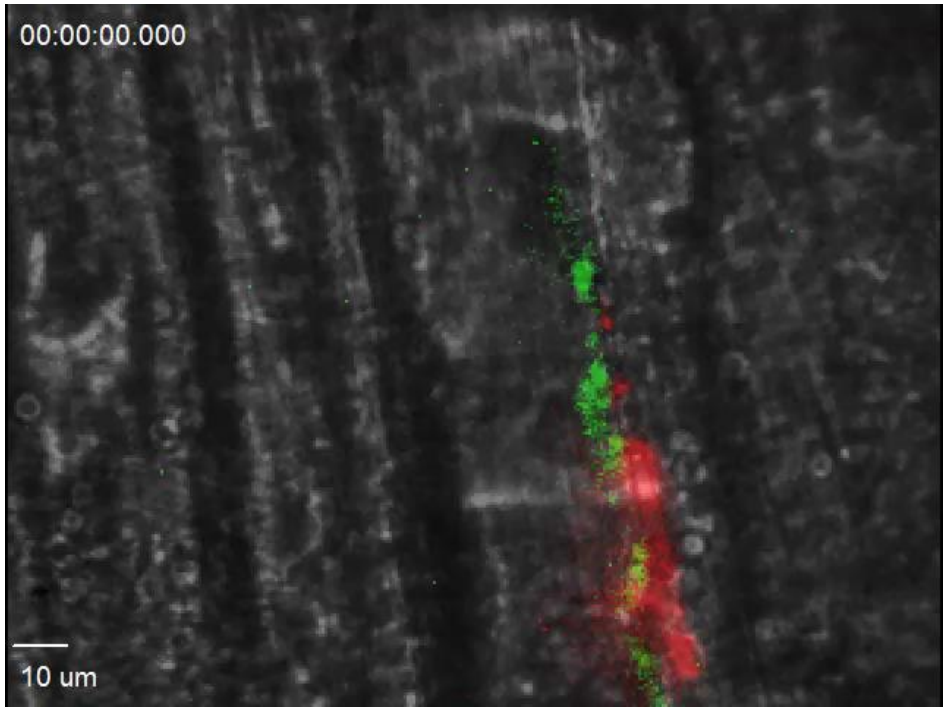
Le cancer favorise l'hypercoagulabilité



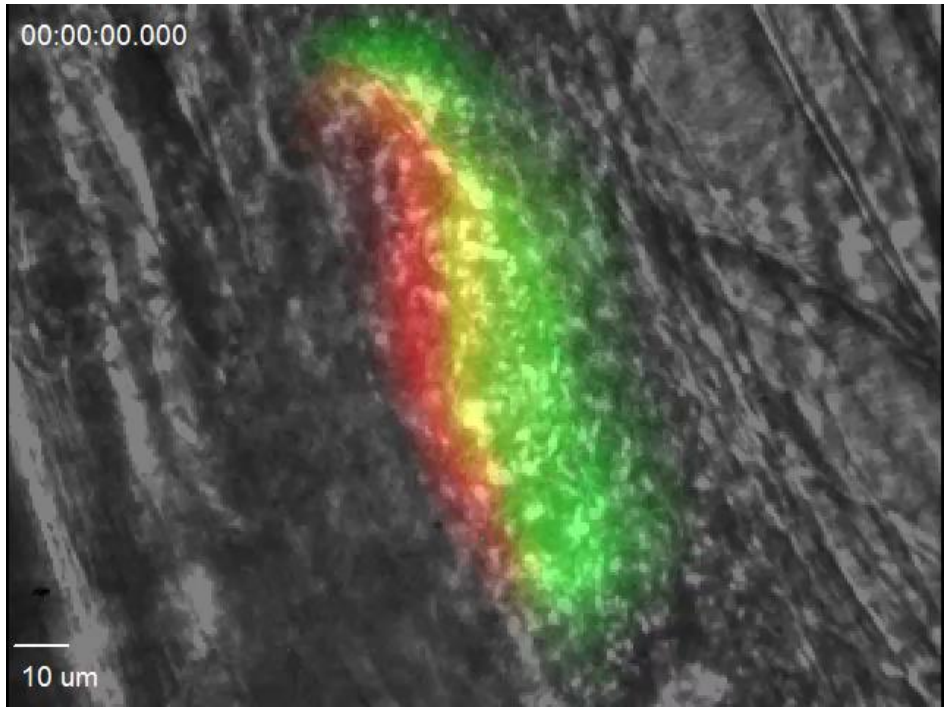
L'hypercoagulabilité favorise la progession tumorale

Cancer et Phénotype prothrombotique

Modèle murin WT



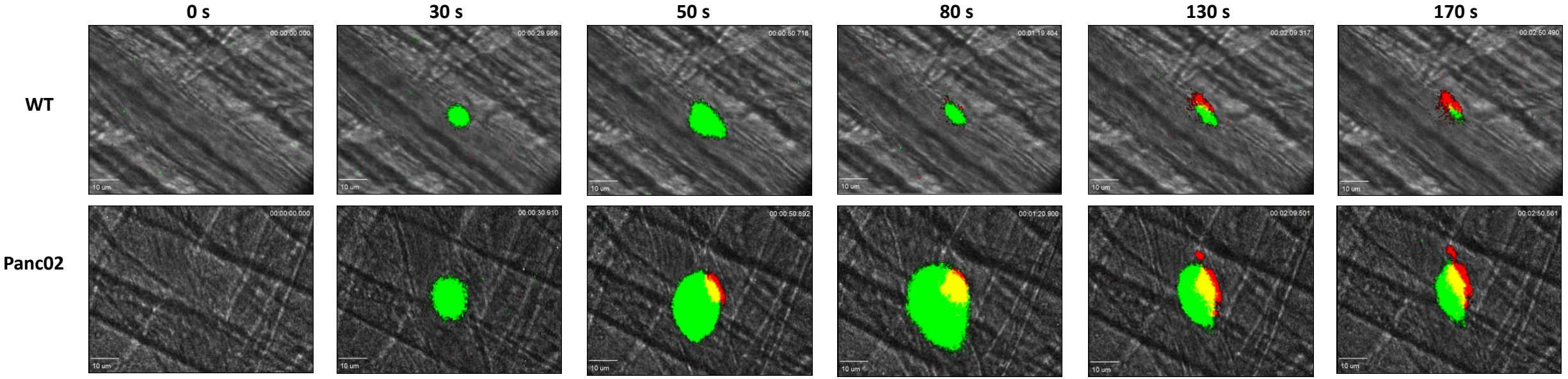
Modèle murin ectopique de cancer du pancréas



Courtesy Soray Mezouar

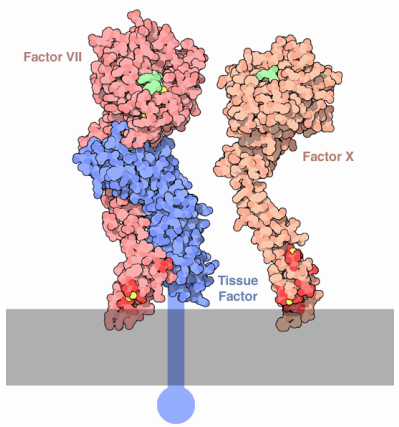
Cancer et Phénotype prothrombotique

Modèle murin ectopique de cancer du pancréas

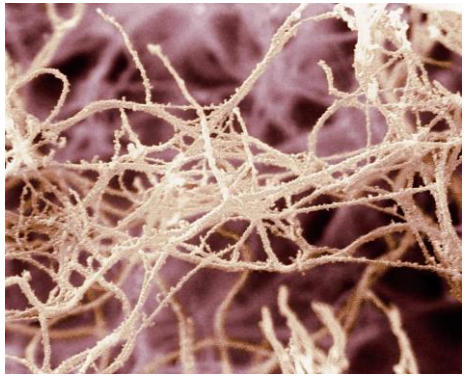


Thomas et al. J Exp Med. 20

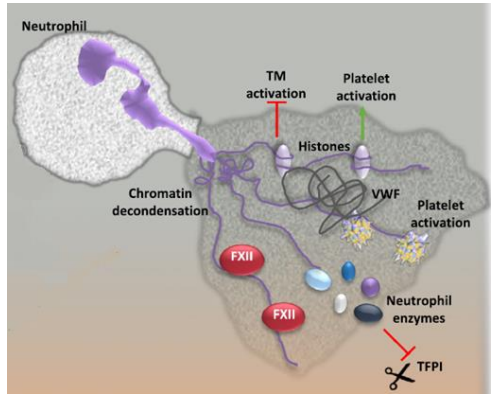
Les Principaux Acteurs



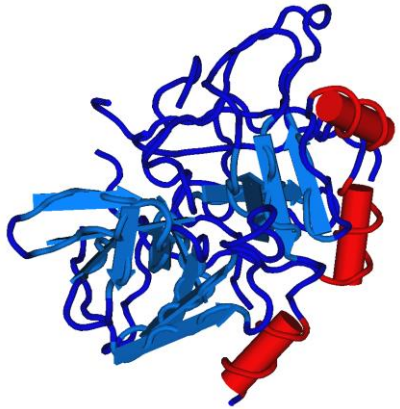
Facteur Tissulaire



Fibrine



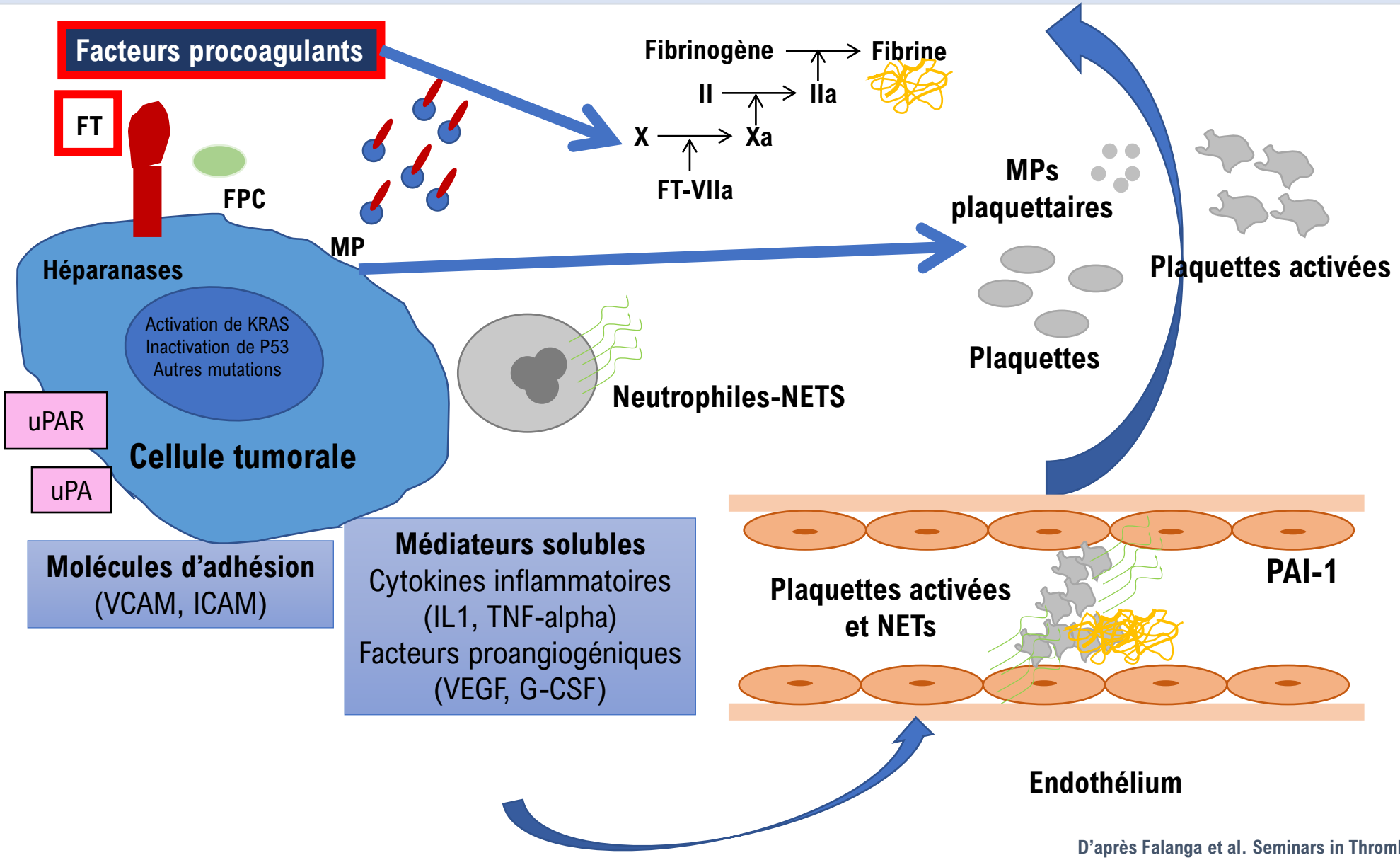
NETs



Thrombine

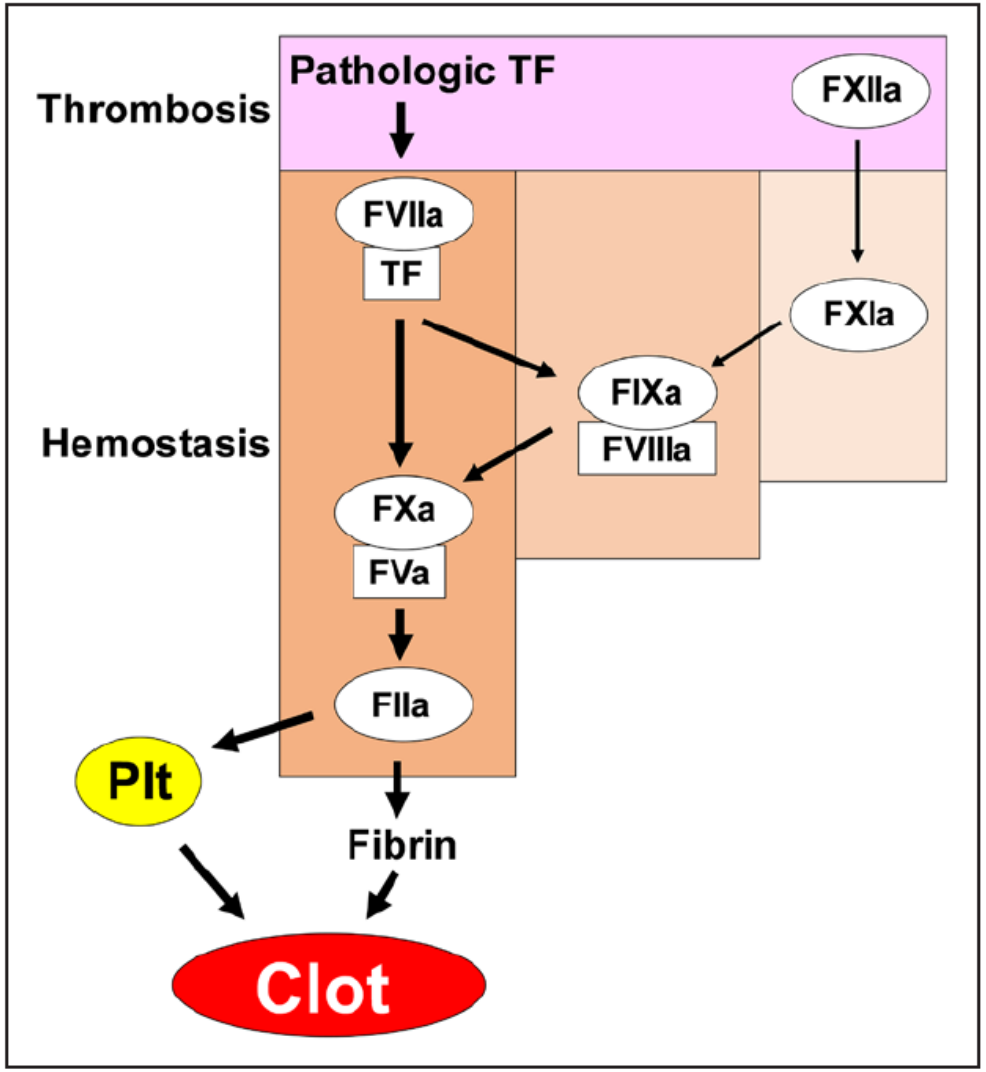
Plaquettes

Les Mécanismes à l'origine de l'Hypercoagulabilité



D'après Falanga et al. Seminars in Thrombosis and Haemostasis 2015

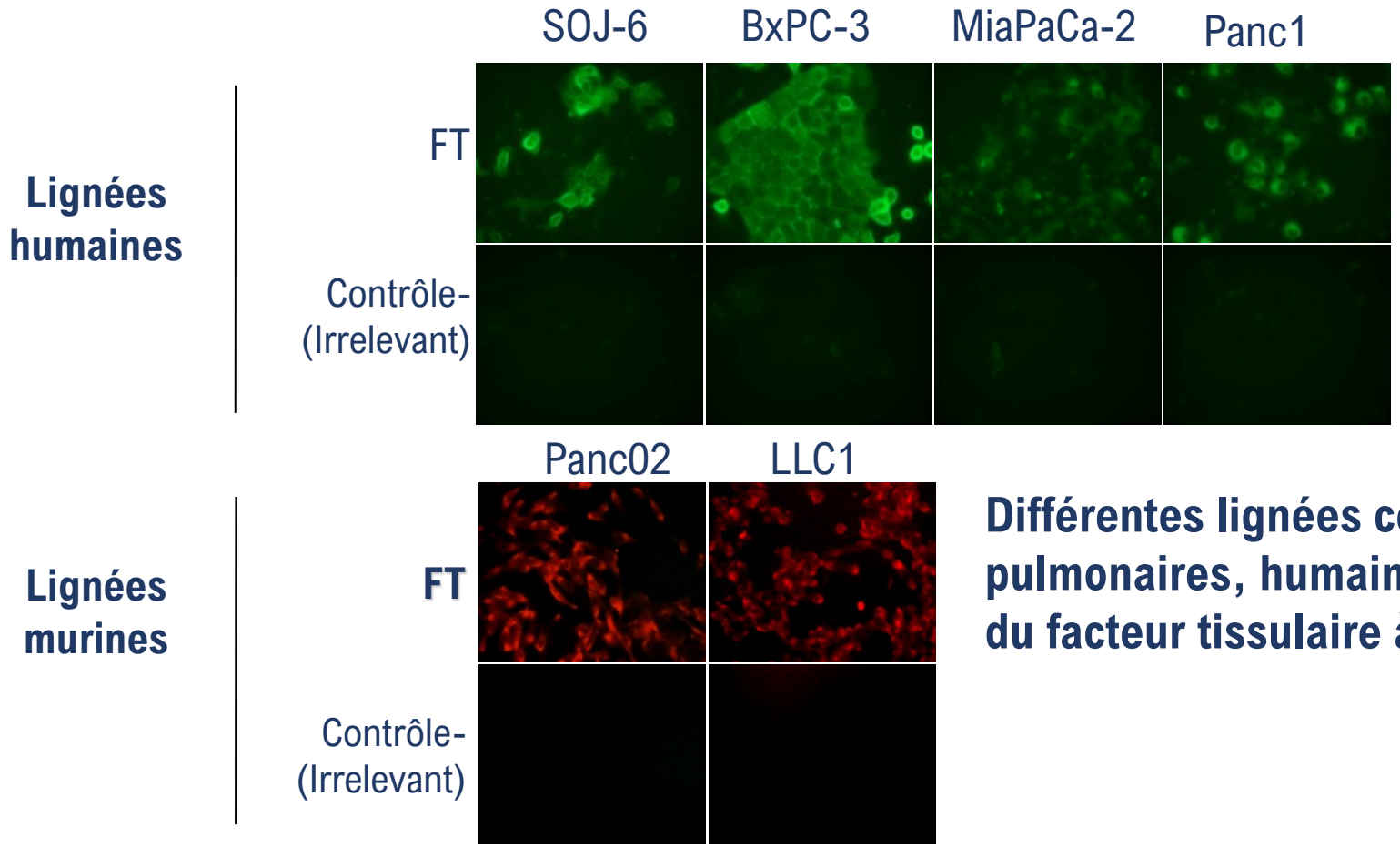
Rôle central du facteur tissulaire



- Glycoprotéine transmembranaire
- Expression constitutive : épiderme, muqueuses, fibroblastes, cellules musculaires…cellules tumorales
- Expression inductible : monocytes, cellules endothéliales (via IL1/ NF-κB)
- Présent à la surface cellulaire sous forme « encryptée » jusqu'à ce qu'une lésion de la membrane survienne et permette son activation
- Principal activateur de la coagulation

Grover et al. Arterioscler Thromb Vasc Biol. 2018 Apr;38(4):709-725.

Expression constitutive de facteur tissulaire par les cellules tumorales



Différentes lignées cellulaires pancréatiques, pulmonaires, humaines et murines expriment du facteur tissulaire à leur surface

Régulation de l'expression du facteur tissulaire par les cellules tumorales

Le niveau d'expression du FT par les cellules cancéreuses est lié a l'activation d'oncogènes ou l'inactivation de gènes suppresseurs de tumeurs

Table 1. Linkage between oncogenic events and procoagulant phenotype of cancer cells

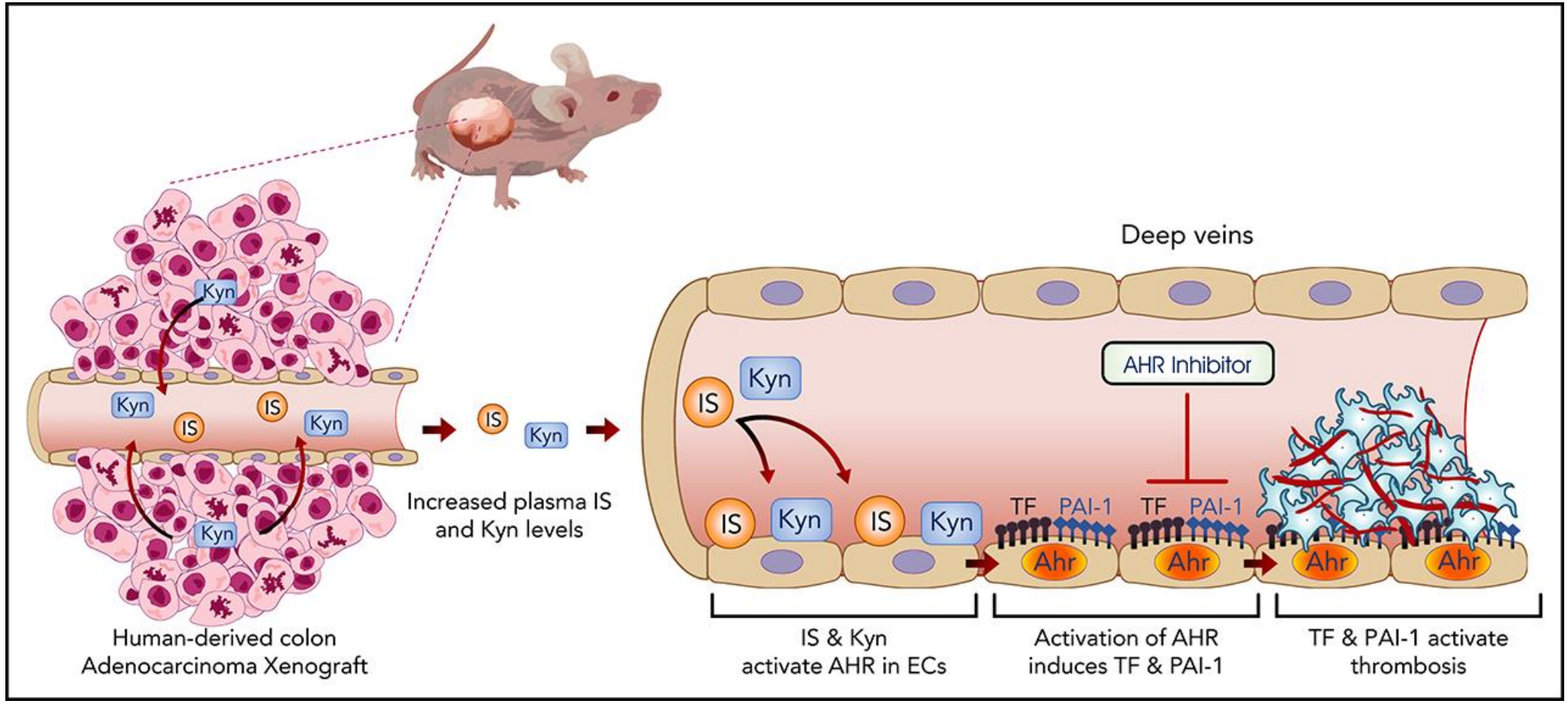
Genetic Influence	Consequence of Deregulation	References
Oncogenes		
K-*ras*	Upregulation of TF in human CRC cells	(37)
H-*ras*	Downregulation of TFPI 2	(44)
H-*ras*	Upregulation of uPA	(45, 46)
H-*ras*	Downregulation of uPA in invasive cells	(47)
H-*ras*	Upregulation of mucins	(48)
src	Upregulation of TF	(49)
EGFR	Upregulation of TF	(50)
EGFRvIII	Upregulation of TF	Milsom, Yu, Magnus & Rak (unpublished)
EGFRvIII	Increase in vesiculation (may contribute to release of procoagulant activity)	(51)
HER-2	Increase in TF expression	Yu & Rak (unpublished)
HER-2	Upregulation of mucins	(48)
Unknown	Ectopic expression of in cancer FVII	(52)
Unknown	Ectopic expression of thrombin-like protein	(53)
PML-RARa	TF-dependent coagulopathy	(54)
c-MET	Deregulation of PAI-1 and COX-2	(55)
Tumor Suppressors		
P53	Upregulation of TF in human CRC cells	(37)
P53	Increase in release TF containing microvesicles into the circulation	(37)
PTEN	Upregulation of TF	(56)

TF: tissue factor; PAI -1: plasminogen activator inhibitor type 1; COX 2: cyclooxygenase; CRC: colorectal carcimoma; TFPI 2: tissue factor pathway inhibitor; FVII: coagulation factor VII; uPA: urokinase plasminogen activator.

Rak J et al. Cancer Metastasis Rev. 2000;19(1-

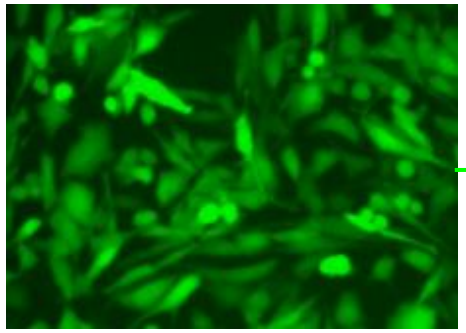
Induction de l'expression du Facteur Tissulaire par les Cellules endothéliales

Metabolites in a mouse cancer model enhance venous thrombogenicity through the aryl hydrocarbon receptor–tissue factor axis



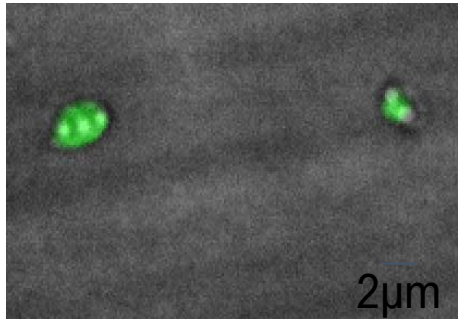
Belghasem et al. Blood 2019

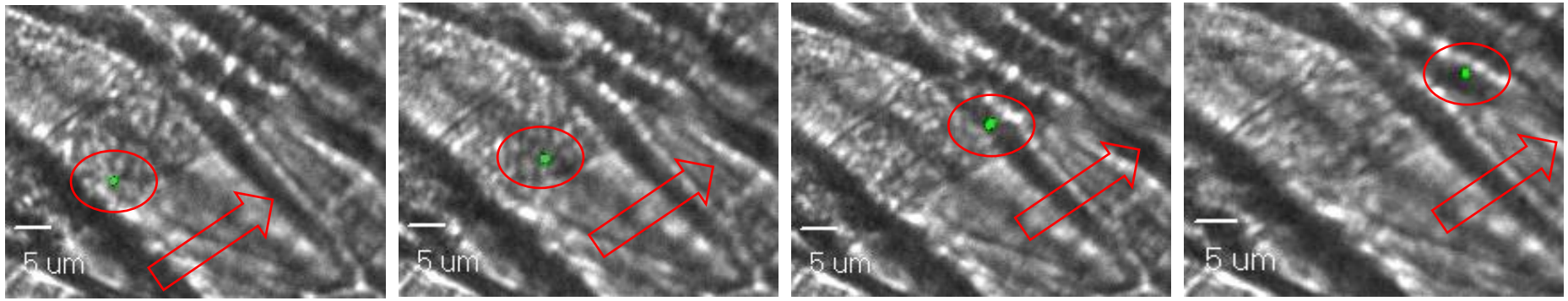
Contact du facteur tissulaire avec le courant sanguin



Panc02-GFP

Tumeur -GFP





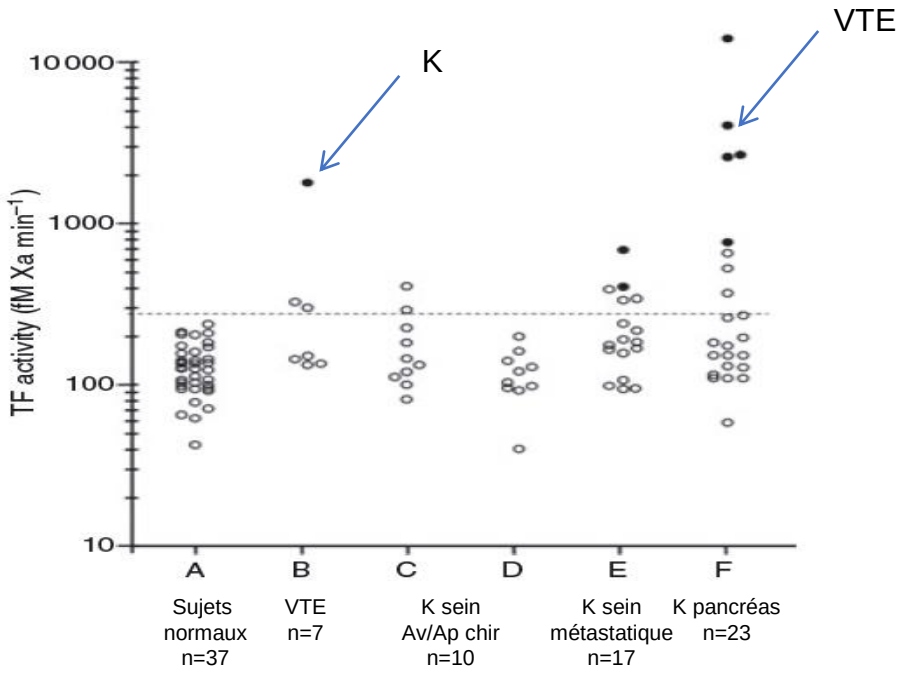
La tumeur libère des vésicules de taille correspondant à celle des microparticules dans la circulation sanguine

Thomas et al. J Exp Med. 2009

Microparticules FT+ : Biomarqueur de risque?

Microparticle-associated tissue factor activity: a link between cancer and thrombosis?

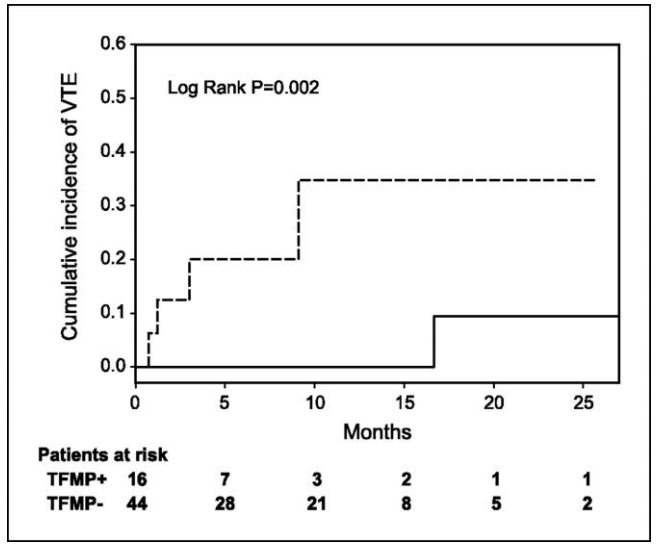
M. E. T. TESSELAAR,* F. P. H. T. M. ROMIJN,† I. K. VAN DER LINDEN,‡ F. A. PRINS,§ R. M. BERTINA‡ and S. OSANTO*



Tesselar et al. J Throm Haemost 2007

Tumor-Derived Tissue Factor–Bearing Microparticles Are Associated With Venous Thromboembolic Events in Malignancy

Jeffrey I. Zwicker,[1] Howard A. Liebman,[3] Donna Neuberg,[2] Romaric Lacroix,[1] Kenneth A. Bauer,[1] Barbara C. Furie,[1] and Bruce Furie[1]

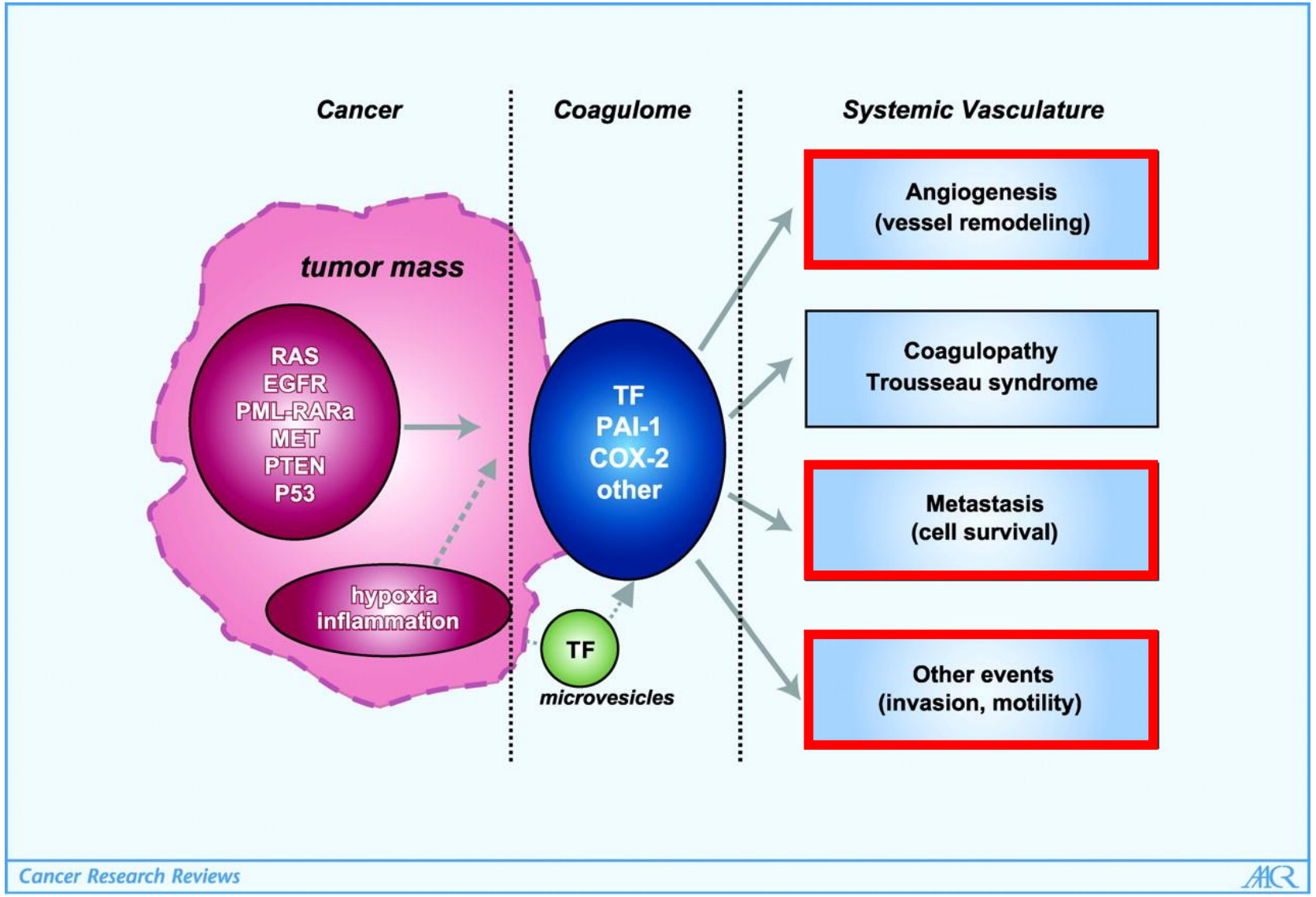


n=60 Patients avec cancer sans thrombose au moment du dosage des MPs

Clinical Cancer Research
AACR American Association for Cancer Research

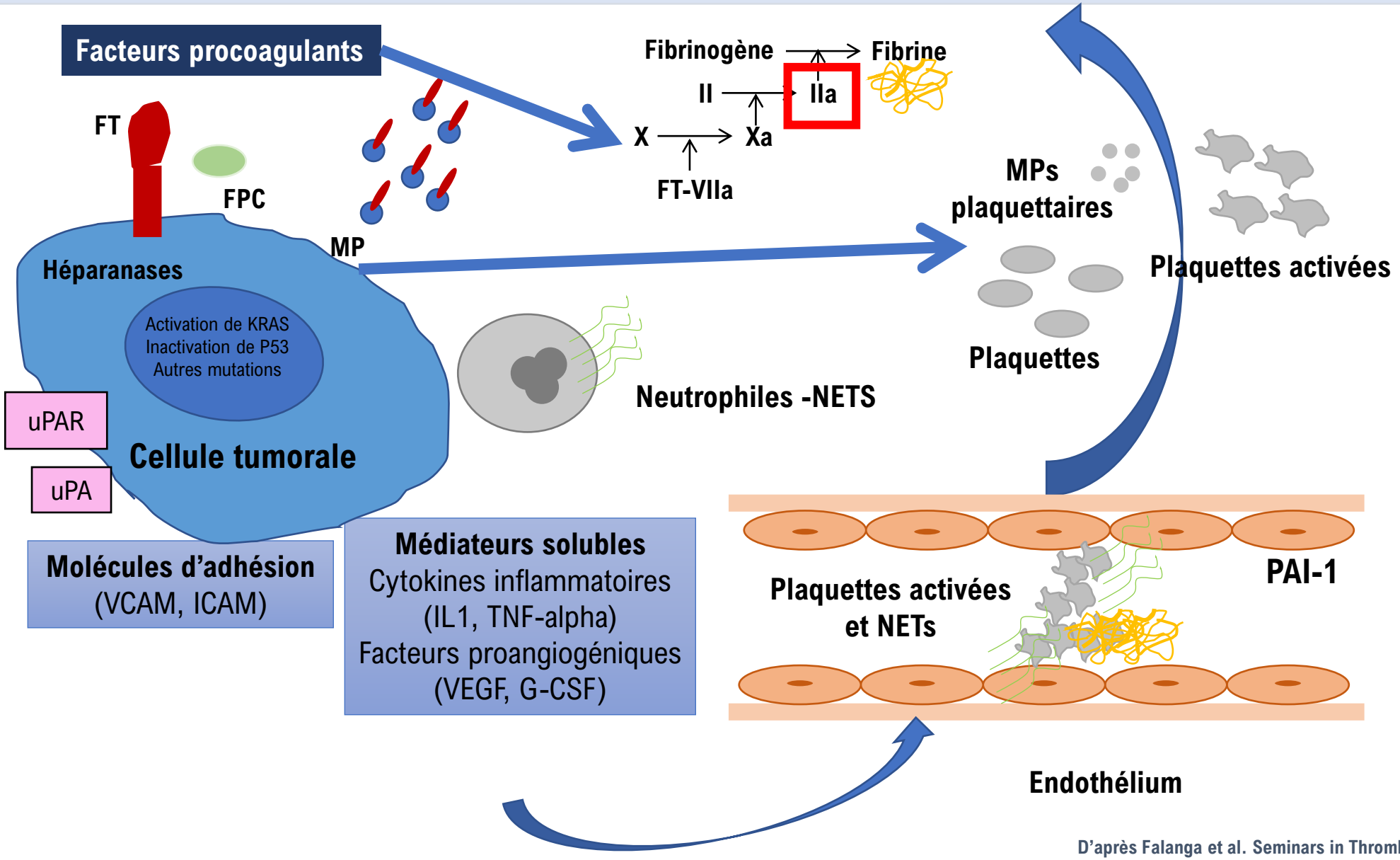
Zwicker et al. Clin Cancer Res 2009

Interrelationships between oncogenic events, state of the coagulome, and angiogensesis



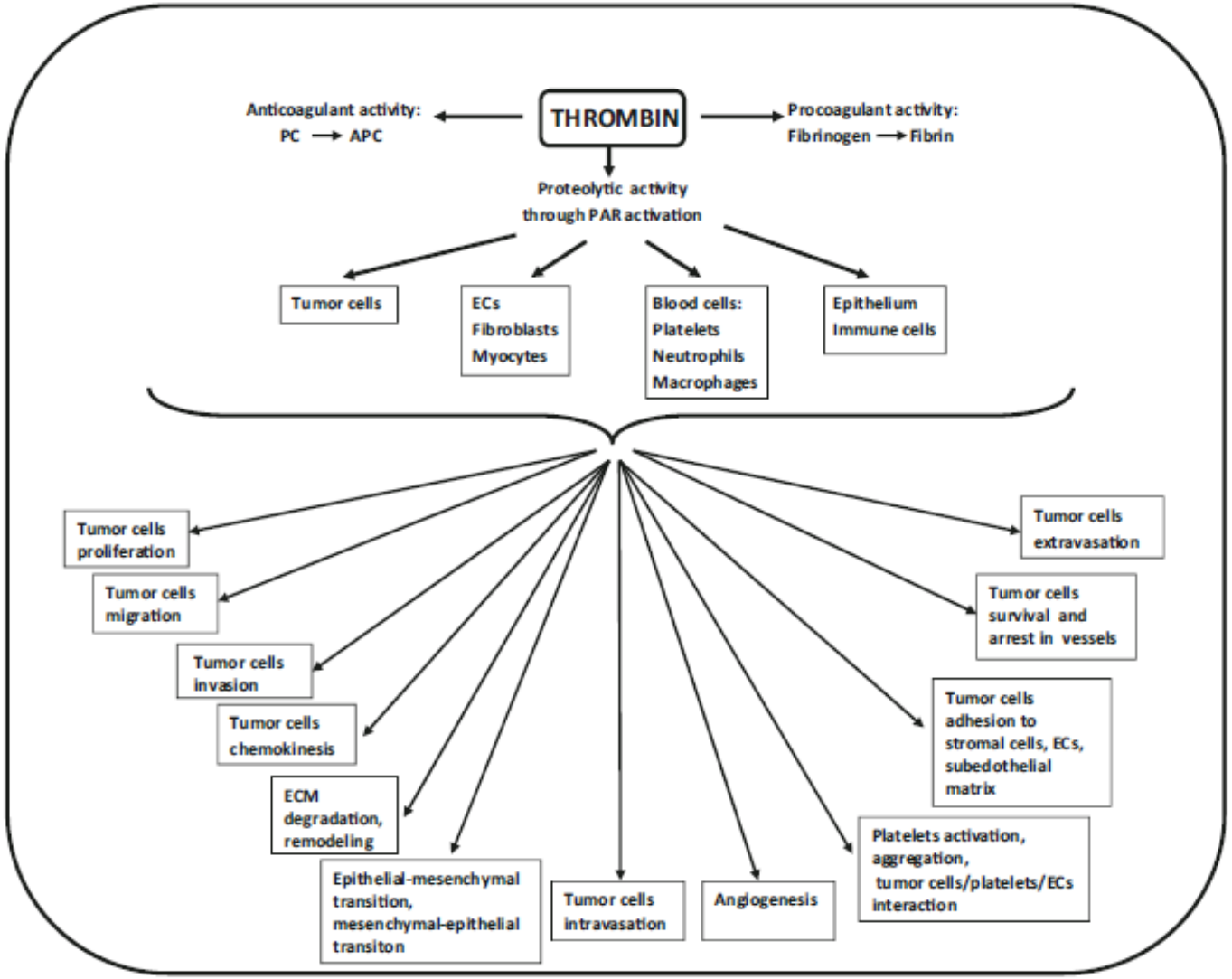
Rak J et al. Cancer Res 2006;66:10643-10646

Les Mécanismes à l'origine de l'Hypercoagulabilité



D'après Falanga et al. Seminars in Thrombosis and Haemostasis 2015

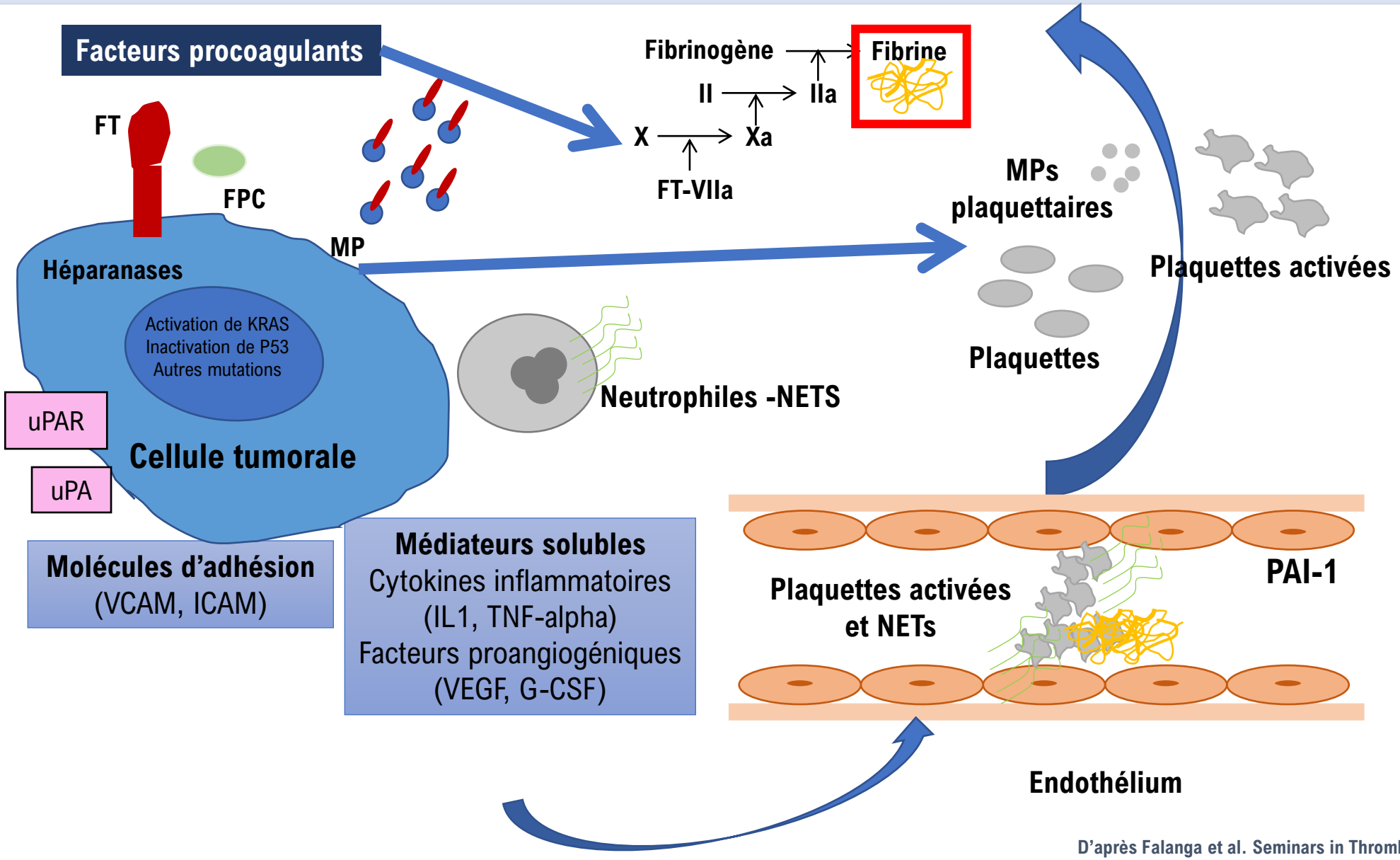
La Thrombine, au-delà de son rôle pivot dans la coagulation…



Induction de signaux intracellulaires au niveau de nombreux systèmes qui favorisent l'angiogénèse, la croissance tumorale et le processus métastatique

Wojtukiewicz et al. Cancer Metastasis Rev 2016

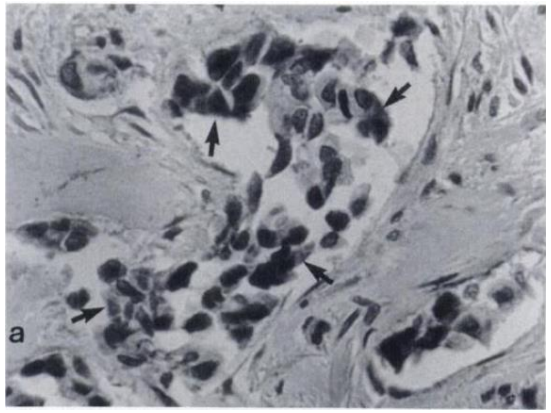
Les Mécanismes à l'origine de l'Hypercoagulabilité



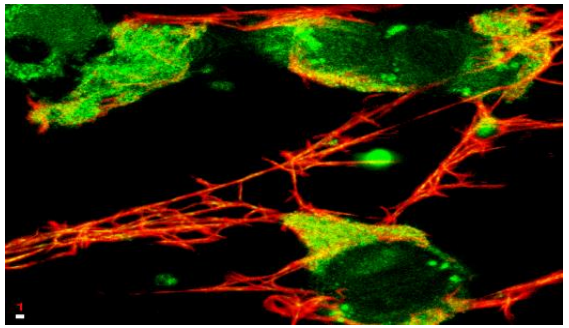
D'après Falanga et al. Seminars in Thrombosis and Haemostasis 2015

Fibrinogène/Fibrine

Présence de fibrine au niveau des tissus cancéreux



Les cellules tumorales ont la capacité de se lier directement au Fg et à la fibrine



Costantini V et al. Cancer Res 1991

Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells

Joseph S. Palumbo, Keith W. Kombrinck, Angela F. Drew, Timothy S. Grimes, John H. Kiser, Jay L. Degen, and Thomas H. Bugge

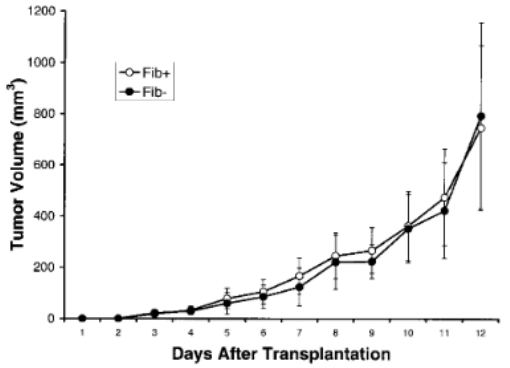
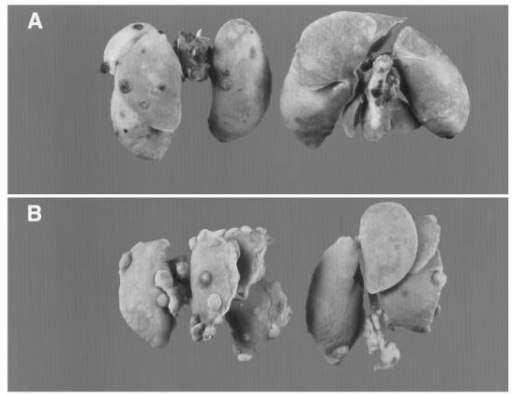


Figure 1. Fibrin(ogen) deficiency does not reduce the growth rate of subcutaneously transplanted LLC. A single cell suspension of 5×10^5 LLC cells was injected subcutaneously into the dorsal, midscapular skin of Fib$^-$ ($n = 16$) and control ($n = 19$) mice. The individual tumor volumes were measured daily by calipation. The data presented are mean values and SDs for each time point. No significant difference was noted in tumor growth between Fib$^-$ and control mice ($P > .6$, random coefficient mixed model).

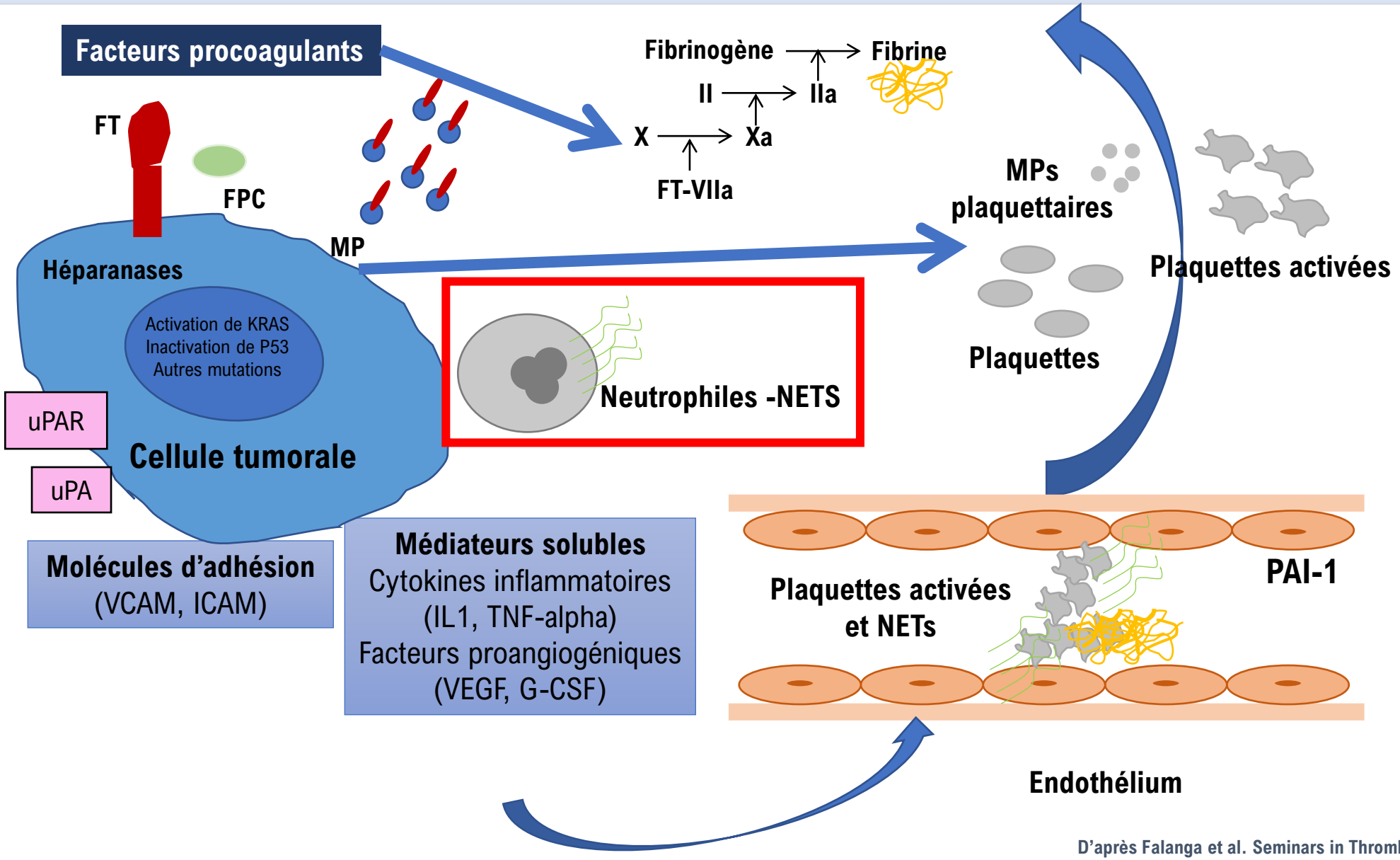


Fib + **Fib -**

Lewis lung carcinoma and B16-BL6 melanoma mice models

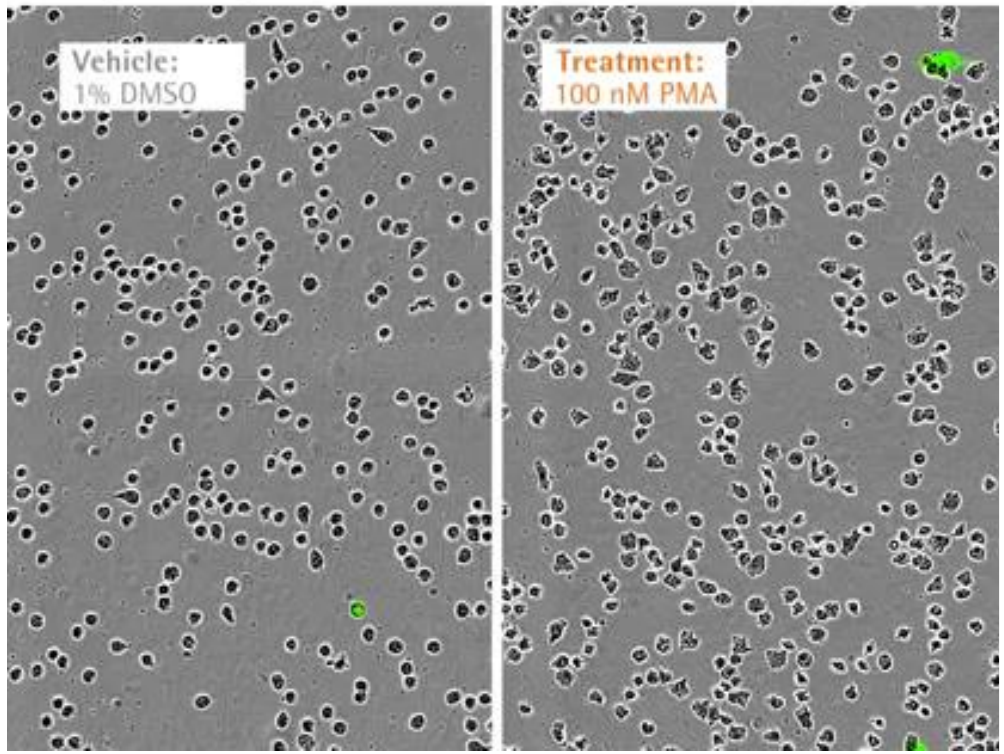
Palumbo et al. Blood 2000;96:3302-09

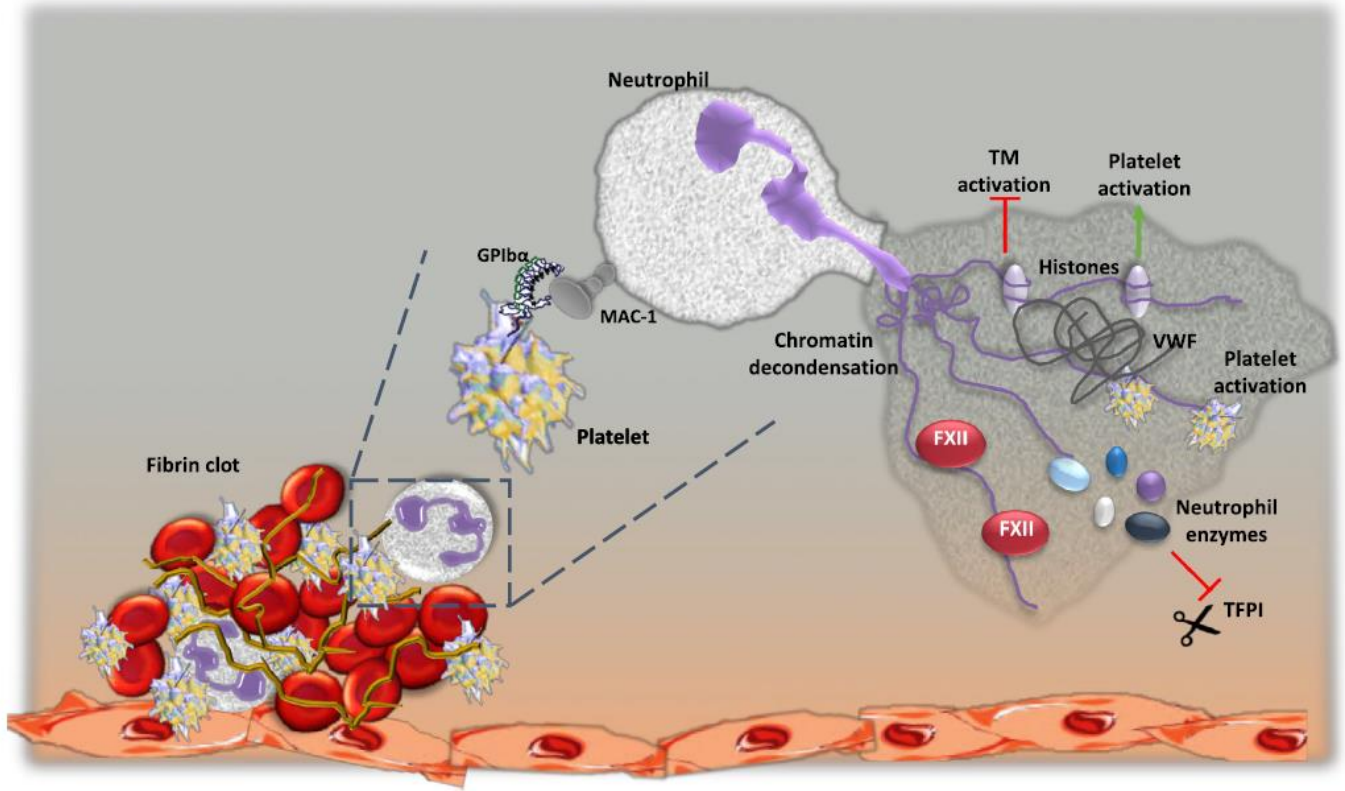
Les Mécanismes à l'origine de l'Hypercoagulabilité



D'après Falanga et al. Seminars in Thrombosis and Haemostasis 2015

NETs, Cancer et Thrombose





Preston et al. British Journal of Haematology, 2019, 186, 13–23

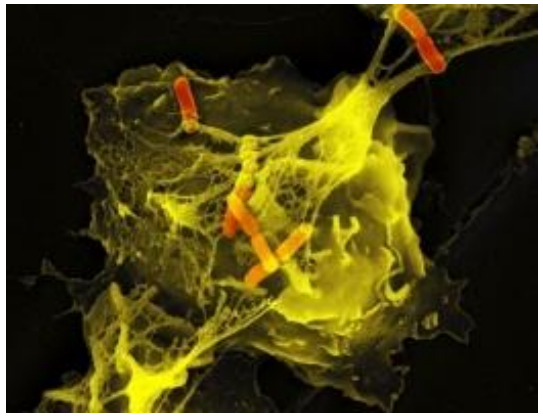
NETs, Cancer et Thrombose

PNAS

Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis

Mélanie Demers[a,b,c], Daniela S. Krause[d,e], Daphne Schatzberg[a,b], Kimberly Martinod[a,b,f], Jaymie R. Voorhees[a,b], Tobias A. Fuchs[a,b,c], David T. Scadden[d], and Denisa D. Wagner[a,b,c,1]

[a]Immune Disease Institute, Boston, MA 02115; [b]Program in Cellular and Molecular Medicine, Boston Children's Hospital, Boston, MA 02115; [c]Department of Pediatrics, Harvard Medical School, Boston, MA 02115; [e]Department of Pathology and [d]Center for Regenerative Medicine, Massachusetts General Hospital, Boston, MA 02114; and [f]Graduate Program in Immunology, Division of Medical Sciences, Harvard Medical School, Boston, MA 02115



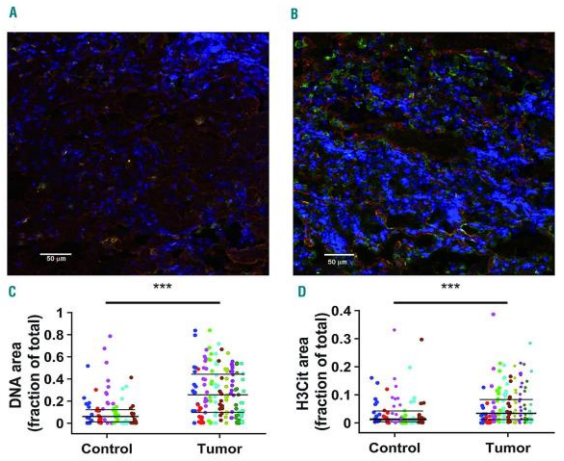
Demers et al. PNAS 2012 Aug 7;109(32):13076-81..

Neutrophils and neutrophil extracellular traps enhance venous thrombosis in mice bearing human pancreatic tumors

Yohei Hisada,[1] Steven P. Grover,[1] Anaum Maqsood,[1] Reaves Houston,[1] Cihan Ay,[2] Denis F. Noubouossie,[1] Brian C. Cooley,[3] Håkan Wallén,[4] Nigel S. Key,[1] Charlotte Thålin,[5] Ádám Z. Farkas,[6] Veronika J. Farkas,[6] Kiril Tenekedjiev,[7,8] Krasimir Kolev[6] and Nigel Mackman[1]

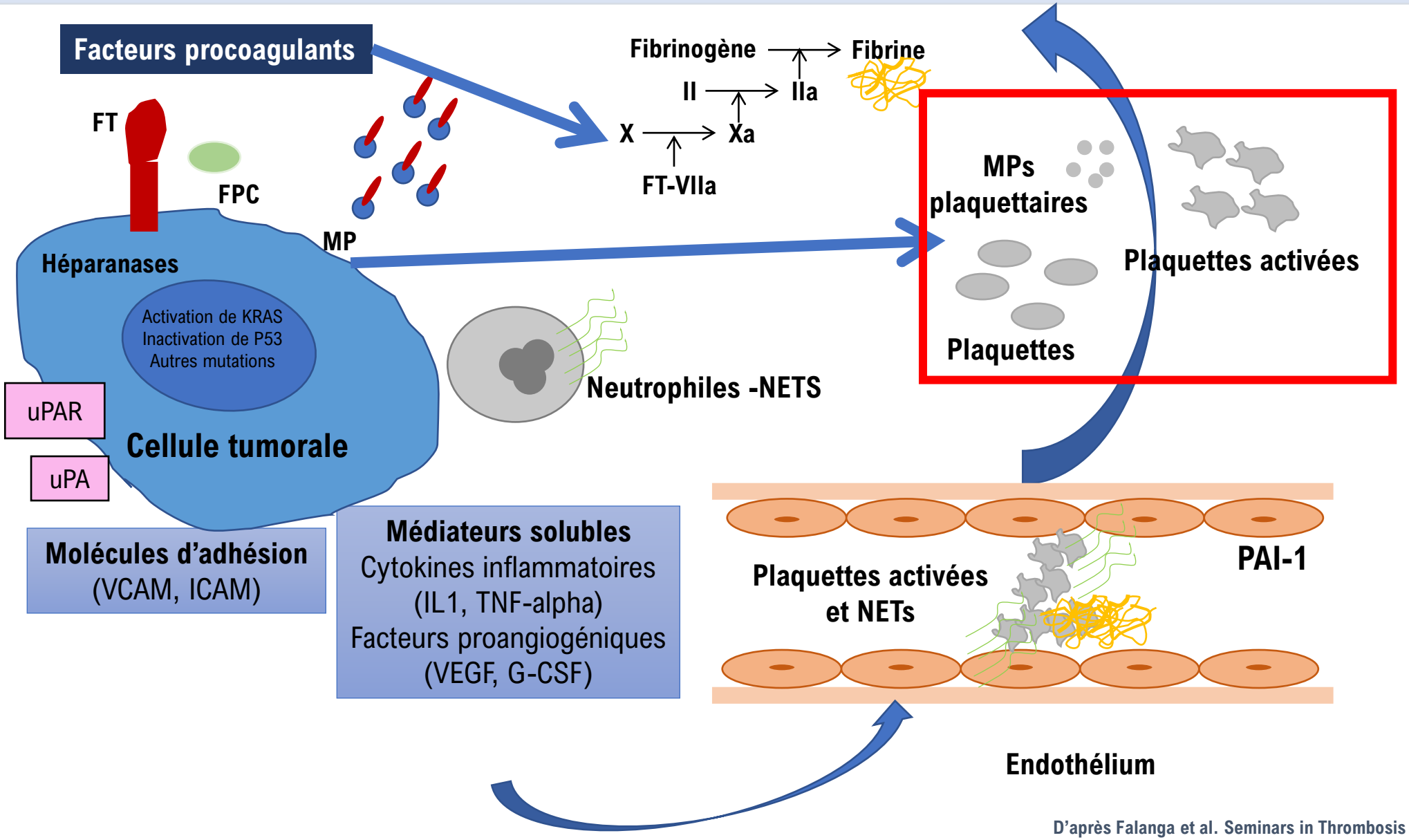
Nude mice bearing human pancreatic tumors (BxPc-3)

IVC stasis model of thrombosis.



Hisada et al. Haematologica. 2020 Jan;105(1):218-225.

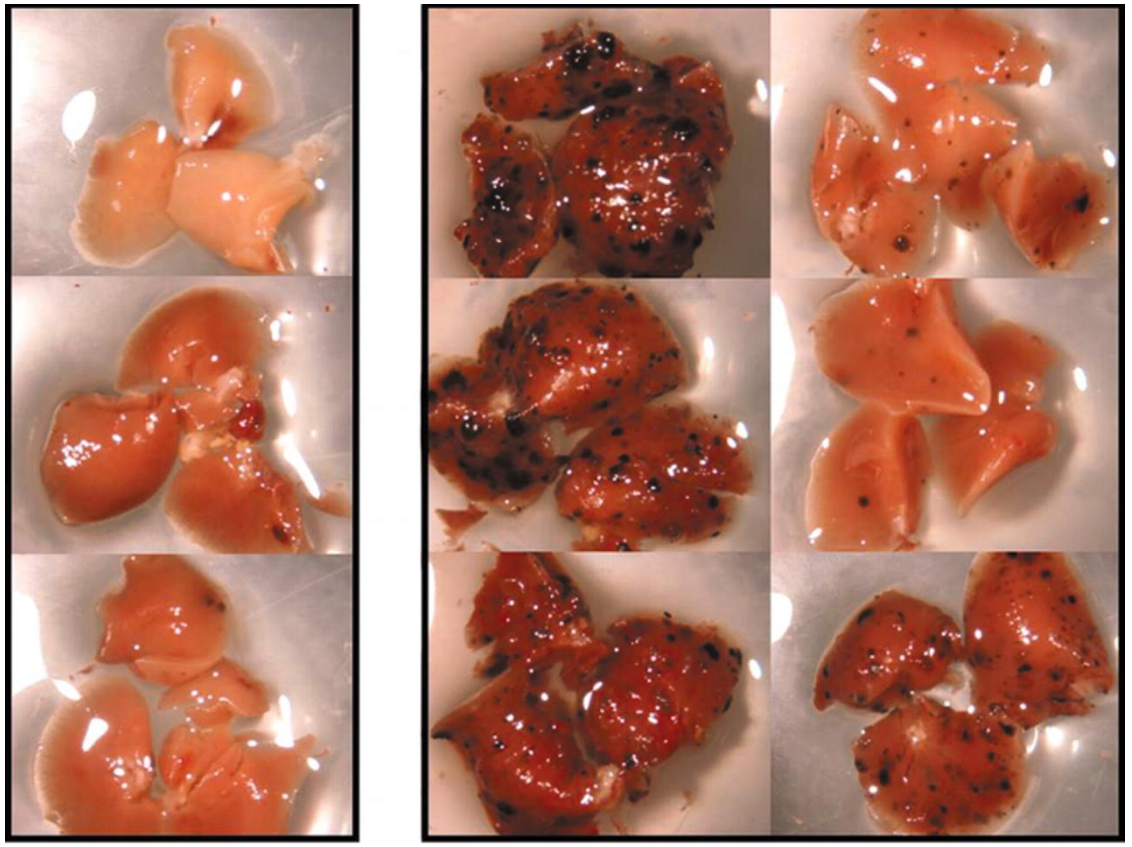
Les Mécanismes à l'origine de l'Hypercoagulabilité



D'après Falanga et al. Seminars in Thrombosis and Haemostasis 2015

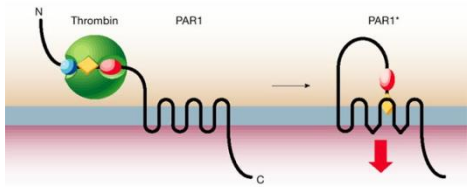
Les Plaquettes

Dans des modèles murins, les souris qui n'expriment pas les récepteurs PAR1 développent moins de métastases pulmonaires



Nf-E2 -/-

Nf-E2 +/+



Camerer, E. et al. Blood 2004;104:397-401

Les Plaquettes

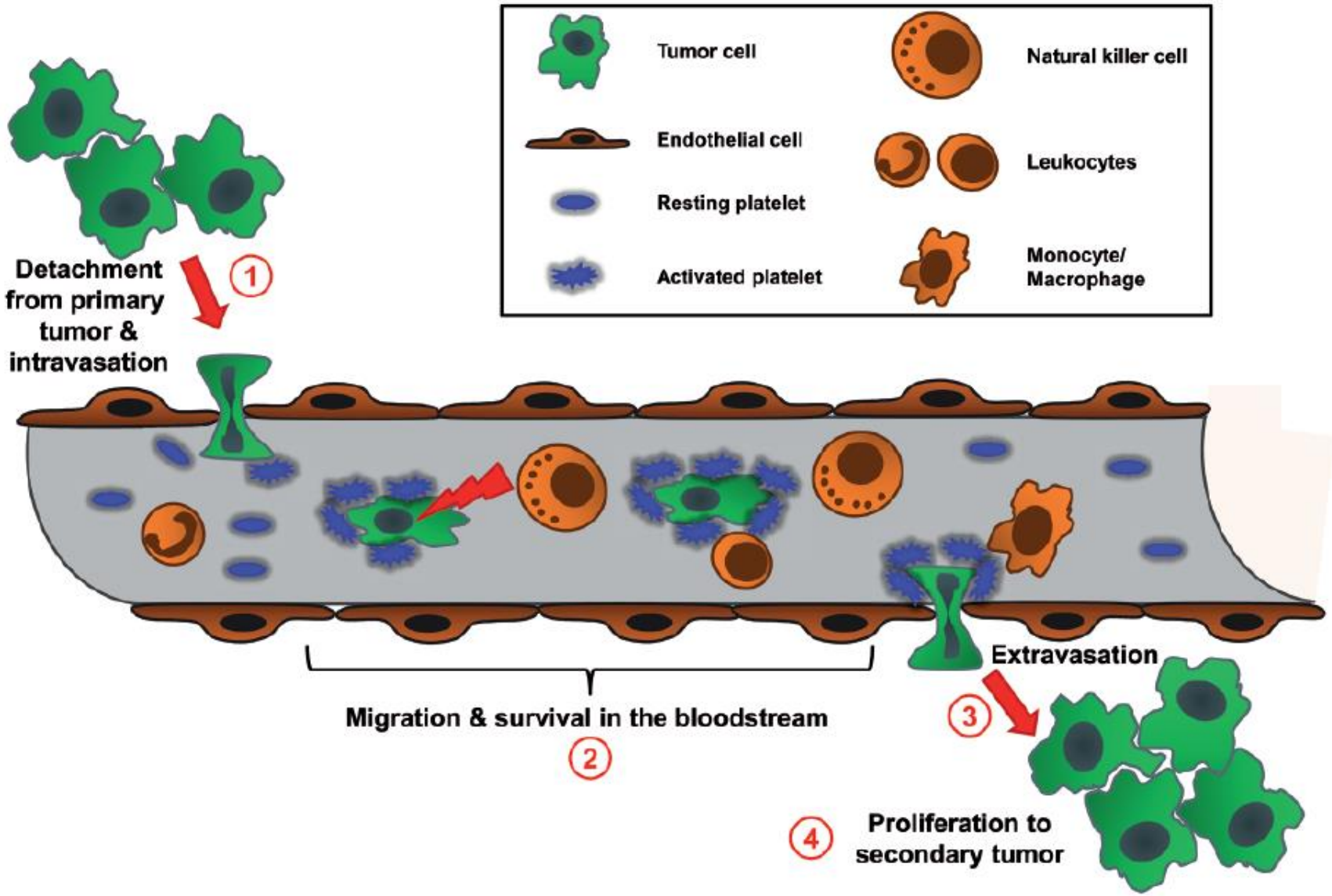
- **Différentes études in vitro ont montré que des cellules cancéreuses pouvaient agréger des plaquettes (TCIPA)**

Medina 2006; Alonso-Escolano 2004; Jurasz 2001; Heinmoller 1995

- **Il a été observé que ces agrégations plaquettaires pouvaient être dépendantes de l'action de :**

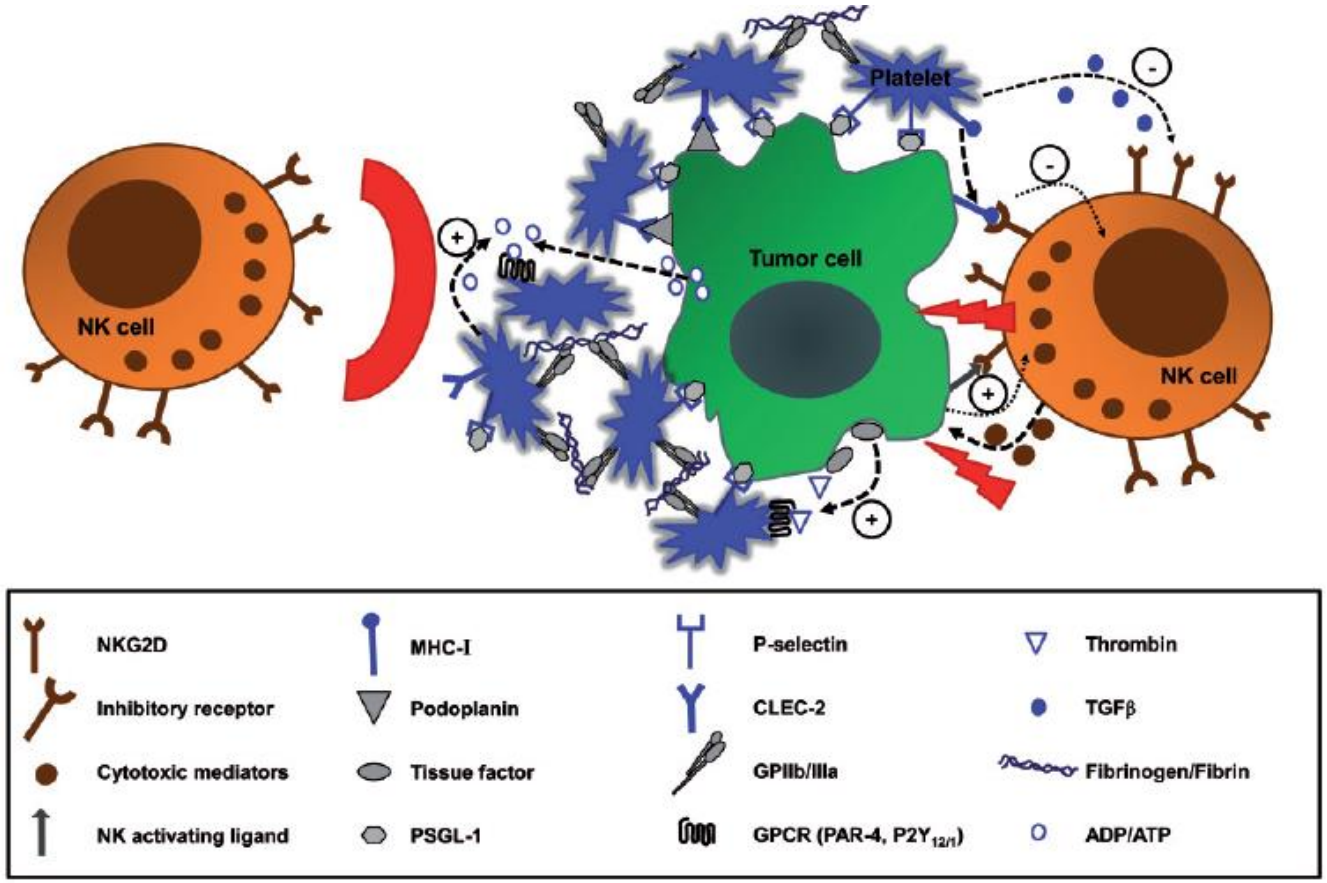
  - ✓**Thromboxane A2** Honn et al. 1982
  - ✓**MMP-1** Jurasz et al. 2001
  - ✓**MMP-2** Alonso-Escolano et al. 2004
  - ✓**ADP** Camez et al. 1986; Alonso-Escolano et al. 2004

Plaquettes et Progression tumorale



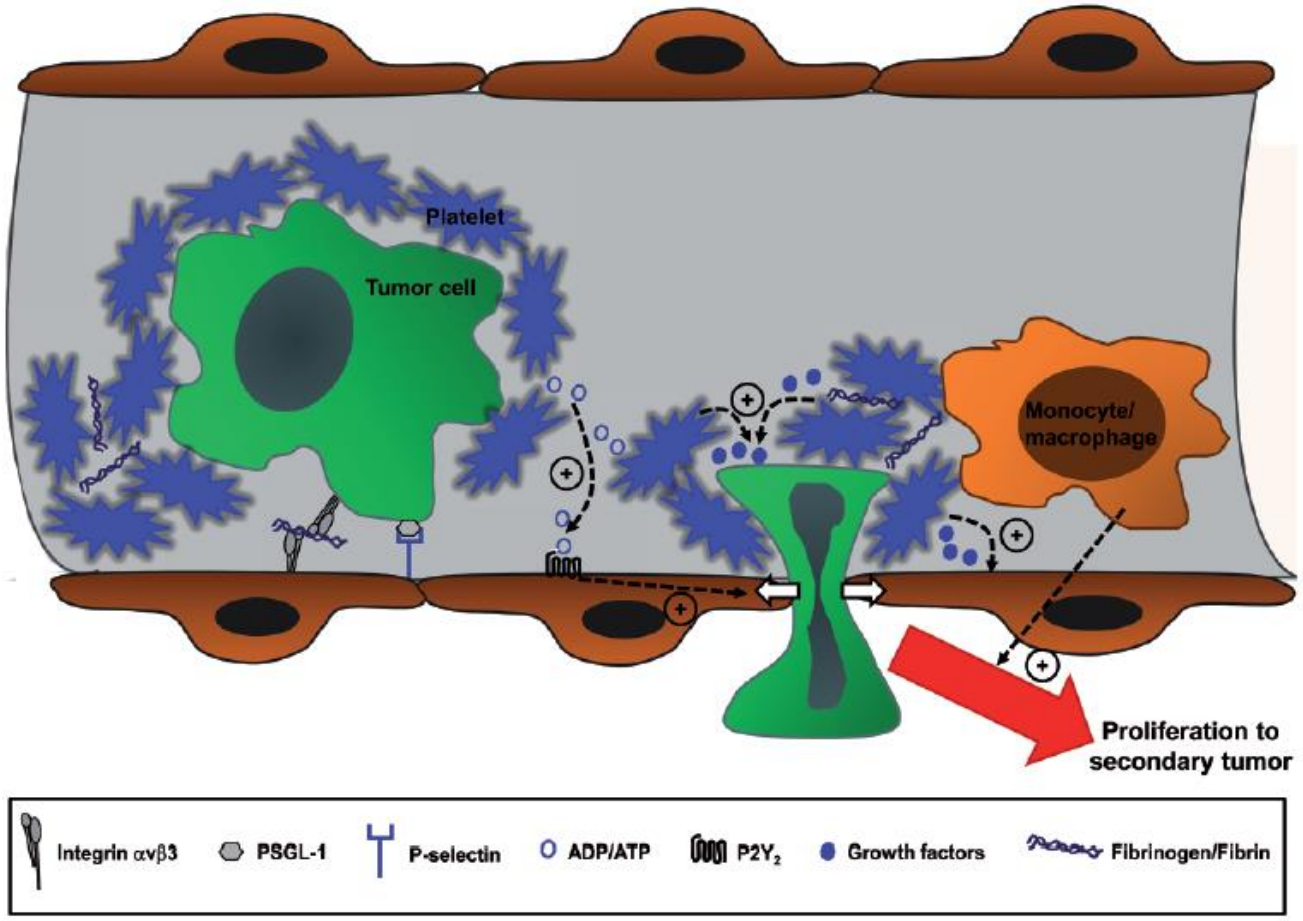
Stegner et al. Thromb Res 2014

Les plaquettes protègent les cellules Tumorales des Cellules Natural Killer



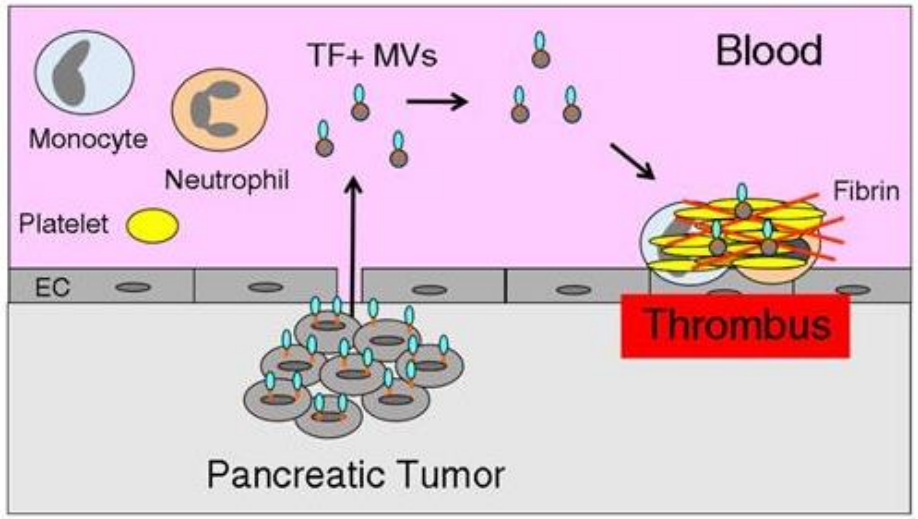
Stegner et al. Thromb Res 2014

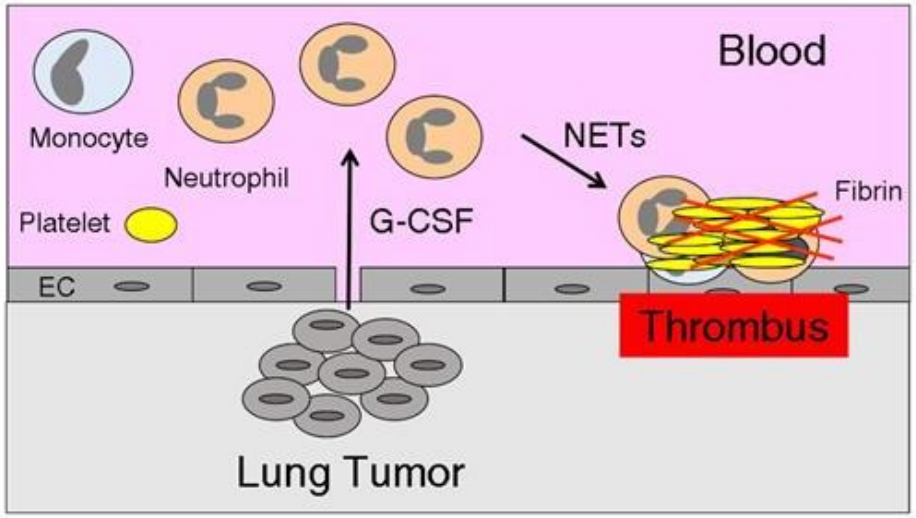
Effet “prolifératif ” et “proangiogénique” des plaquettes au cours du cancer

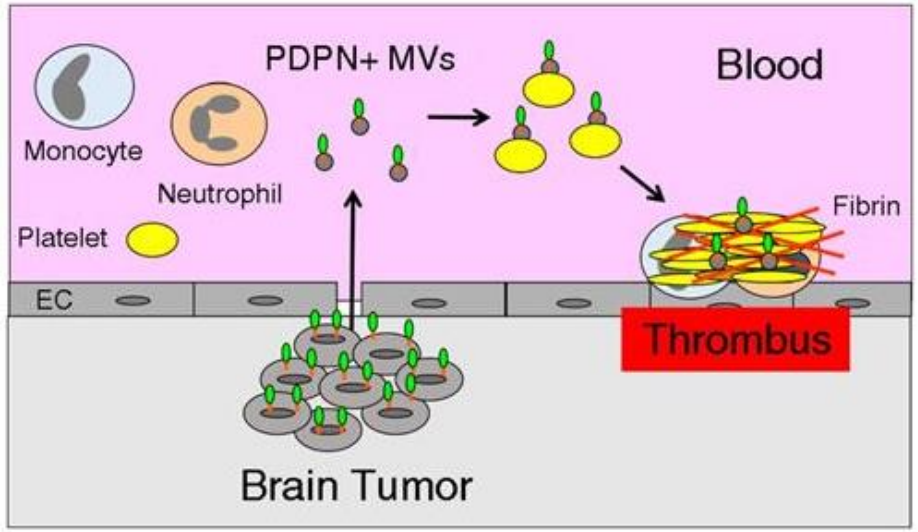


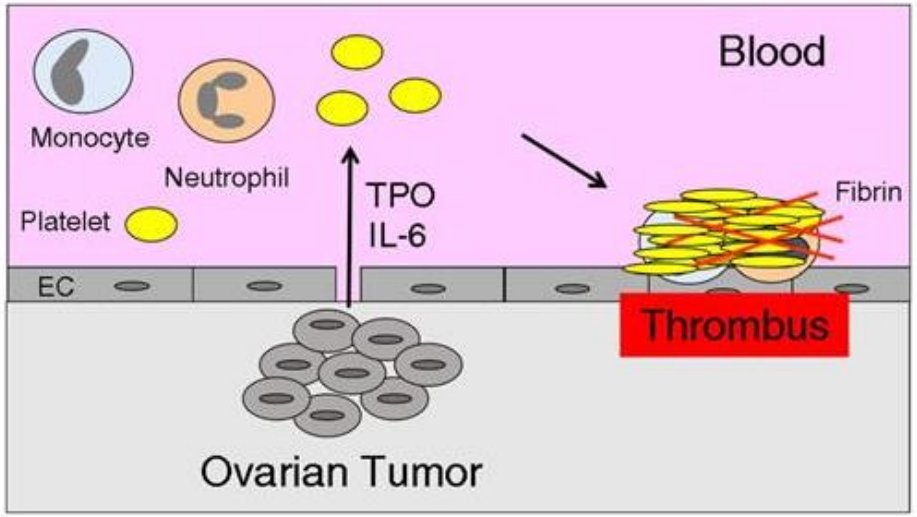
Stegner et al. Thromb Res 2014

Cancer et Thrombose : Différents Mécanismes physiopathologiques









Hisada et al. Blood 2017; 130 (13): 1499–1506.

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Plusieurs cercles, 1926