

EZIOPATOLOGIA DEL TEV NEL PAZIENTE ONCOLOGICO

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DI TORINO
ALMA UNIVERSITAS
TAURINENSIS



American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer

- ♣ Venous thromboembolism (VTE) is a major complication of cancer, occurring in **4% to 20% of patients**, and is one of the **leading causes of death** in patients with cancer.
- ♣ The risk of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE) is **increased several-fold** in patients with cancer.
- ♣ Hospitalized patients with cancer and those receiving active therapy seem to be at the greatest risk for development of VTE. In a population-based study, **cancer was associated with a 4.1-fold greater risk of thrombosis**, whereas the use of **chemotherapy increased the risk 6.5-fold**.

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CONSEQUENCES OF CANCER-ASSOCIATED VTE

- ♣ Cancer diagnosed within 1 yr. of an episode of VTE is associated with a *3-fold greater mortality* at a year
- ♣ Hospitalized pts., with or without metastatic disease, with VTE have a *greater mortality rate (OR 2.01)*
- ♣ The risk of fatal PE in pts. with cancer *undergoing surgery is 3 x greater* than in non-cancer pts
- ♣ Cancer pts. with VTE require long-term anticoagulation, with a *2 x greater risk of bleeding* complications
- ♣ VTE in pts. with cancer also *consumes health care resources*



The American Journal of Medicine (2006) 119, 60-68



ELSEVIER

CLINICAL RESEARCH STUDY

Incidence of Venous Thromboembolism in Patients Hospitalized with Cancer

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INCIDENCE OF VTE IN PATIENT HOSPITALIZED WITH CANCER - METHODS AND RESULTS

- ♣ The number of patients discharged with a diagnostic code for 19 types of malignancies, pulmonary embolism or deep venous thrombosis from 1979 through 1999 was obtained from the National Hospital Discharge Survey.
- ♣ In patients with any of the 19 malignancies studied, 827 000 of 40 787 000 (2.0%) had VTE (DVT/PE), which was twice the incidence in patients without these malignancies, 6 854 000 of 662 309 000 (1.0 %).



RISK FACTORS FOR VTE IN PTS. WITH CANCER

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Patient-related factors

1. Older age
2. Race (Africans)
3. Comorbidities
4. Prior history of VTE
5. Thrombocytosis
6. Prothrombotic mutations

♣ The factor V Leiden and prothrombin mutations appeared **only slightly** increase the risk of VTE in cancer patients

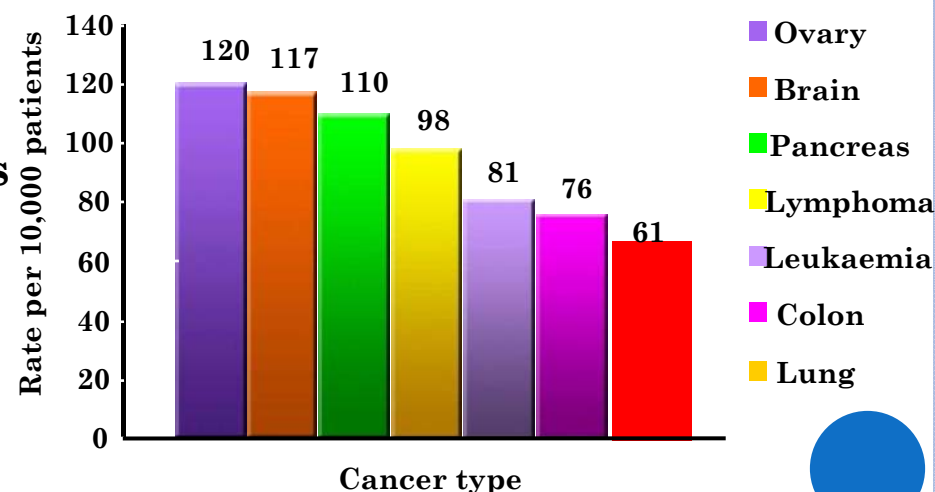
♣ Rather than screening for the two prothrombotic mutations, it may be **more cost-effective to consider prophylactic anticoagulant therapy** for pts. with cancer at increased risk of VTE

Cancer-related factors

1. Primary site of cancer
2. Initial 3-6 mos. after diagnosis
3. Metastatic disease

Treatment-related factors

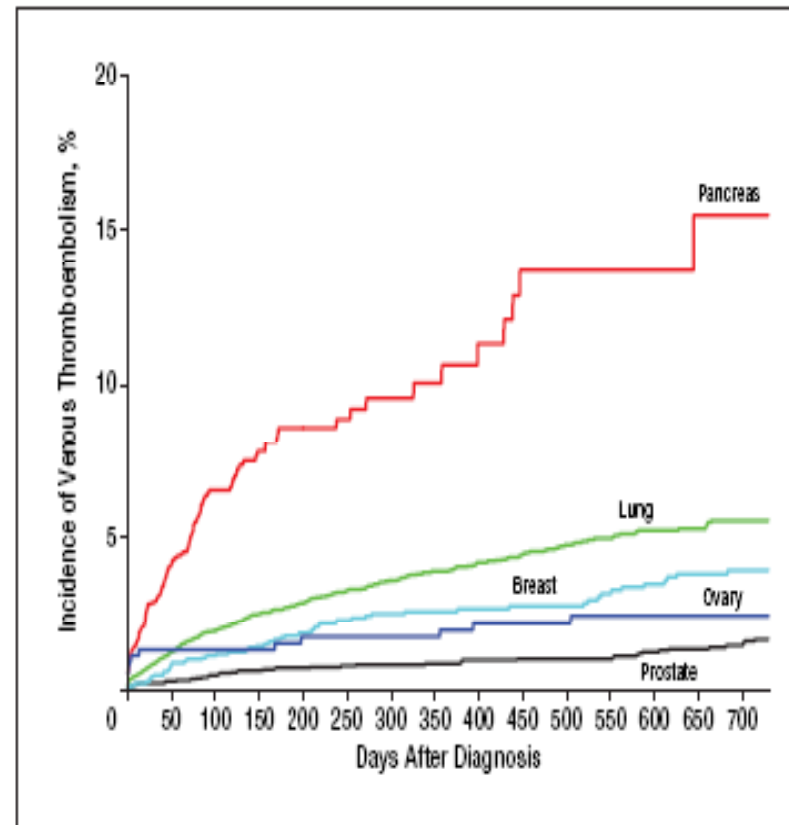
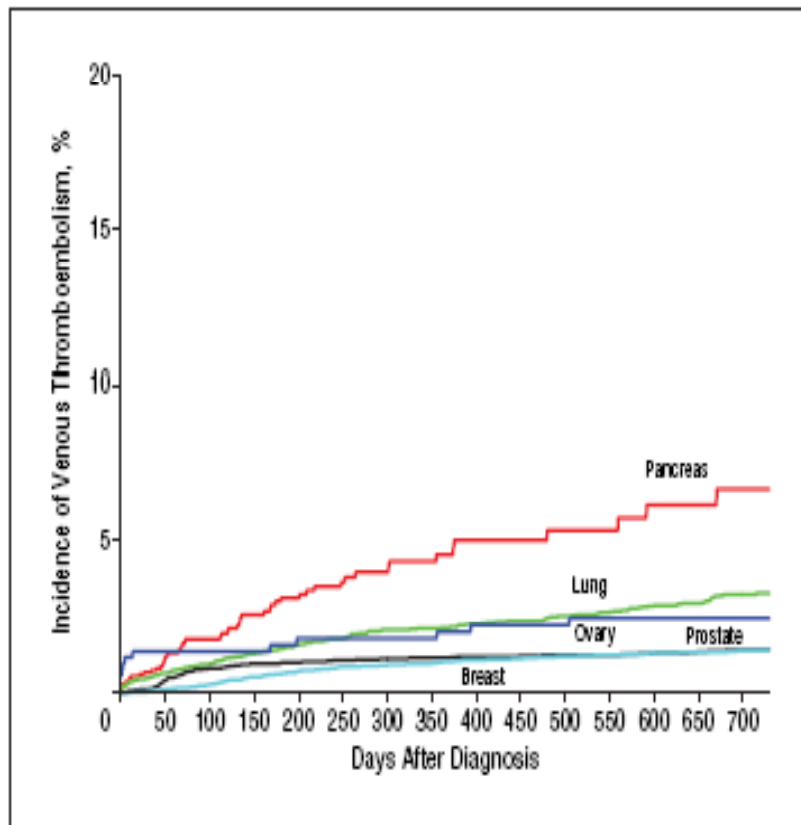
1. Recent major surgery
2. Current hospitalization
3. Active chemotherapy/hormonal/antiangiogenic /EPO therapy
4. Presence of CVC



INCIDENCE OF VTE WITHIN 2 YEARS OF DIAGNOSIS OF 5 DIFFERENT TYPES OF CANCER (235,149 CASES)

With regional-stage disease

With metastatic disease



Adapted from Chew et al, *Arch Intern Med* 2006.

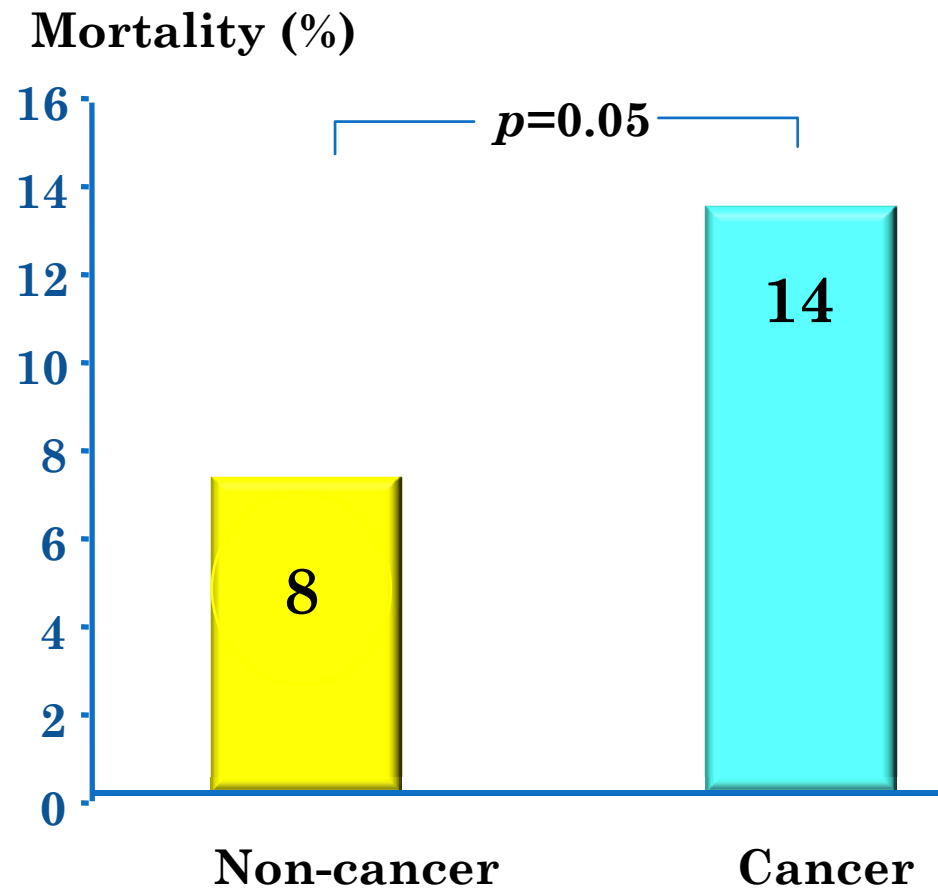
POSTOPERATIVE DVT IN CANCER PATIENTS

	Postoperative DVT	
	Cancer	Non-cancer
Kakkar, 1970	24/59 (41%)	38/144 (26%)
Hills, 1972	8/16 (50%)	7/34 (21%)
Walsh, 1974	16/45 (35%)	22/217 (10%)
Rosenberg, 1975	28/66 (42%)	29/128 (23%)
Pineo, 1979	10/30 (33%)	13/134 (10%)
Allan, 1983	31/100 (31%)	21/100 (21%)
Sasahara, 1984	9/37 (22%)	13/53 (24%)
Sue-Ling, 1986	12/23 (52%)	16/62 (26%)
TOTAL	138/376 (37%)	159/872 (18%)



ENOXACAN II Study, adapted from Bergqvist et al, 2002.

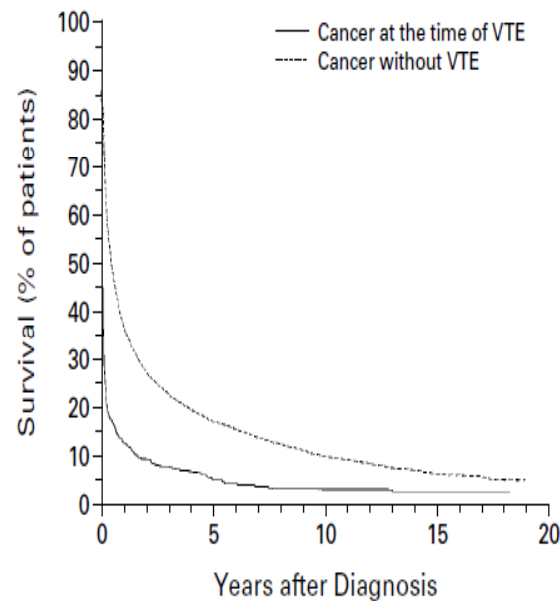
IN HOSPITAL MORTALITY RATE DUE TO PULMONARY EMBOLISM IN IMMOBILIZED PATIENTS WITH AND WITHOUT CANCER



Adapted from Shen and Pollak, *South Med J*, 1980.

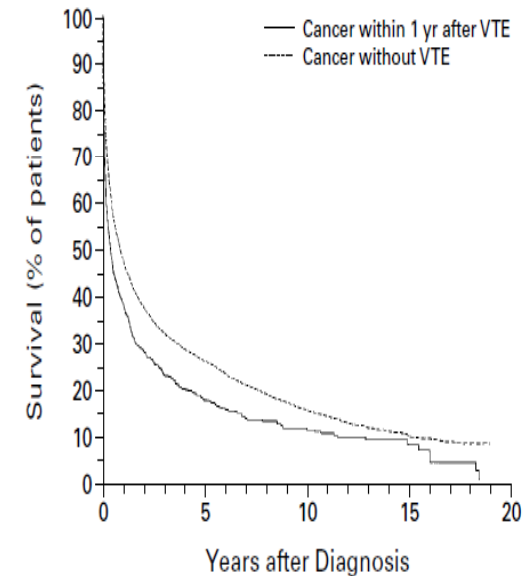
PROGNOSIS OF CANCERS ASSOCIATED WITH VENOUS THROMBOEMBOLISM

HENRIK TOFT SØRENSEN, DR.MED.SCI., LENE MELLEMKJÆR, PH.D., JØRGEN H. OLSEN, DR.MED.SCI.,
AND JOHN A. BARON, M.D.



NO. AT RISK				
Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87

Figure 1. Survival Curves for Patients with a Diagnosis of Cancer at the Time of Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.



NO. AT RISK				
Cancer within 1 yr after VTE	560	72	37	7
Cancer without VTE	5586	1181	419	106

Figure 2. Survival Curves for Patients with a Diagnosis of Cancer within One Year after Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.

N Engl J Med 2000; 343:1846-1850

THERE IS SOME EVIDENCE THAT

PATIENTS WITH CANCER WHO

DEVELOP THROMBOEMBOLISM

HAVE *SHORTENED SURVIVAL*



REDUCING VTE IN PTS. WITH CANCER COULD
HAVE A SIGNIFICANT IMPACT ON

MORBIDITY

OUTCOMES

USE OF HEALTH CARE RESOURCES

above all

mortality

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Pathophysiology
of Haemostasis
and Thrombosis

The Pathophysiology of Cancer and Thrombosis

Editors

Anna Falanga, Bergamo

Hugo ten Cate, Maastricht

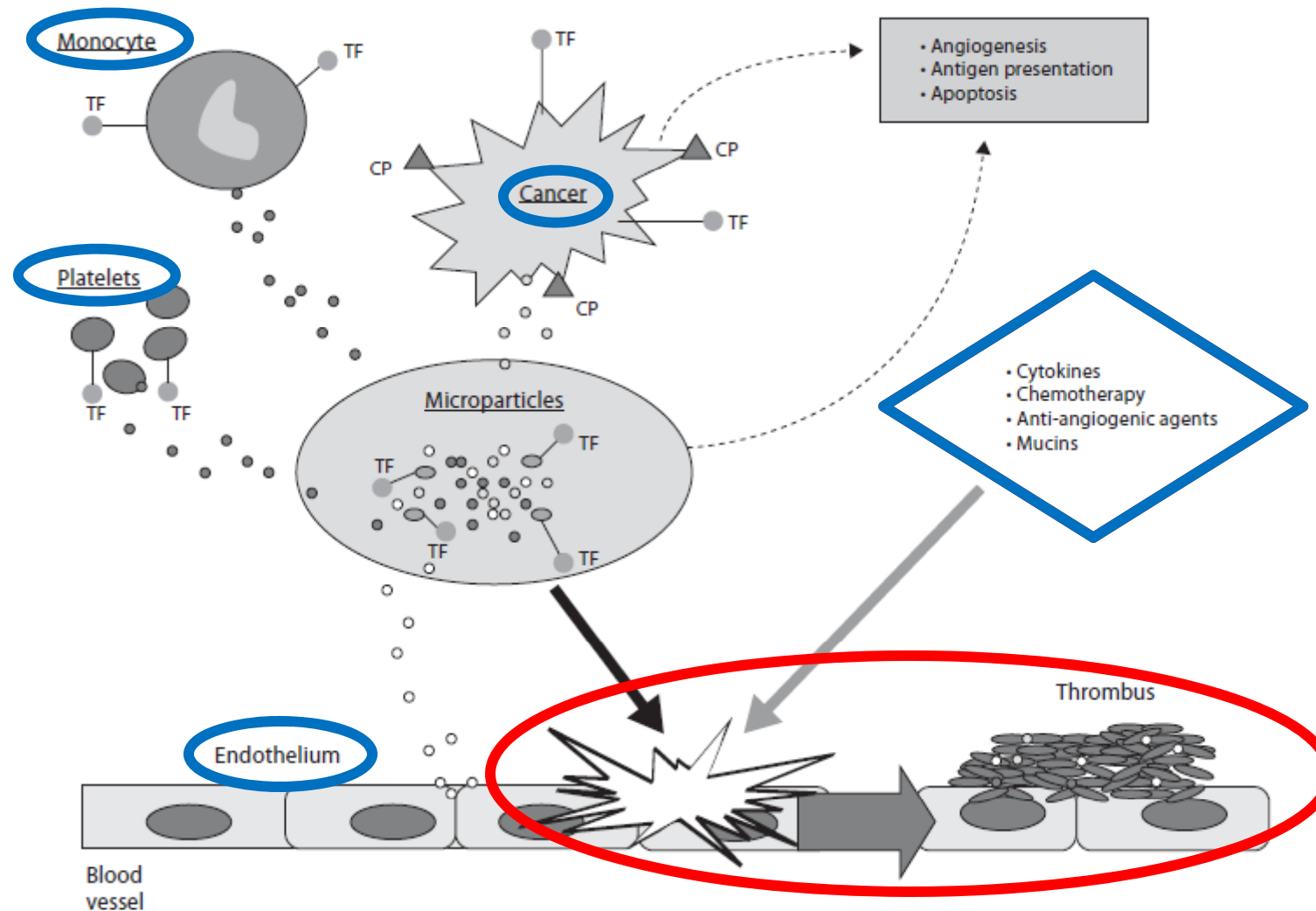
18 figures and 10 tables, 2009

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The multifactorial process of venous thromboembolism in cancer



Virchow's triad in cancer


Abnormal blood flow

- (i) Increased plasma viscosity [114, 115]
- (ii) Increased stasis due to immobility (e.g., being bed-bound, in a wheelchair)

Abnormal blood constituents

- (i) Increased platelet activation and aggregability, for example, increased soluble P selectin, beta thromboglobulin [15–51]
- (ii) Loss of haemostasis with increase in procoagulants for example, increased fibrinogen, cancer procoagulant, PAI-1 [66–89]

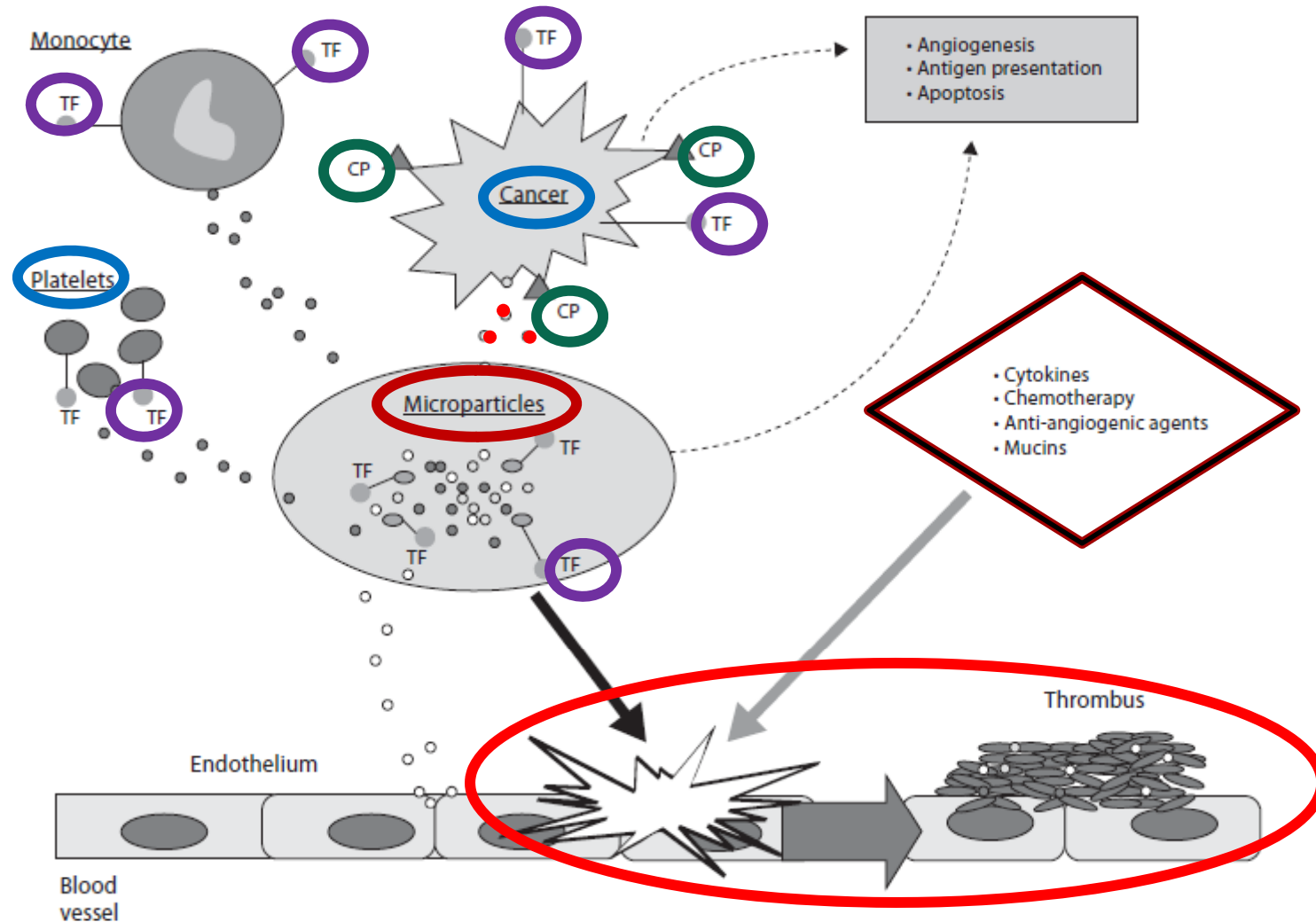
Abnormal blood vessel wall

- (i) Damaged or dysfunctional endothelium (e.g., increased soluble E selectin, increased soluble thrombomodulin, possibly also related to chemotherapy) [95–97]
 - (ii) Loss of anticoagulant nature and therefore acquisition of a procoagulant nature (e.g., increased von Willebrand factor, tissue factor, reduced tPA, possibly also related to chemotherapy) [83, 93, 94]
 - (iii) Angiogenesis (altered release of, and response to, growth factors) [101–107]
- 

THE MULTIFACTORIAL PROCESS OF VENOUS THROMBOEMBOLISM IN CANCER

- ♣ **Microparticles (MPs)** = fragments of plasma membrane that are released from most types of cells as a result of apoptosis, or in response to cellular activation that may accompany inflammatory or hypercoagulable states.
- ♣ **Tissue Factor (TF)** = transmembrane protein acting as the receptor for f. VIIa and **principal regulator of blood coagulation**. Its expression is usually **restricted to the subendothelial layer** of blood vessels. Endothelial cells **do not** express TF and platelets bear TF on the inner membrane layer. **Its exposure to blood flow triggers the coagulation cascade**
- ♣ **Cancer Procoagulant (CP)** = proteinase growth factor acting as a direct activator of f. X in the presence of f.V. It **enhances thrombin generation up to 3-fold**. Expressed only in malignant and fetal tissues (melanoma, leukemia).

The multifactorial process of venous thromboembolism in cancer



MICROPARTICLES (MPs)

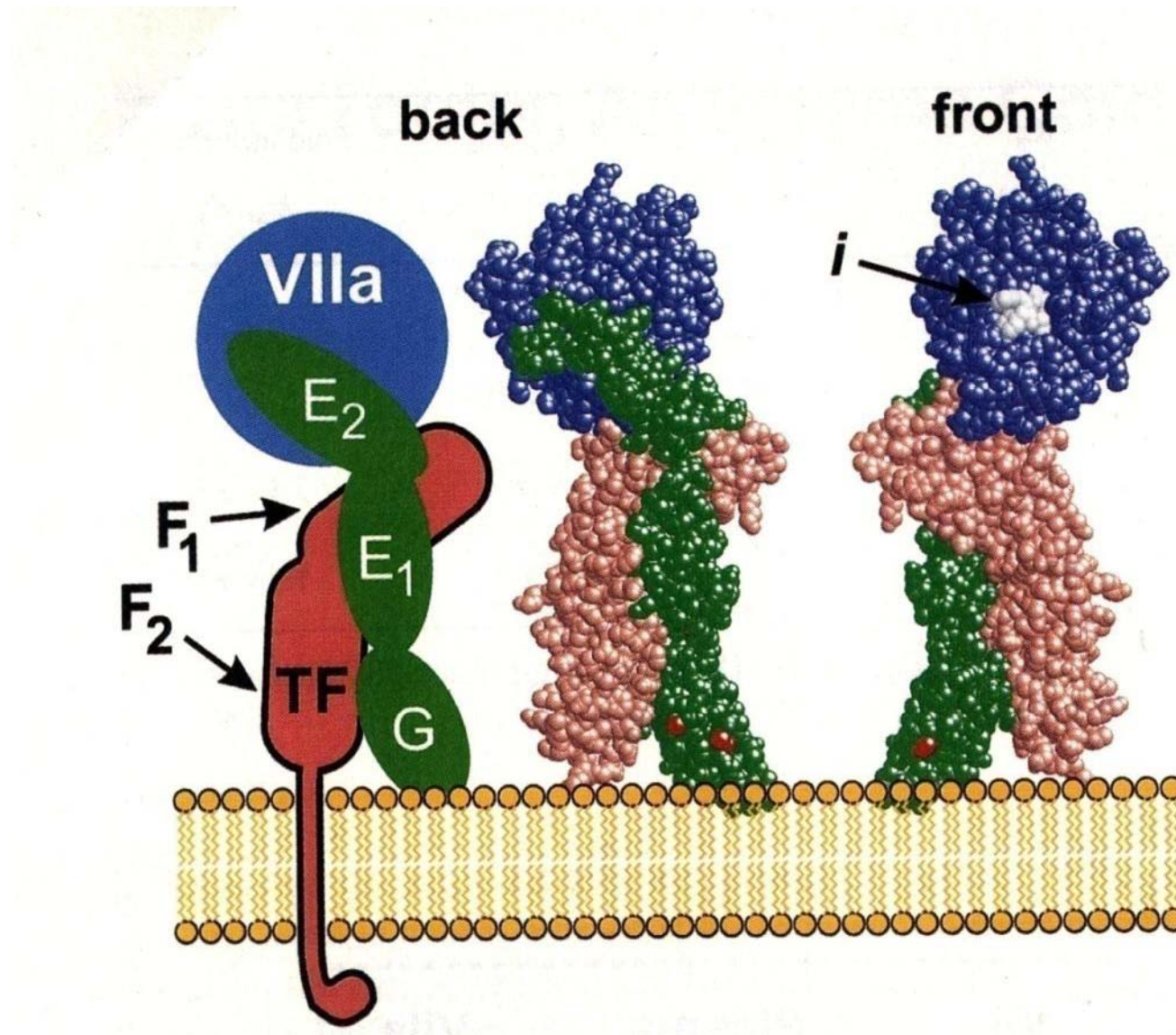
- ♣ Cellular fragments shed in vitro and in vivo by several cell strains (tumor cells, platelets, endothelial cells, apoptotic normal cells)
- ♣ Composed of protein and lipids
- ♣ Characterized by the expression of antigenic markers that are specific of their cell of origin
- ♣ Their budding and release yields to normal bilayer membrane disruption and abnormal phospholipid (PS/PE) and protein (TF) distribution
- ♣ MPs derived from platelets acquire the ability to bind coagulation factors VIIIa, IXa, Va, Xa
- ♣ MPs exposing PS/PE and TF on the outer layer can play a role as catalysts for thrombin generation by providing a surface for Xase assembly



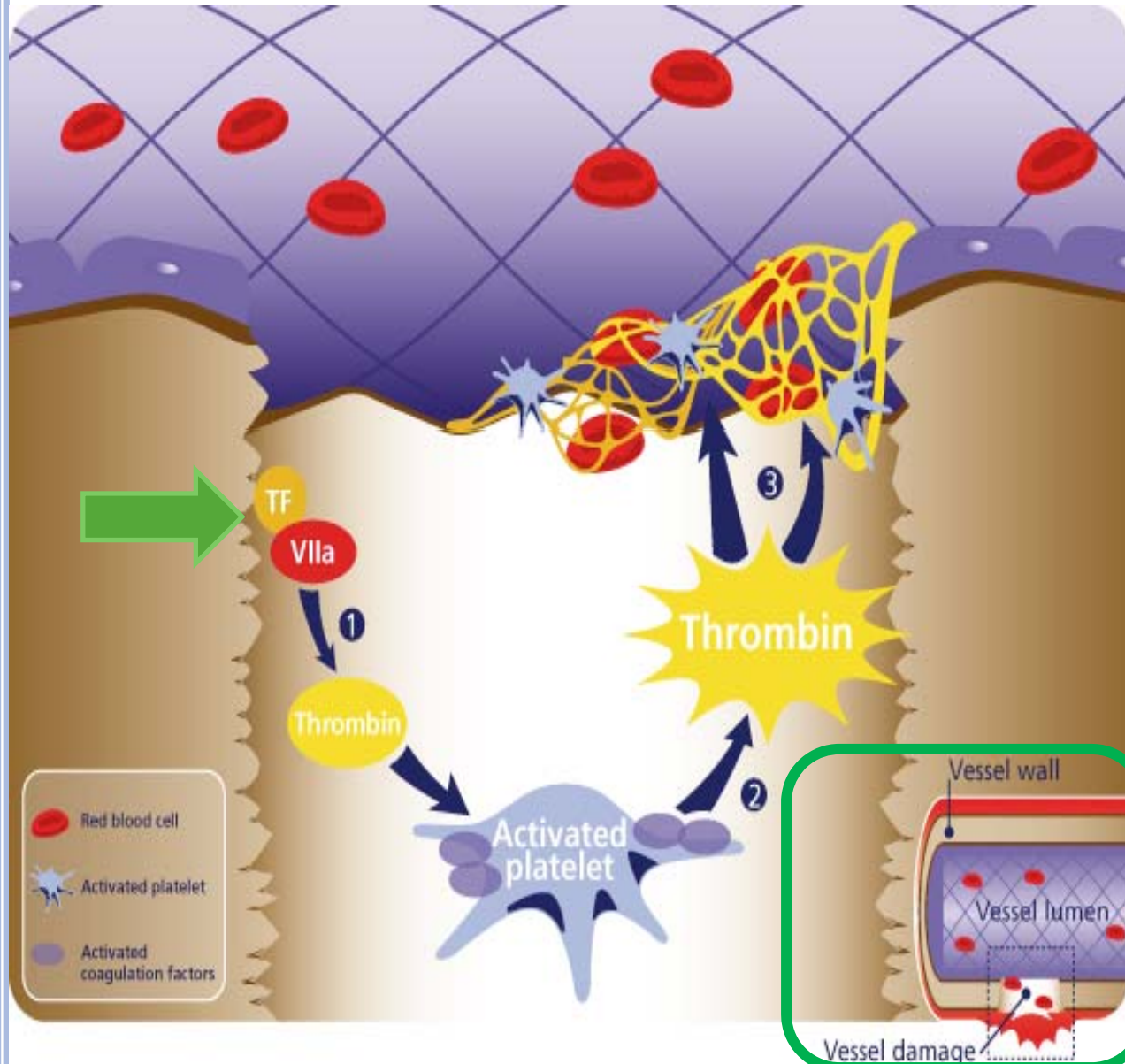
MICROPARTICLES (MPs) – CLINICAL STUDIES

- ♣ It is unclear if elevated numbers of MPs **correlate with thrombosis risk** (conflicting results)
- ♣ Elevated numbers of circulating MPs in epithelial cancers was primarily accounted for by **platelets** and **elevation directly correlates with prognosis**
- ♣ **Few** studies demonstrate **endothelial cell-derived** MPs in cancer patients
- ♣ Patients with cancer-associated acute VTE are much more likely to have detectable MPs than matched controls without VTE or with acute VTE and no cancer
- ♣ Recent studies have demonstrated that **CT and antiangiogenic therapy enhance both MPs generation and endothelial activation**, thus doubling the thrombotic risk

TISSUE FACTOR (TF)



OVERVIEW OF SECONDARY HEMOSTASIS

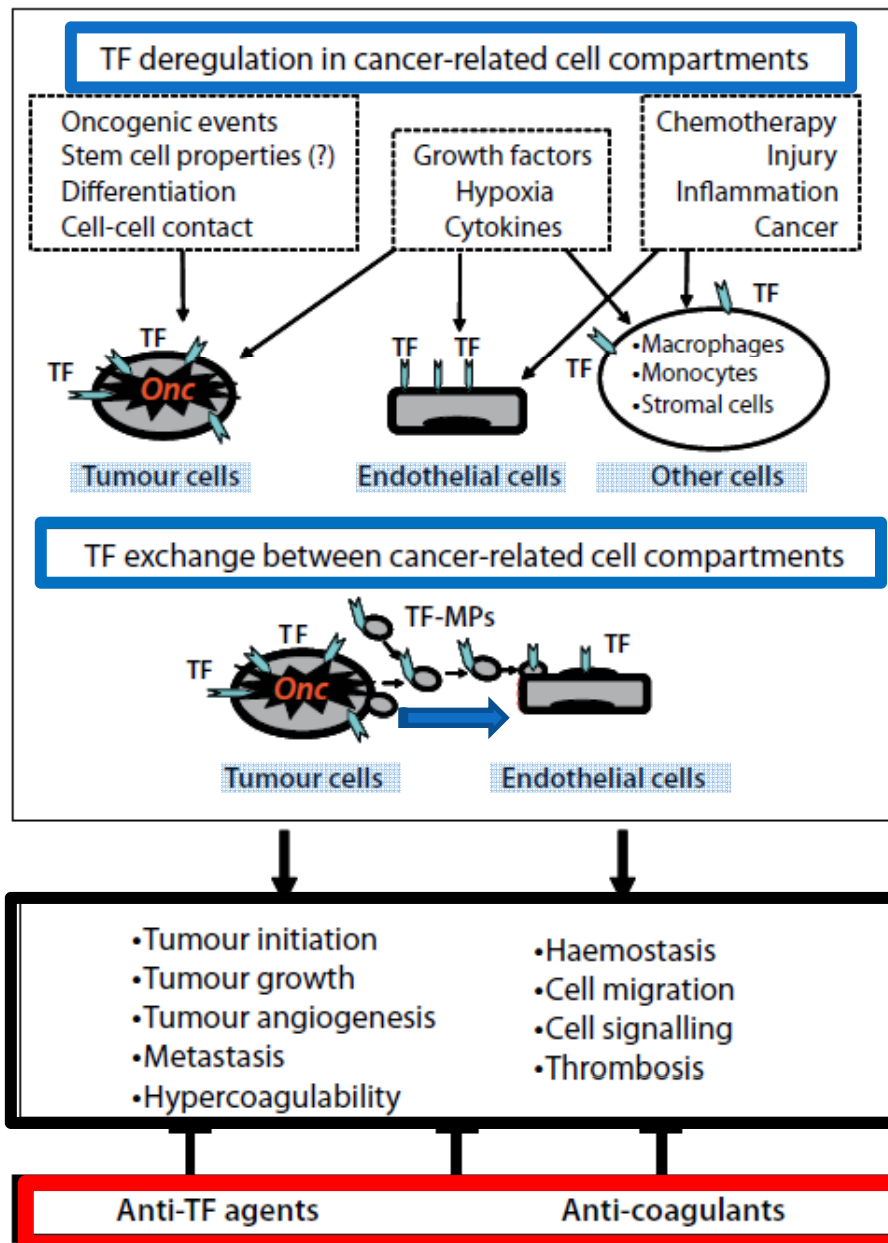


1. At the site of vascular injury **binding of endogenous factor VII/VIIa to tissue factor (TF)** leads to the generation of small amounts of thrombin
2. **Thrombin activates platelets** and additional coagulation factors which subsequently generate **large amounts of thrombin**
3. This “thrombin burst” induces the **generation of a haemostatic plug** that prevents further blood loss

TISSUE FACTOR (TF) AND CANCER

- ♣ TF is expressed in most human cancers in a manner that seems to parallel the disease progression
- ♣ Copious amounts of TF antigen are often detected on the surface of cancer cells (up to 1000-fold higher levels than corresponding normal cells)
- ♣ Increased levels of circulating TF are commonly detected in patients with advanced cancer
- ♣ TF seems to play a role in tumor angiogenesis (in colorectal ca. TF parallels VEGF)
- ♣ In experimental systems, TF-dependant signals were found to influence the expression of angiogenic effectors such as VEGF
- ♣ Anti-TF activity has produced anti-angiogenic effects in some, but not all, experimental cancers

TISSUE FACTOR (TF) AND CANCER



Influence of host-
and cancer cell
TF in the
progression of
malignant disease



TISSUE FACTOR (TF) AND CANCER

Initial clinical studies further show that the detection of TF-MPs may be a suitable approach to identify patients at increased risk for venous thromboembolism

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

Jeffrey I. Zwicker, Howard A. Liebman, Donna Neuberg, et al.

Clin Cancer Res 2009;15:6830-6840. Published OnlineFirst October 27, 2009.

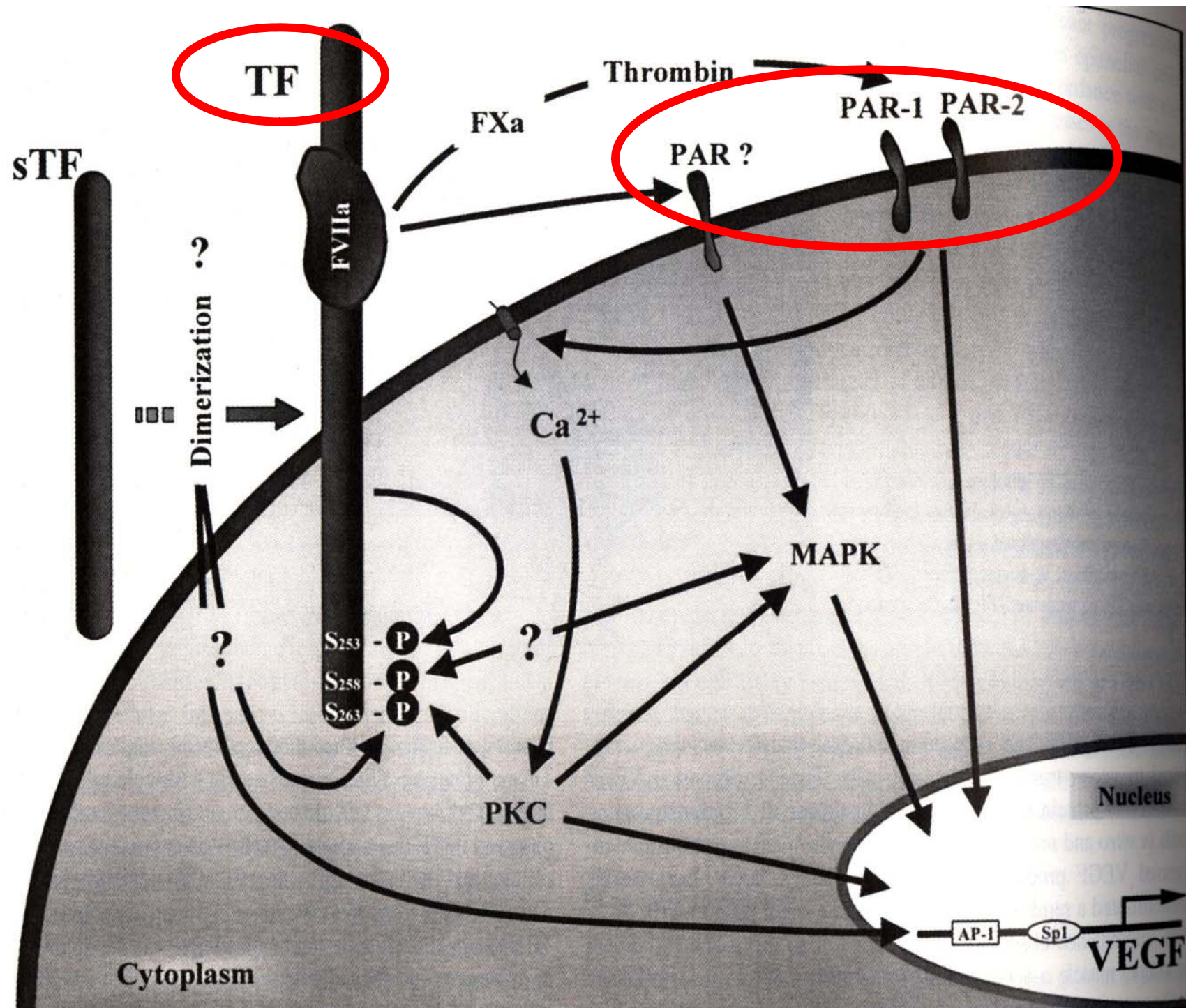
Tissue factor and its measurement in whole blood, plasma, and microparticles.

Key NS, Mackman N.

Semin. Thromb. Haemost. 2010 Nov;36(8):865-75.

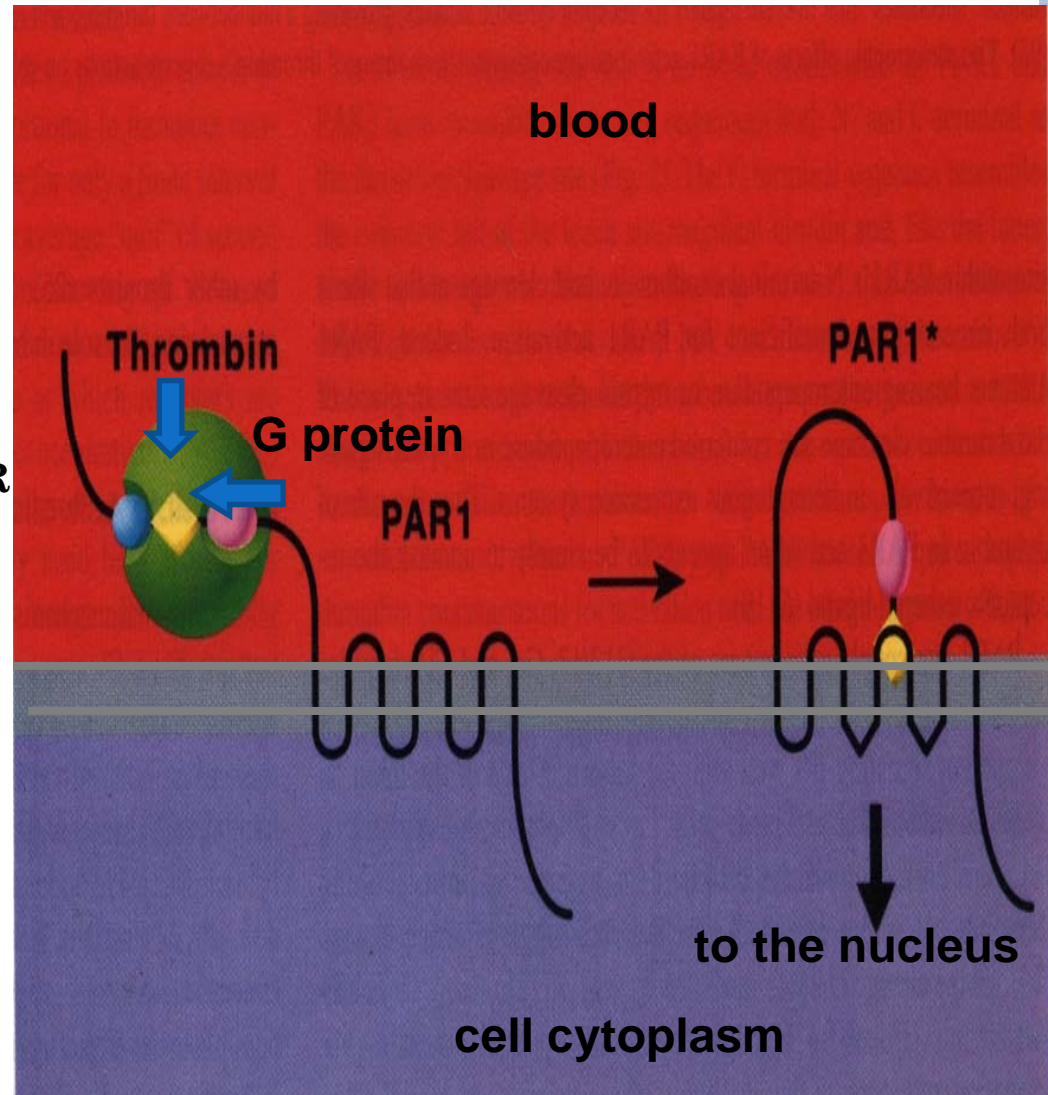
Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina 27599, USA



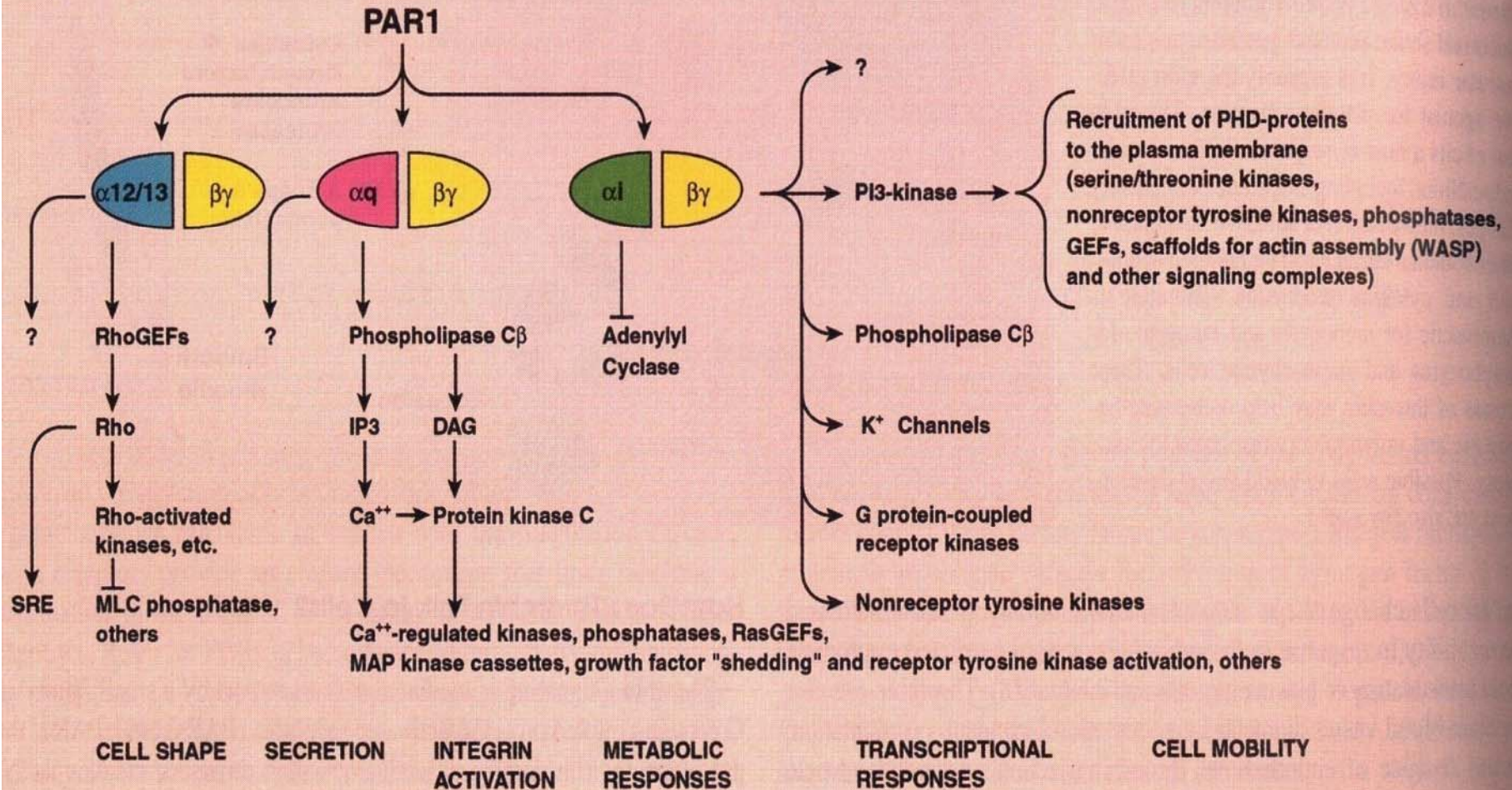


PROTEASE-ACTIVATED RECEPTORS (PARs)

- ♣ **Cellular receptors** (EC, platelets, fibroblasts) coupled with membrane G-proteins, **converting extracellular proteolytic events into transmembrane signals**
- ♣ **Mechanism of action:**
 1. thrombin, TF, VIIa, Xa, kallikrein recognize the N-terminal end of a G-protein/PAR on cell surface and cleave Arg41-Ser42
 2. the “new” peptide bound to protease works as a bridge with the cell inner structures
 3. G-protein-bound PAR-1 mediates platelet shape change, cell permeability and activates phospholipase C which in turn activates several endocellular tyrosin-kinases crucial for cell growth and differentiation



PAR1 SIGNALING



PARS AND CANCER – “IN VITRO” STUDIES

- ♣ TF on tumour cells generates thrombin, which activates platelets via activation of PAR-4 and PAR-1
- ♣ F. VIIa and Xa activate PAR-2 which in turn promotes **cell migration** and **expression of adhesion proteins** on cell surface ⇒ **role in metastatization?**
- ♣ Cancer cell TF-VIIa-PAR-2 signalling **regulates angiogenesis and prevents apoptosis** (breast cancer)
- ♣ Specific blockade of the signalling function of TF-VIIa **suppresses tumour growth** (invasive breast cancer, glioma, melanoma)
- ♣ PAR-2 deficient mice display significant delay in the transition from adenoma to invasive breast carcinoma. Reconstitution of PAR-2 in mouse cell culture showed breast cancer development only in PAR + tumour cells



LINKAGE BETWEEN ONCOGENIC EVENTS AND PROCOAGULANT CONVERSION IN CANCER

Genetic influence	Consequence of deregulation	Group (first author), year and reference
Oncogenes		
<i>K-ras</i>	Upregulation of TF	Yu, 2005 [57]
<i>EGFR</i>	Upregulation of TF	Yu, 2004 [88]
<i>EGFRvIII</i>	Upregulation of TF	Milsom, 2008 [279] (Magnus & Rak, unpubl.)
<i>PML-RARa</i>	TF-dependent coagulopathy	Tallman, 2004 [89]
<i>c-Met</i>	Deregulation of PAI-1 COX-2	Boccaccio, 2005 [84]
Tumour suppressors		
p53	Upregulation of TF	Yu, 2005 [57]
PTEN	Upregulation of TF	Rong, 2005 [90]



CONCLUSIONS

Rather than screening for prothrombotic mutations, it may be **more cost-effective to consider prophylactic anticoagulant therapy** for pts. with cancer at increased risk of VTE



...THANK YOU !!!

