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ΔΙΟΡΓΑΝΩΣΗ
ΠΑΓΚΡΗΤΙΑ
ΕΝΩΣΗ
ΥΓΕΙΑΣ



Mechanisms of Thromboinflammation: *lessons from human diseases*



Παναγιώτης Σκένδρος
Αναπλ. Καθηγητής Παθολογίας



ΔΗΜΟΚΡΙΤΕΙΟ
ΠΑΝΕΠΙΣΤΗΜΙΟ
ΘΡΑΚΗΣ

DEMOCRITUS
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OF THRACE



INFLATHRACE

ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΛΕΞΑΝΔΡΟΥΠΟΛΗΣ



Α' Πανεπιστημιακή Παθολογική Κλινική
& Εργαστήριο Μοριακής Αιματολογίας ΔΠΘ
Πανεπιστημιακό Νοσοκομείο Αλεξανδρούπολης

**Δεν υπάρχει καμία σύγκρουση συμφερόντων
σε σχέση με την παρούσα ομιλία**

Rudolf Virchow recognized the inflammatory nature of atherosclerotic plaques (mid 19th century)

“In some, particularly violent cases the softening manifests itself even in the arteries not as the consequence of a really fatty process, but as a direct product of inflammation.”



Virchow R. Cellular Pathology. London: John Churchill; 1858.

The New England Journal of Medicine

Review Article

January 14, 1999

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D.

FACTORS THAT INDUCE AND PROMOTE INFLAMMATION OR ATHEROGENESIS

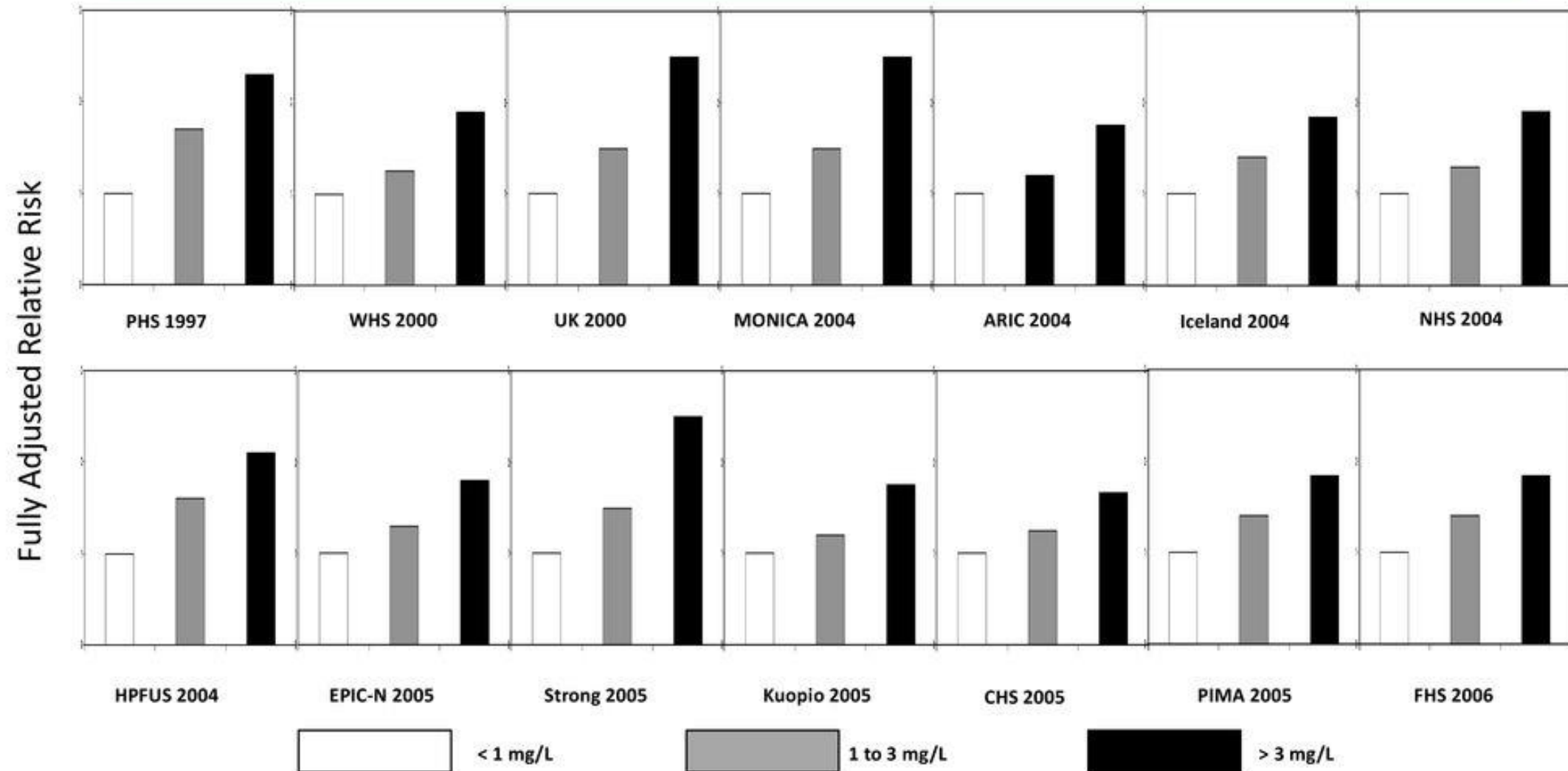
Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis.⁶ The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; if unabated and excessive, this process will result in an advanced, complicated

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Thus, although hypercholesterolemia is important in approximately 50 percent of patients with cardiovascular disease,⁵ other factors need to be taken into consideration. Atherosclerosis is clearly an inflammatory disease and does not result simply from the accumulation of lipids. If we can selectively modify the

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Observation studies: hsCRP and CVD



Inflammation and thrombosis in real-life

- Common chronic inflammatory and autoimmune diseases are associated with high cumulative risk for atherosclerosis and thrombotic complications
- Infectious inflammation (sepsis) and thrombosis (DIC)
- Metabolic syndrome and subclinical, low grade systemic inflammation
- Emerging anti-inflammatory strategies against thrombosis

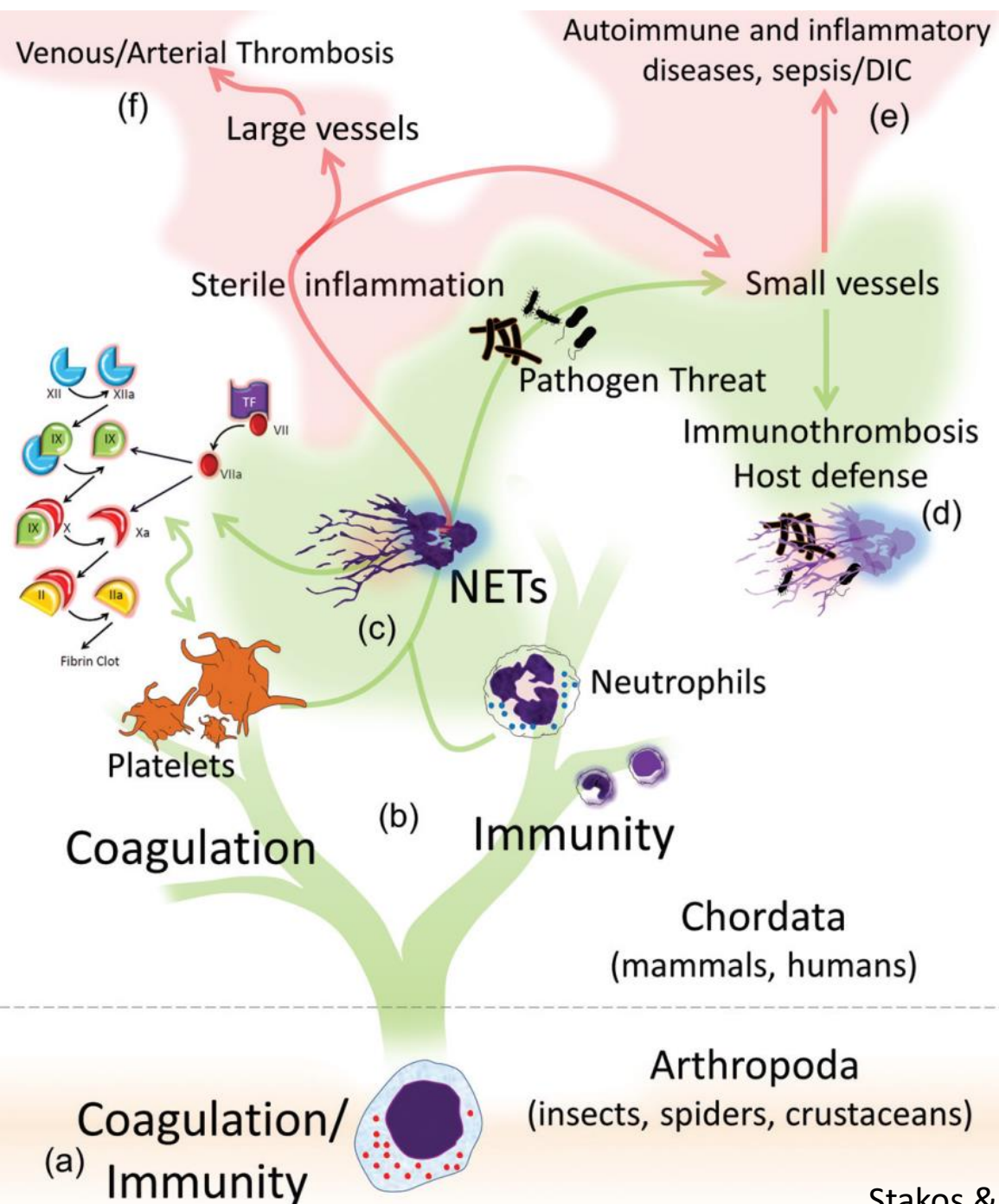
High CVD risk patients

1. **HELLENIC SCORE 5-10%**
2. **One but very high CVD risk factor (eg severe hypertension, excessive smoking)**
3. **Familial hypercholesterolemia (FH)**
4. **Autoimmune rheumatic diseases**

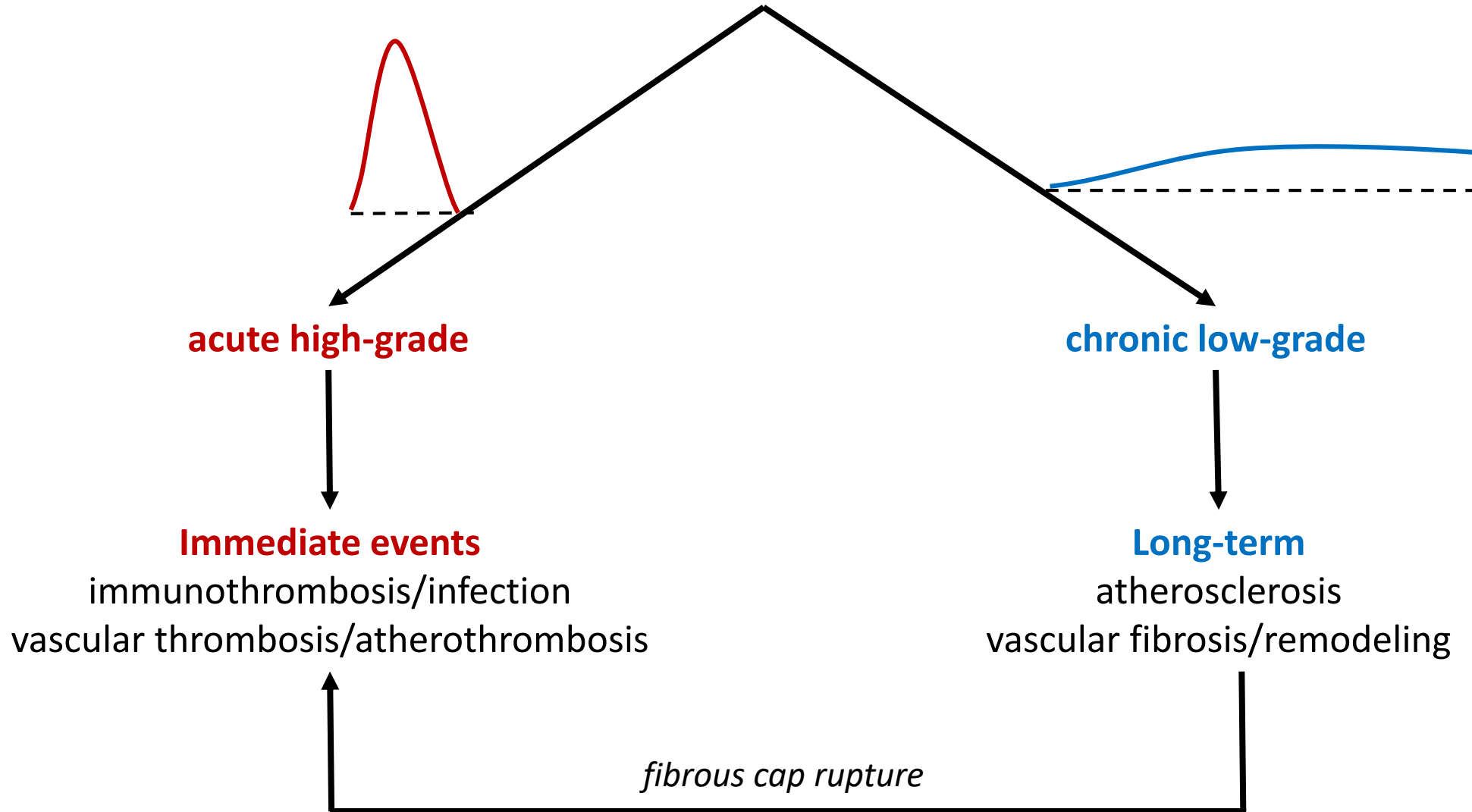


Immunothrombosis/ thromboinflammation

- Inflammation and thrombosis are tightly interrelated using common molecular pathways and mechanisms in a host defense effector mechanism termed **immunothrombosis**
- The dysregulated and excessive activation of immunethrombosis results in **thromboinflammation**, causing tissue damage and organ dysfunction (micro- and macro-vascular thrombosis)
- Vicious circle(s) of **innate immune cells (mainly neutrophils)**, **platelets**, **complement system** and **coagulation cascade** activation

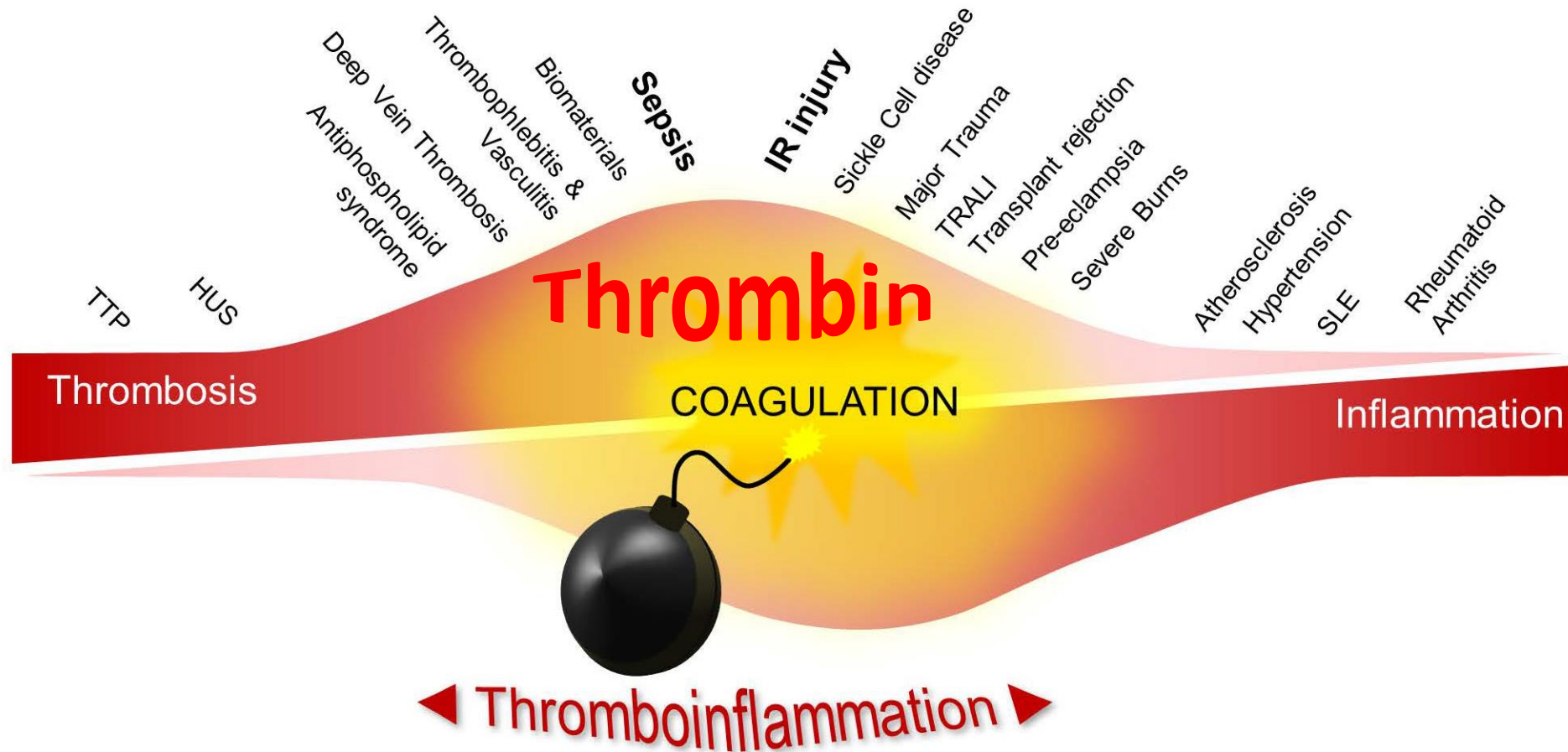


Thromboinflammation



The concept of thromboinflammation

Reciprocal relationship and dynamic interplay between inflammation and thrombosis



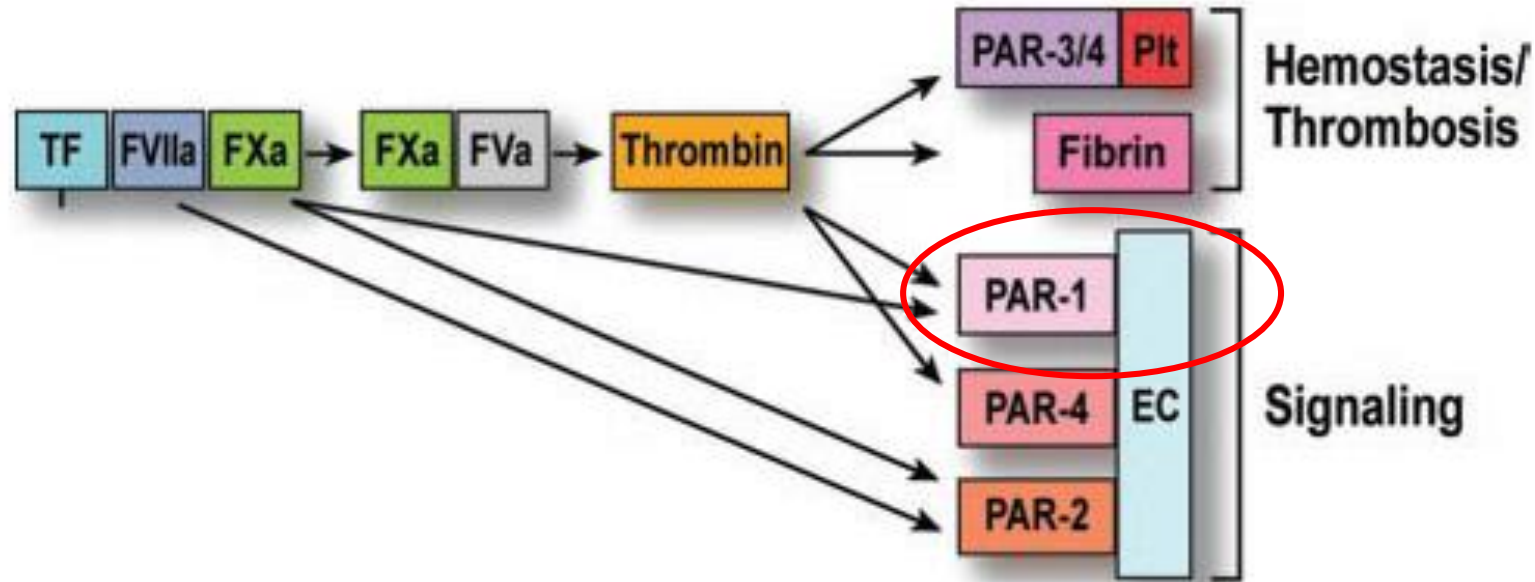
Atherothrombosis

Venous thrombosis

- Cancer
- Myeloproliferative disorders
- Antiphospholipid syndrome

DIC

- Cancer
- Sepsis



Inflammatory Responses

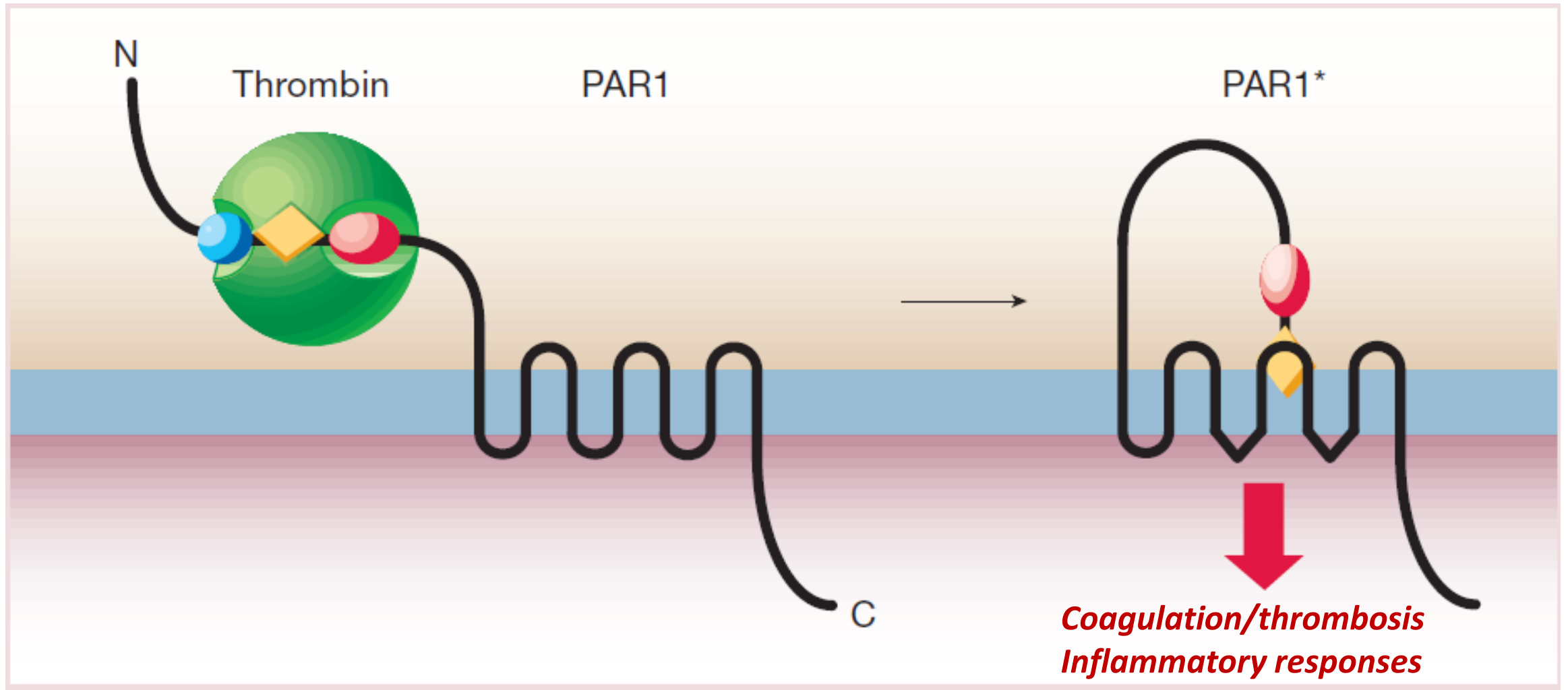
- Sepsis
- Ischemia/Reperfusion Injury
- Antiphospholipid syndrome
- Arthritis

Cancer biology

- Tumor growth
- Angiogenesis
- Metastasis

Fibrosis

Mechanism of PAR1 activation

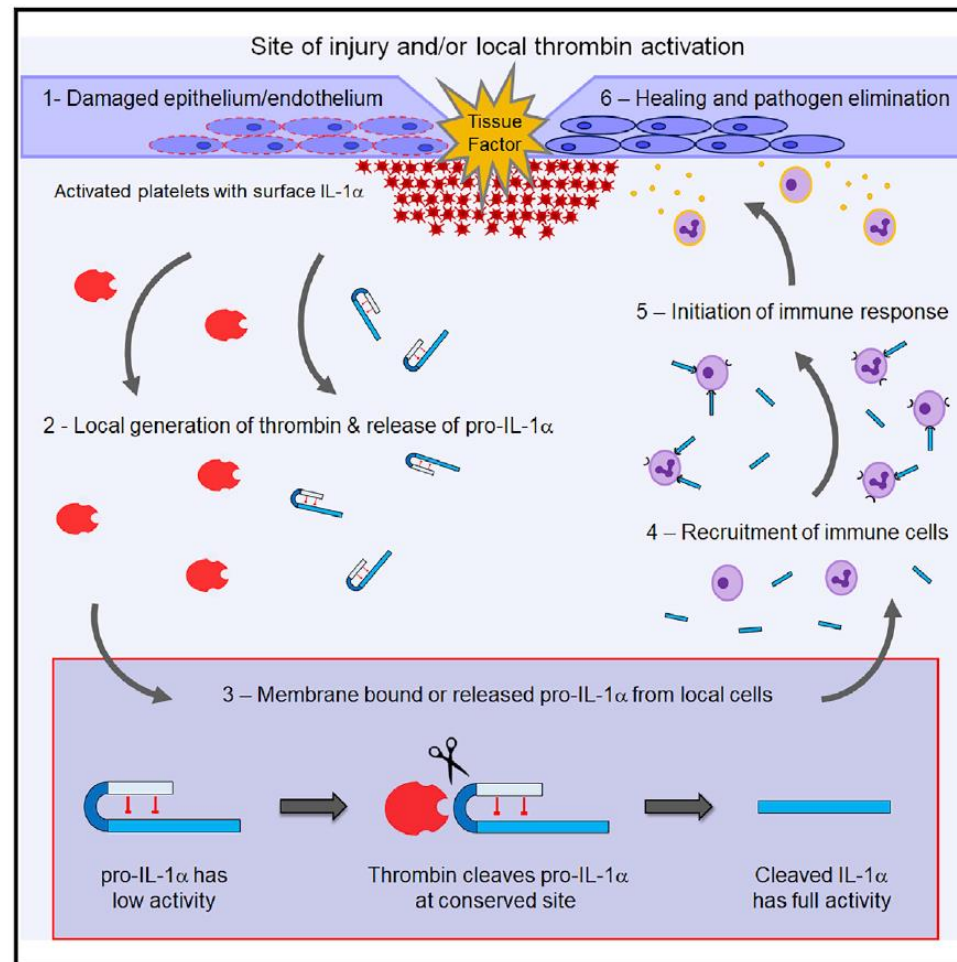


Modified: Coughlin SR. Nature 2000

Immunity

The Coagulation and Immune Systems Are Directly Linked through the Activation of Interleukin-1 α by Thrombin

Graphical Abstract



Authors

Laura C. Burzynski, Melanie Humphry, Katerina Pyrillou, ..., Paul B. Martin, Martin R. Bennett, Murray C.H. Clarke

Correspondence

mchc2@cam.ac.uk

In Brief

Burzynski et al. reveal that the coagulation protease thrombin directly cleaves pro-interleukin (IL)-1 α , rapidly activating the downstream inflammatory cascade. This cleavage site in IL-1 α is conserved throughout mammals, suggesting that this link between coagulation and inflammation may be relevant in multiple disease settings.

Burzynski et al., 2019, *Immunity* 50, 1033–1042

Thrombin proteolytically cleaves and activates C5 and C3

Generation of C5a in the absence of C3: a new complement activation pathway

Markus Huber-Lang^{1,6}, J Vidya Sarma^{2,6}, Firas S Zetoune^{2,6}, Daniel Rittirsch², Thomas A Neff², Stephanie R McGuire², John D Lambris³, Roscoe L Warner², Michael A Flierl², Laszlo M Hoesel², Florian Gebhard¹, John G Younger⁴, Scott M Drouin⁵, Rick A Wetsel⁵ & Peter A Ward²

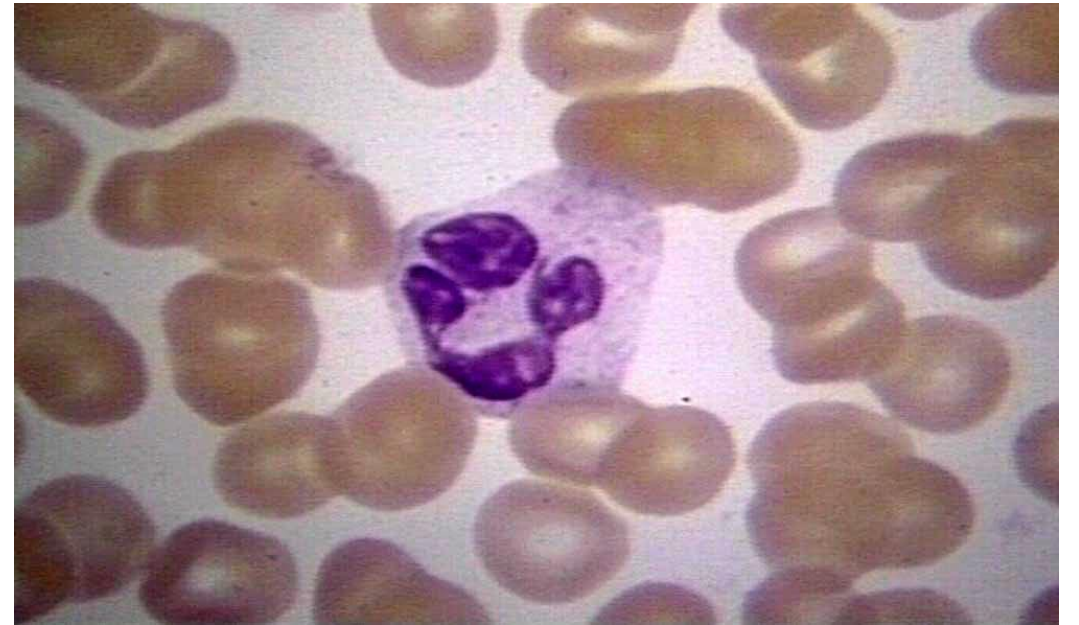
JUNE 2006 **NATURE MEDICINE**



Molecular Intercommunication between the Complement and Coagulation Systems

Umme Amara, Michael A. Flierl, Daniel Rittirsch, Andreas Klos, Hui Chen, Barbara Acker, Uwe B. Brückner, Bo Nilsson, Florian Gebhard, John D. Lambris and Markus Huber-Lang

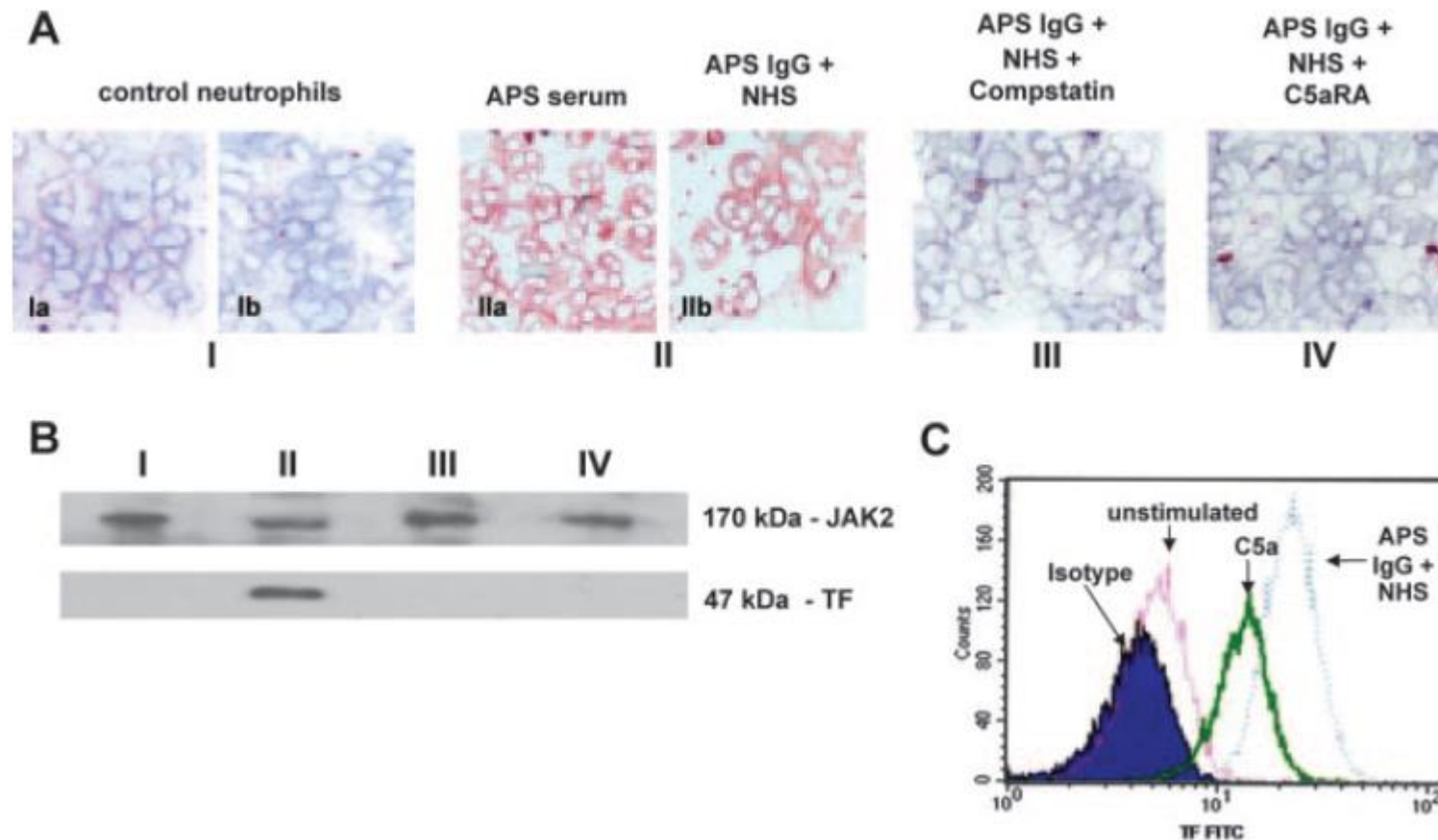
J Immunol 2010; 185:5628-5636;



Neutrophil: key player in thromboinflammation

A Novel C5a Receptor-Tissue Factor Cross-Talk in Neutrophils Links Innate Immunity to Coagulation Pathways¹

Konstantinos Ritis,^{2*} Michael Doulas,^{*} Dimitrios Mastellos,[†] Anastasia Micheli,^{*} Stavros Giaglis,^{*} Paola Magotti,[‡] Stavros Rafail,^{*} Georgios Kartalis,^{*} Paschalis Sideras,[†] and John D. Lambris^{2‡}



Complement activated neutrophils are able to produce TF

Redecha P, Tilley R, Tencati M, et al. Tissue factor: a link between C5a and neutrophil activation in antiphospholipid antibody induced fetal injury.

Blood 2007;110:2423-31

Redecha P, Franzke CW, Ruf W, et al. Neutrophil activation by the tissue factor/Factor VIIa/PAR2 axis mediates fetal death in a mouse model of antiphospholipid syndrome.

J Clin Invest 2008;118:3453-61

Kambas K, Markiewski MM, Pneumatikos IA, et al. C5a and TNF-alpha up-regulate the expression of tissue factor in intra-alveolar neutrophils of patients with the acute respiratory distress syndrome.

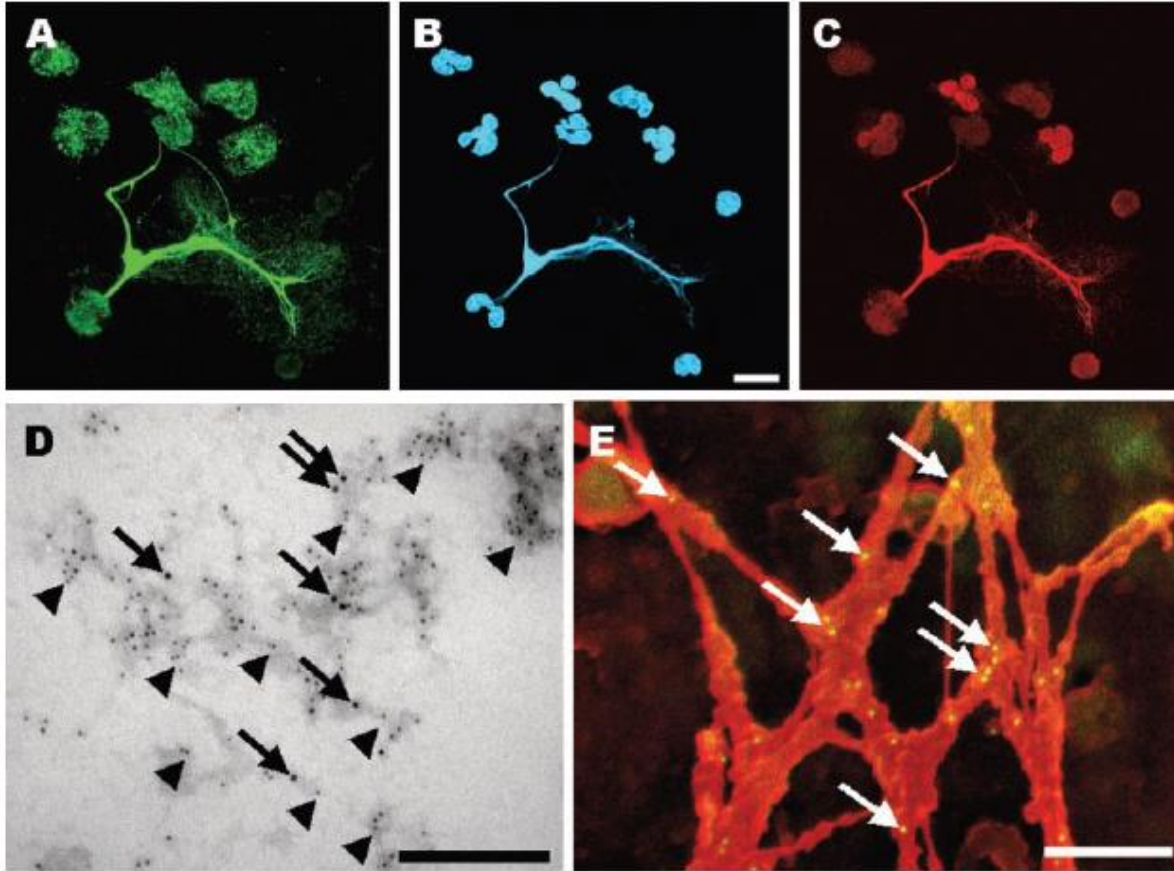
J Immunol. 2008;180:7368-75.

Kourtzelis I, Markiewski MM, Doumas M, et al. Complement anaphylatoxin C5a contributes to hemodialysis-associated thrombosis.

Blood. 2010;116:631-9.



2004: “ Neutrophil extracellular traps (NETs) is a new antimicrobial mechanism”



Neutrophil Extracellular Traps Kill Bacteria
Volker Brinkmann, *et al.*
Science **303**, 1532 (2004);
DOI: 10.1126/science.1092385

Excess NET formation can drive a variety of severe pathologies

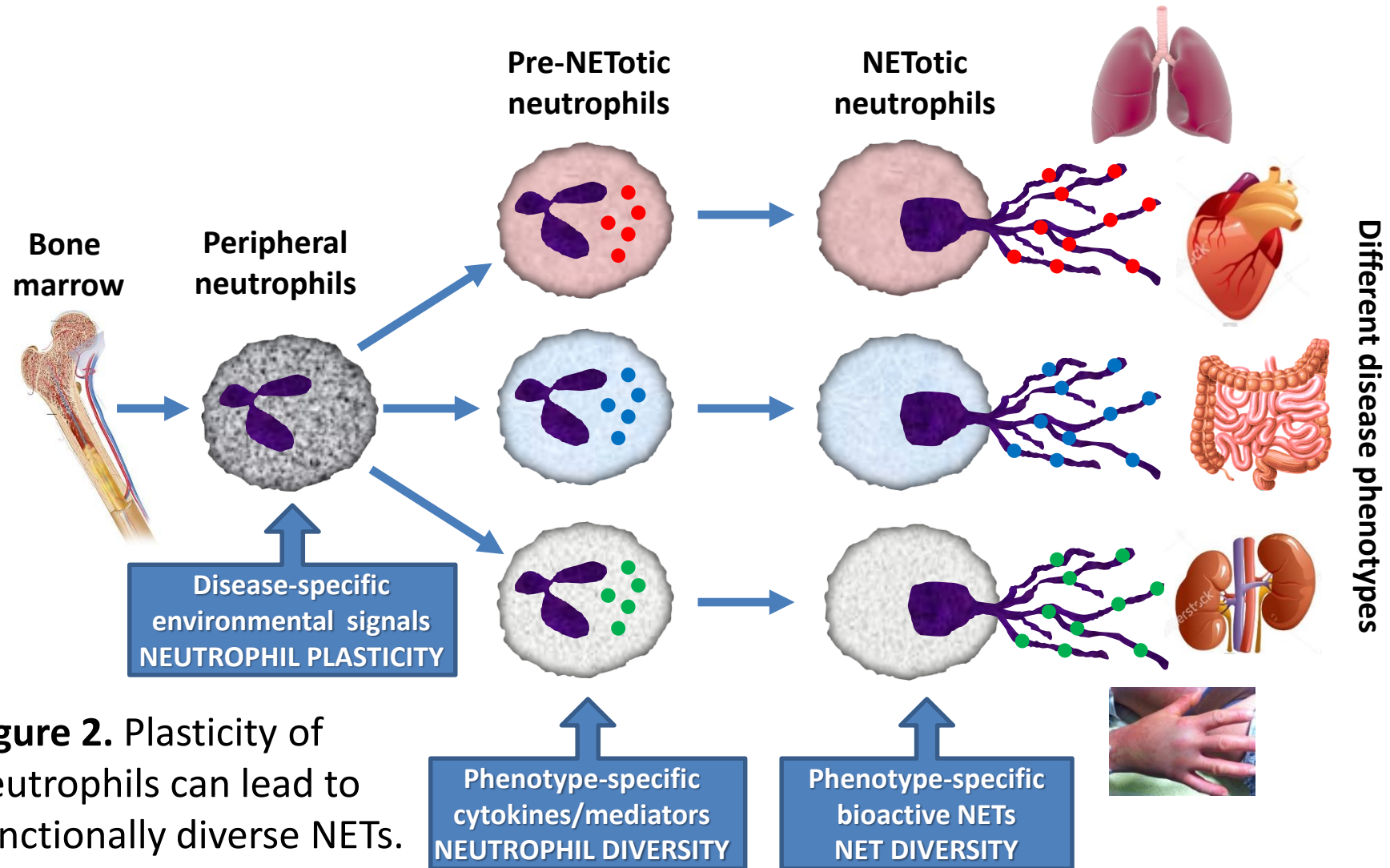
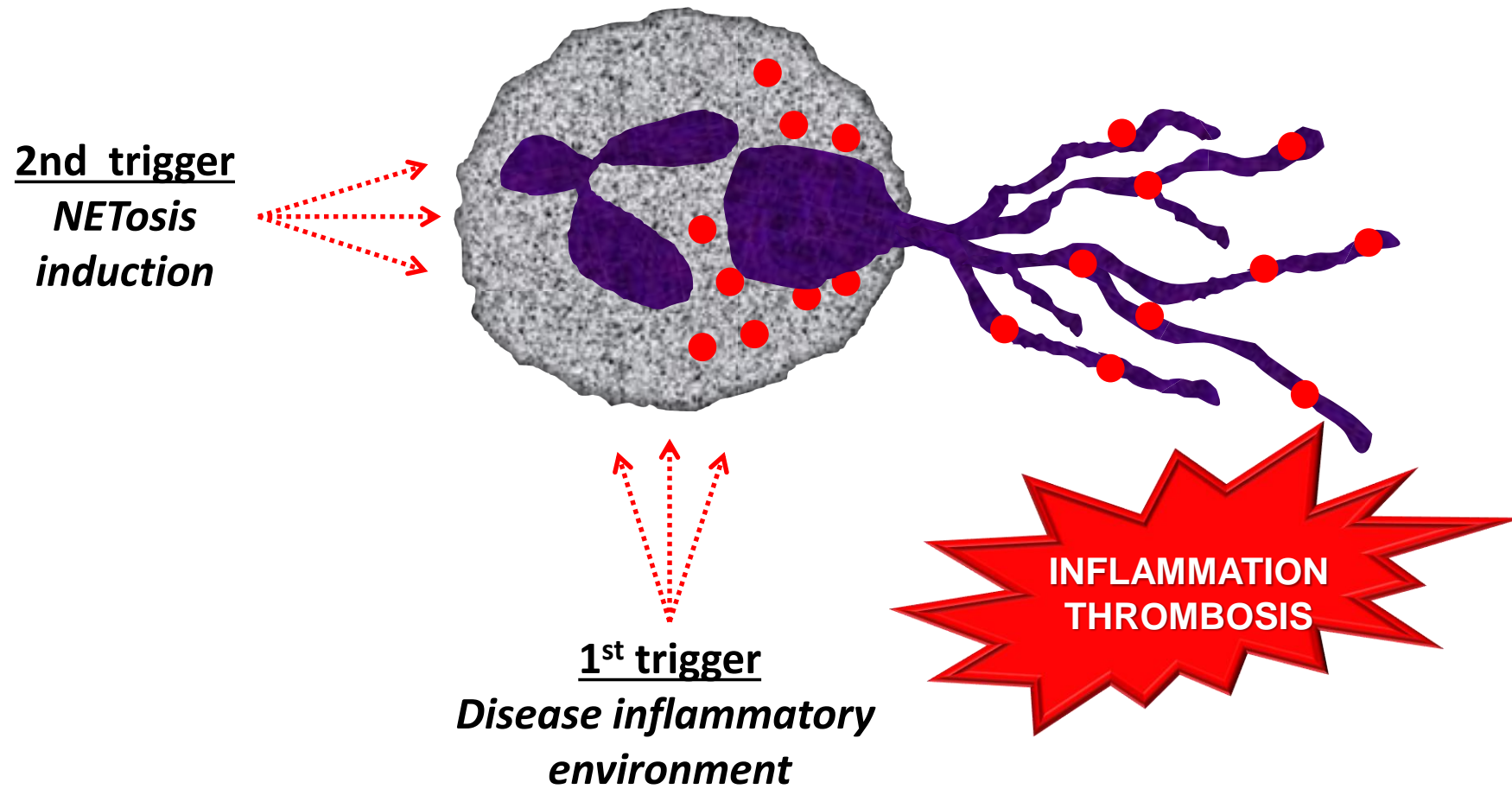
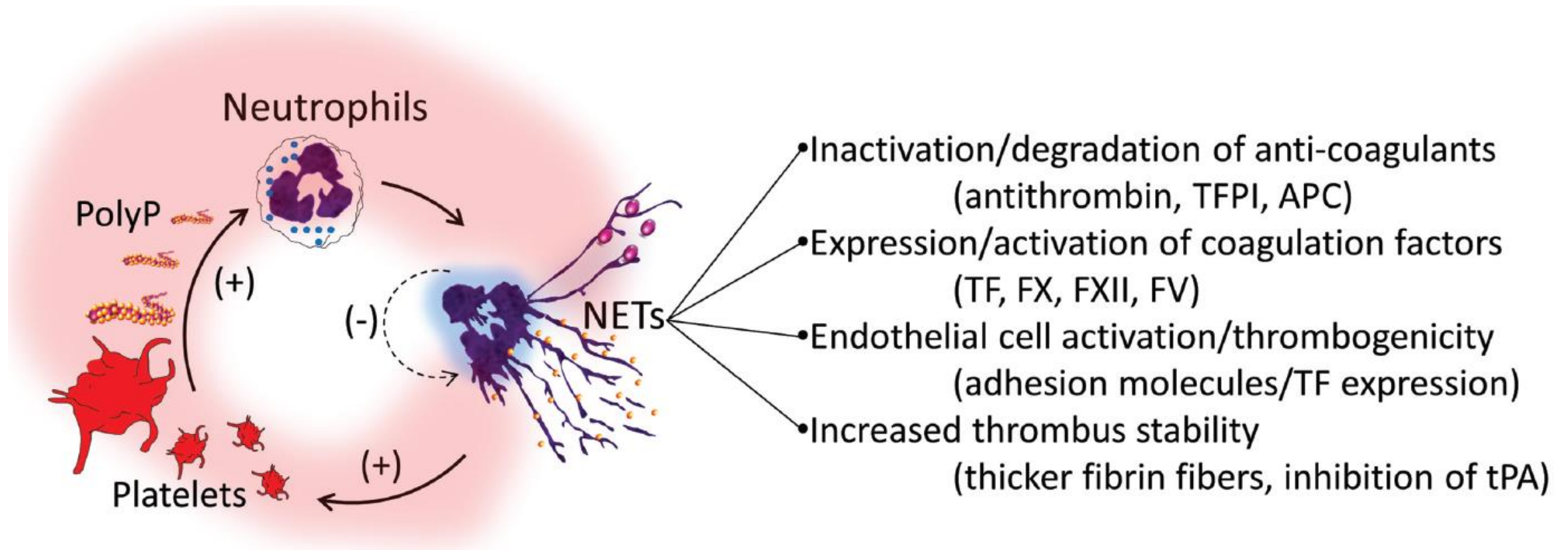


Figure 2. Plasticity of neutrophils can lead to functionally diverse NETs.

NET release (NETosis) “Two hits model”



Mechanisms of neutrophil extracellular trap (NET) thrombogenicity



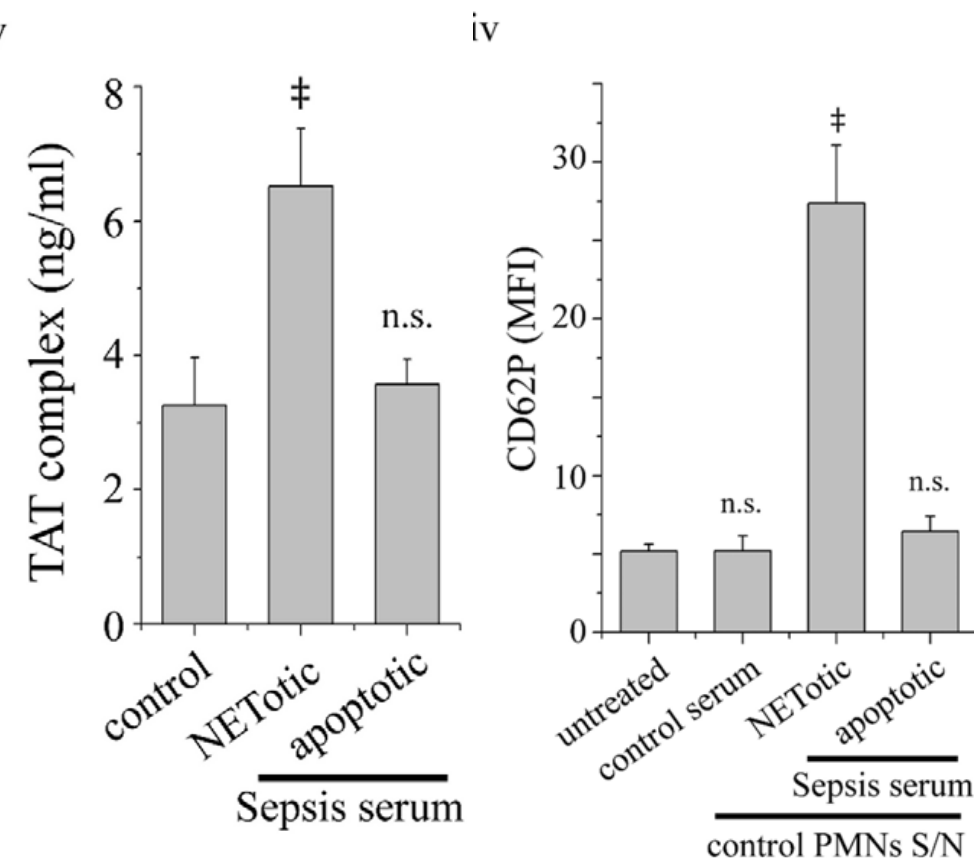
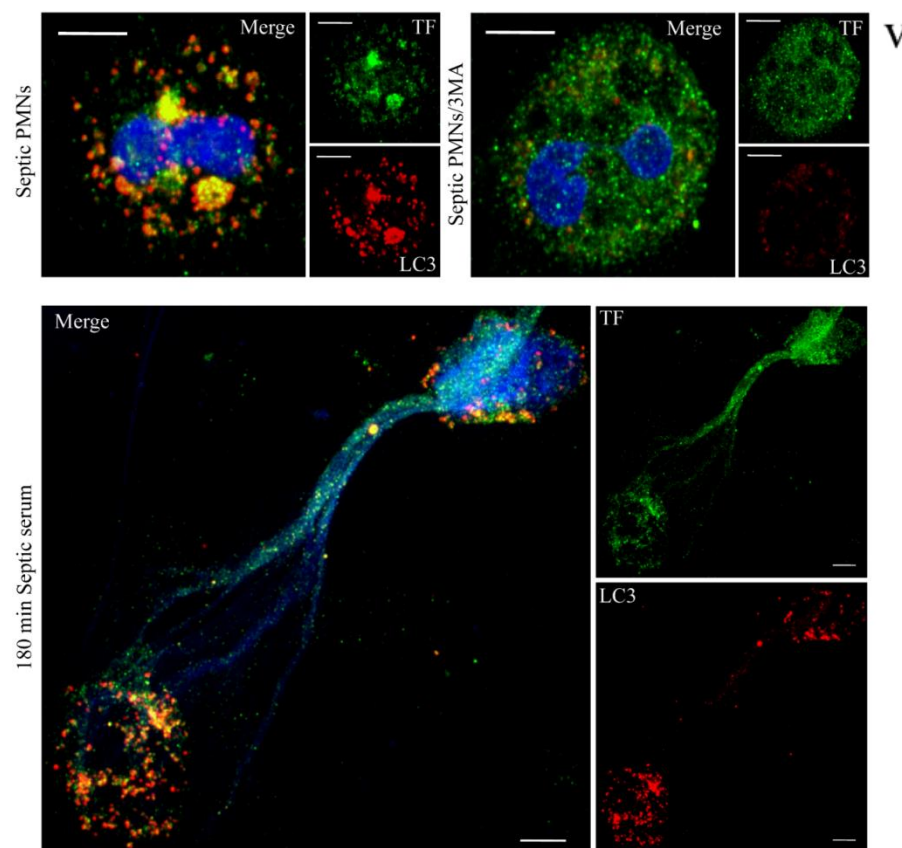
**Neutrophils/NETs are key factors linking
innate immunity/inflammation to thrombus formation in
various clinical models**

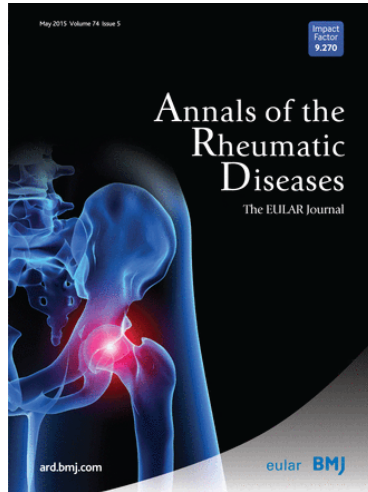


Autophagy Mediates the Delivery of Thrombogenic Tissue Factor to Neutrophil Extracellular Traps in Human Sepsis

PLoS One. 2012;7(9):e45427

Konstantinos Kambas^{1§}, Ioannis Mitroulis^{1§}, Eirini Apostolidou¹, Andreas Girod², Akrivi Chrysanthopoulou¹, Ioannis Pneumatikos³, Panagiotis Skendros¹, Ioannis Kourtzelis⁴, Maria Koffa⁵, Ioannis Kotsianidis⁶, Konstantinos Ritis^{1*}



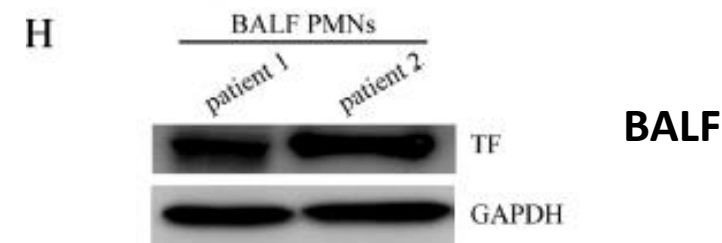
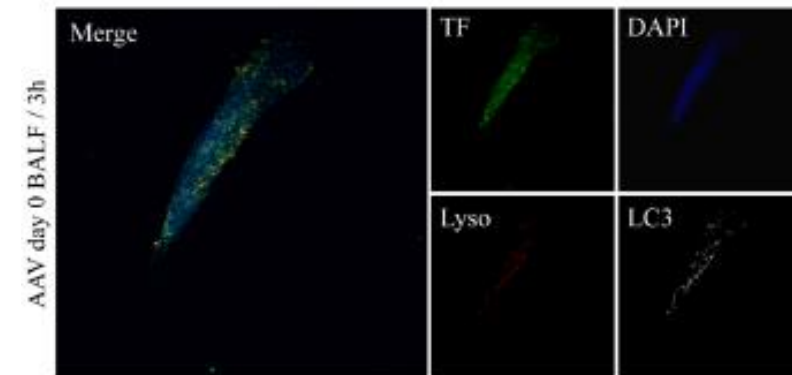
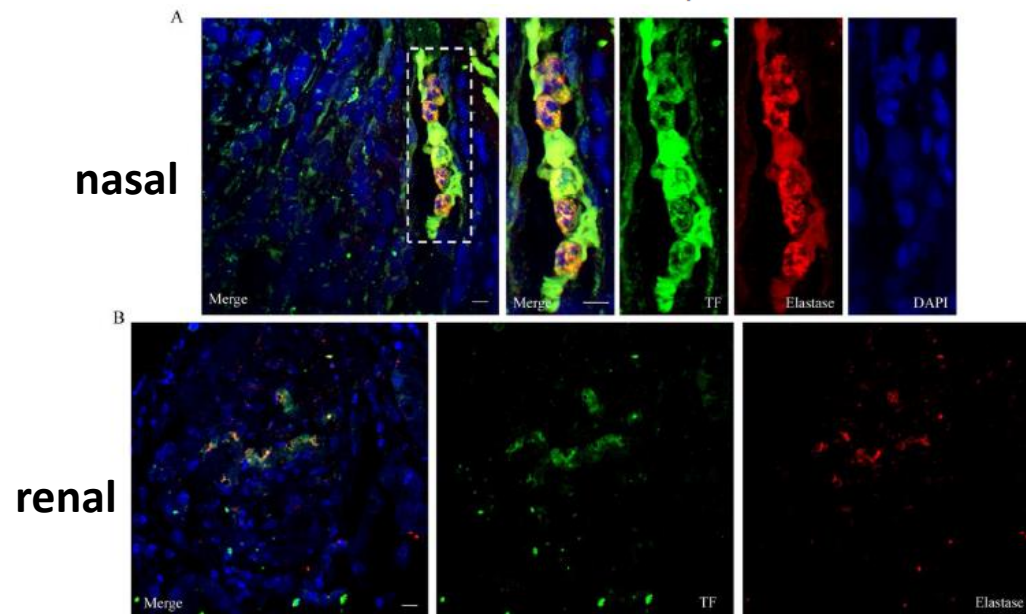


Ann Rheum Dis 2014

EXTENDED REPORT

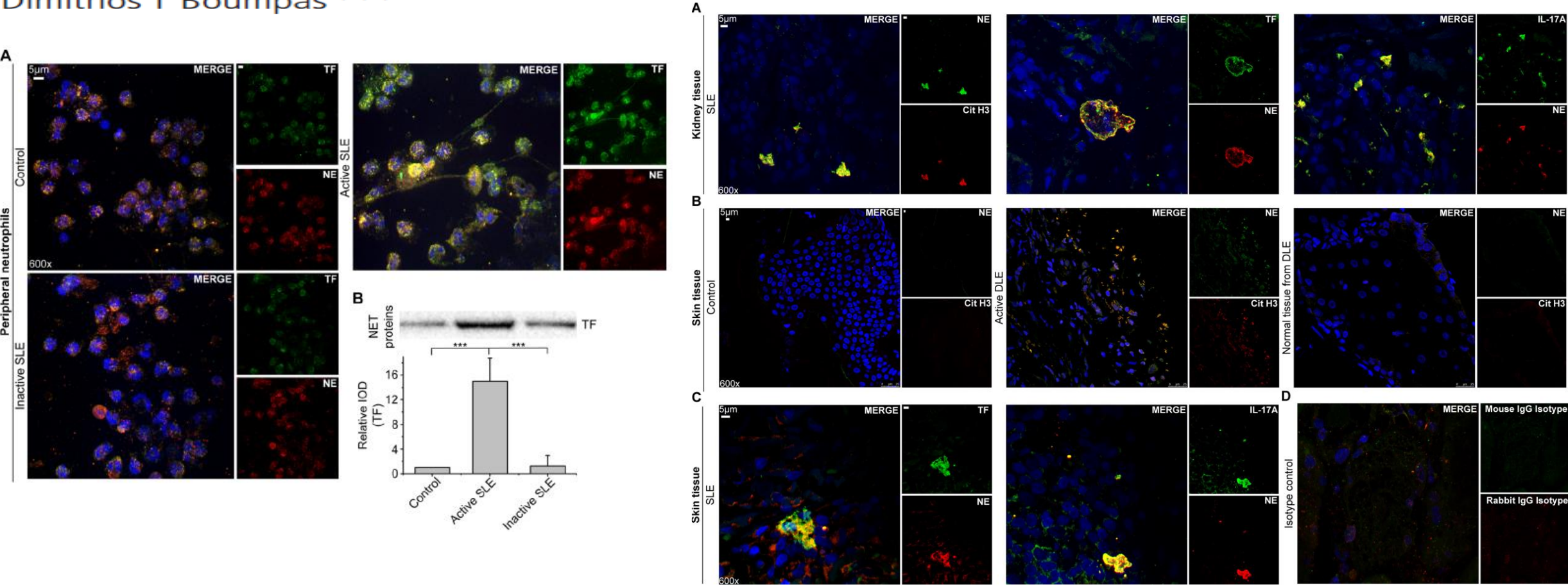
Tissue factor expression in neutrophil extracellular traps and neutrophil derived microparticles in antineutrophil cytoplasmic antibody associated vasculitis may promote thromboinflammation and the thrombophilic state associated with the disease

Konstantinos Kambas,¹ Akrivi Chrysanthopoulou,¹ Dimitrios Vassilopoulos,² Eirini Apostolidou,¹ Panagiotis Skendros,³ Andreas Girod,⁴ Stella Arelaki,¹ Marios Froudarakis,⁵ Lydia Nakopoulou,⁶ Alexandra Giatromanolaki,⁷ Prodromos Sidiropoulos,⁸ Maria Koffa,⁹ Dimitrios T Boumpas,^{10,11} Konstantinos Ritis,^{1,3} Ioannis Mitroulis^{1,3,12}



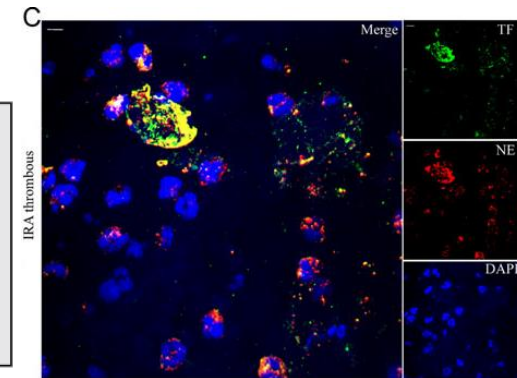
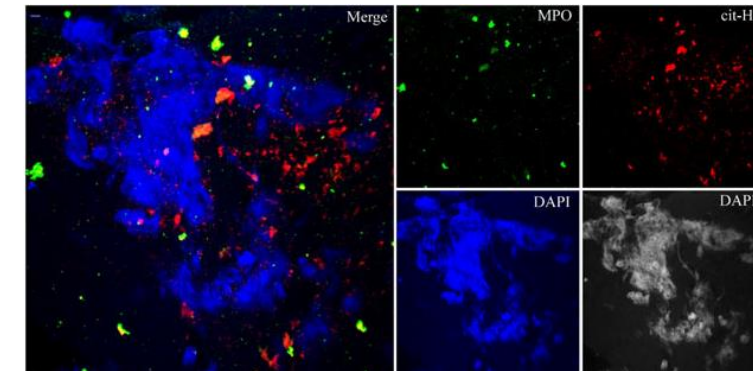
REDD1/autophagy pathway promotes thromboinflammation and fibrosis in human systemic lupus erythematosus (SLE) through NETs decorated with tissue factor (TF) and interleukin-17A (IL-17A)

Eleni Frangou,^{1,2,3} Akriyi Chrysanthopoulou,⁴ Alexandros Mitsios,⁴ Konstantinos Kambas,⁴ Stella Arelaki,⁵ Iliana Angelidou,⁴ Athanasios Arampatzoglou,⁴ Hariklia Gakiopoulou,⁶ George K Bertsiyas,⁷ Panayotis Verginis,¹ Konstantinos Ritis,^{4,8} Dimitrios T Boumpas^{1,2,9,10}



Expression of functional tissue factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction

Dimitrios A. Stakos^{1†}, Konstantinos Kambas^{2†}, Theocharis Konstantinidis², Ioannis Mitroulis³, Eirini Apostolidou², Stella Arelaki⁴, Victoria Tsironidou², Alexandra Giatromanolaki⁴, Panagiotis Skendros², Stavros Konstantinides^{1,5}, and Konstantinos Ritis^{2*}



Translational perspective

Neutrophils are involved in the pathophysiology of infarcted coronary arteries in STEMI via NET structures. Platelets, activated by thrombin, are required for NET formation, while the integrity of NET scaffold contributes to the functionality of NET-bound TF. The blockage of NET formation or local neutralization of NET-mediated TF signalling constitutes candidate therapeutic targets.

Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the prevention of late stent thrombosis by an interdisciplinary global European effort consortium[†]

[PRESTIGE Investigators](#)

Results

Overall 253 thrombus specimens were analysed; 79 (31.2%) from patients presenting with early ST, 174 (68.8%) from late ST; 79 (31.2%) were from bare metal stents, 166 (65.6%) from drug-eluting stents, 8 (3.2%) were from stents of unknown type. Thrombus specimens displayed heterogeneous morphology with platelet-rich thrombus and fibrin/fibrinogen fragments most abundant; mean platelet coverage was 57% of thrombus area. Leukocyte infiltrations were hallmarks of both early and late ST (early: 2260 ± 1550 per mm^2 vs. late: 2485 ± 1778 per mm^2 ; $P = 0.44$); neutrophils represented the most prominent subset (early: 1364 ± 923 per mm^2 vs. late: 1428 ± 1023 per mm^2 ; $P = 0.81$). Leukocyte counts were significantly higher compared with a control group of patients with thrombus aspiration in spontaneous myocardial infarction. Neutrophil extracellular traps were observed in 23% of samples. Eosinophils were present in all stent types, with higher numbers in patients with late ST in sirolimus- and everolimus-eluting stents.

Conclusion

In a large-scale study of histological thrombus analysis from patients presenting with ST, thrombus specimens displayed heterogeneous morphology. Recruitment of leukocytes, particularly neutrophils, appears to be a hallmark of ST. The presence of NETs supports their pathophysiological relevance. Eosinophil recruitment suggests an allergic component to the process of ST.

Neutrophil extracellular traps are increased in patients with acute ischemic stroke: prognostic significance

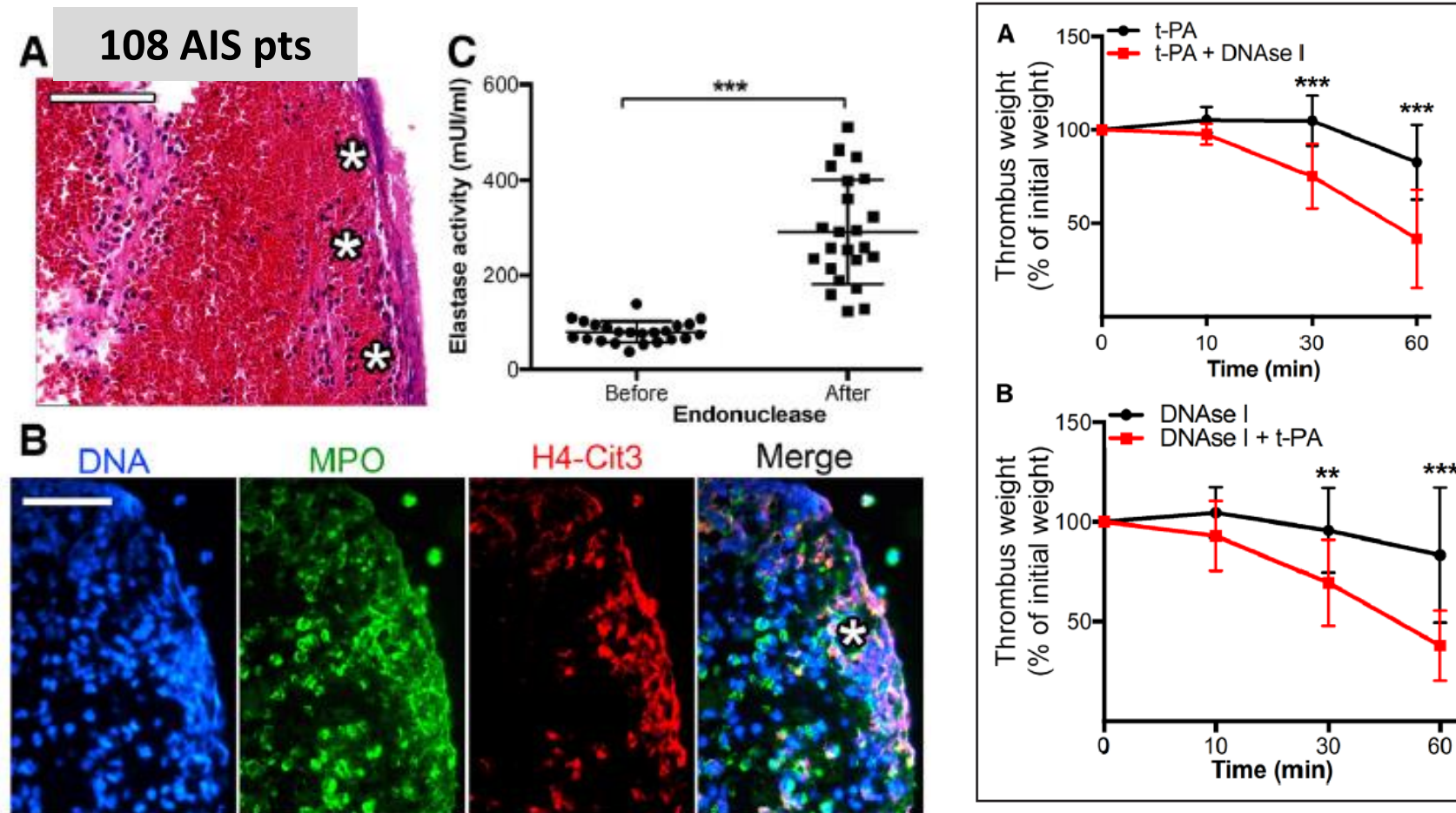
Juana Vallés¹; Aida Lago²; María Teresa Santos¹; Ana María Latorre¹; José I. Tembl²; Juan B. Salom^{3,4}; Candela Nieves²; Antonio Moscardó^{1†}

¹Hemostasis, Thrombosis, Atherosclerosis, and Vascular Biology Unit, Health Research Institute La Fe, Valencia, Spain; ²Department of Neurology, University and Polytechnic Hospital La Fe, Valencia, Spain; ³Cerebrovascular Research Joint Unit, Health Research Institute La Fe, Valencia, Spain; ⁴Department of Physiology, University of Valencia, Valencia, Spain

- 243 patients with acute ischemic stroke
- follow-up 12 months after the ischemic event
- plasma citrullinated histone 3 (citH3) candidate prognostic & therapeutic target in stroke

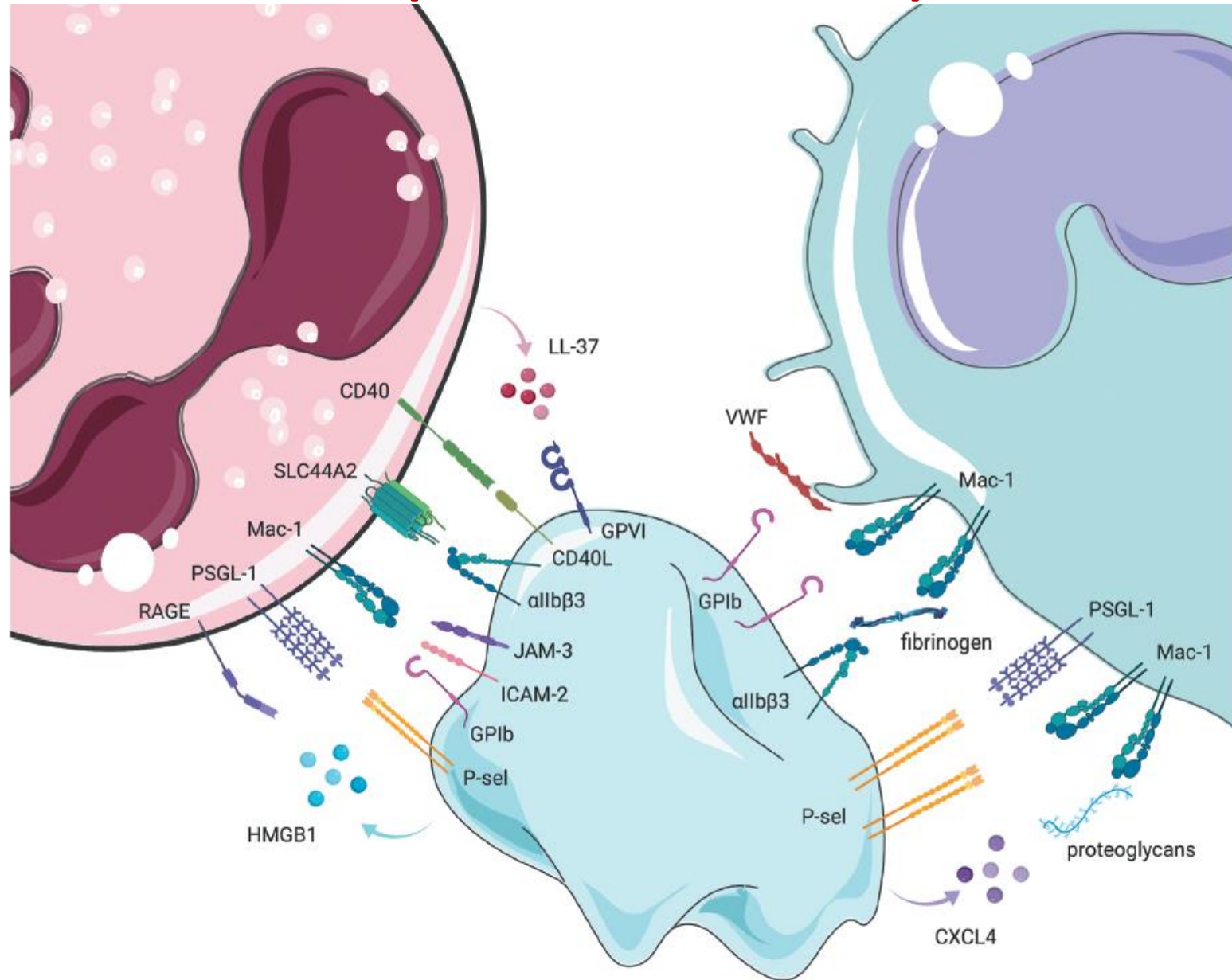
- NETs are elevated in acute ischemic stroke, and related with age, atrial fibrillation or glucose levels.
- Higher NETs at the moment of stroke are independently associated with worse outcome at one year.

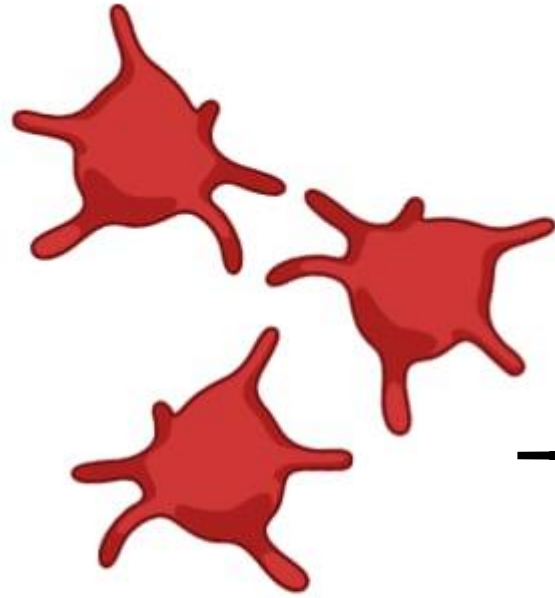
Thrombus Neutrophil Extracellular Traps Content Impair tPA-Induced Thrombolysis in Acute Ischemic Stroke



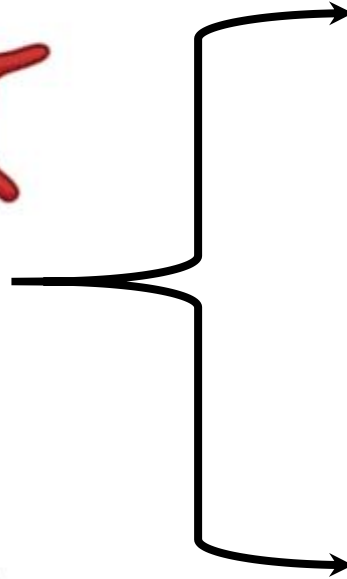
- NETs content was associated with endovascular procedure length & device number of passes
- tPA and DNase 1 co-administration accelerated ex vivo thrombolysis

Key interactions between platelets and neutrophils or macrophages





Platelets



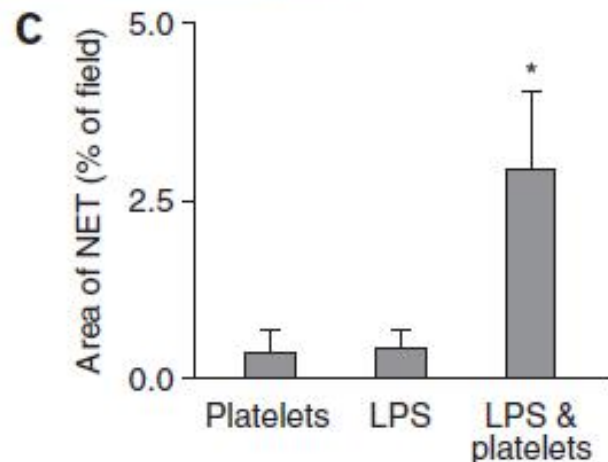
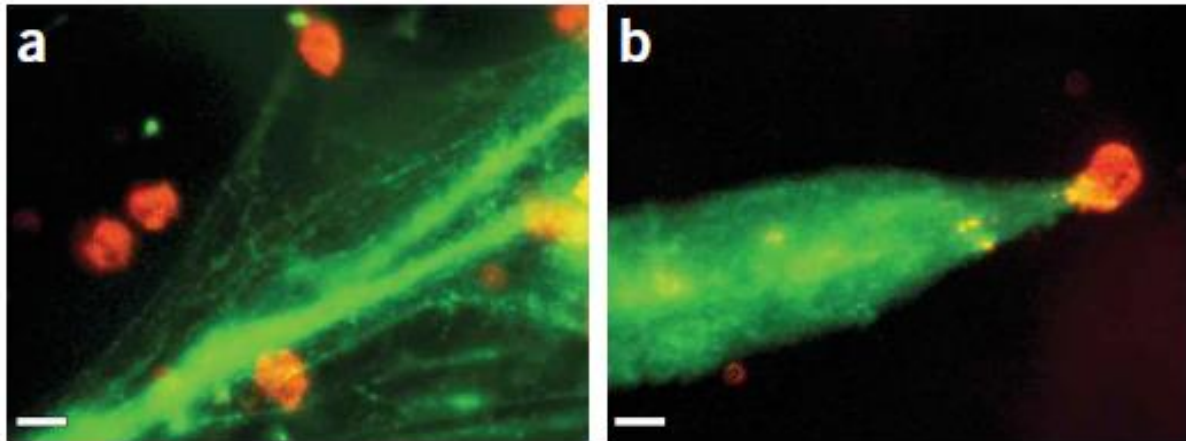
**Support/induce
NET formation**

**Influence the migratory
properties of
neutrophils**

Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood

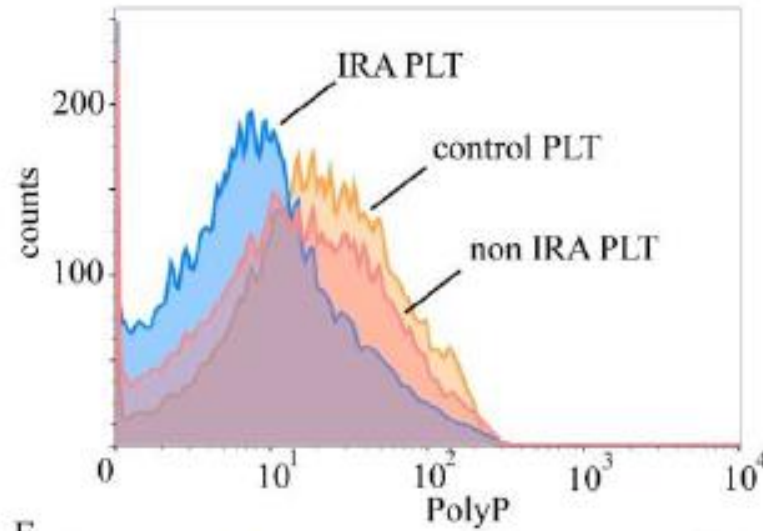
Stephen R Clark^{1,6}, Adrienne C Ma^{1,6}, Samantha A Tavener¹, Braedon McDonald¹, Zahra Goodarzi¹, Margaret M Kelly^{1,2}, Kamala D Patel^{1,3}, Subhadeep Chakrabarti^{1,3}, Erin McAvoy¹, Gary D Sinclair^{2,3}, Elizabeth M Keys², Emma Allen-Vercoe⁴, Rebekah DeVinney⁴, Christopher J Doig⁵, Francis H Y Green² & Paul Kubes¹

NATURE MEDICINE VOLUME 13 | NUMBER 4 | APRIL 2007

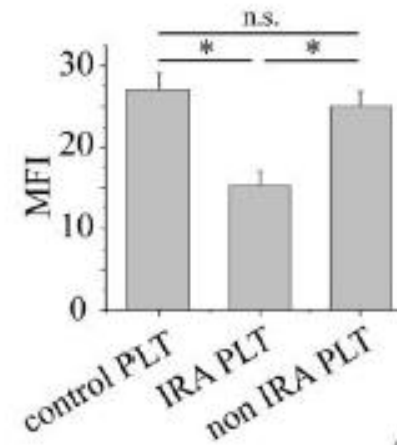


- Platelet TLR4 regulates adhesion of platelets to neutrophils
- Platelets are necessary for LPS-induced neutrophil NET formation
- NETs retain their integrity under flow conditions
- NET release occurs primarily in the sinusoidal capillaries
- NETosis occurs at the expense of injury to endothelium and tissue

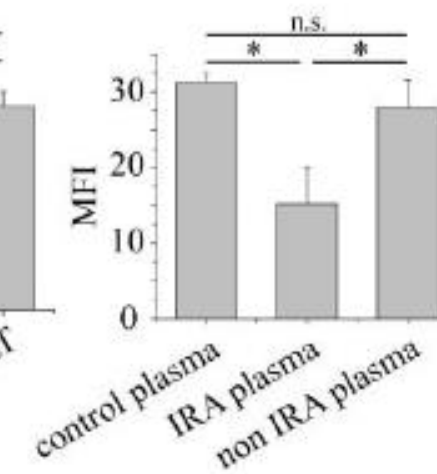
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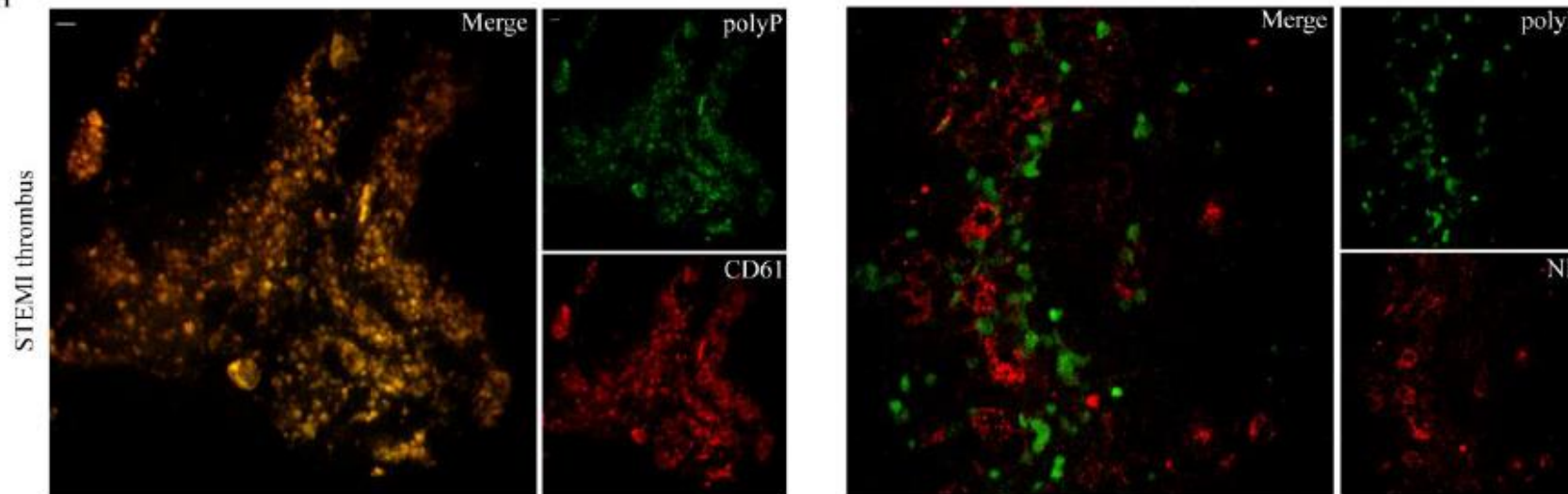


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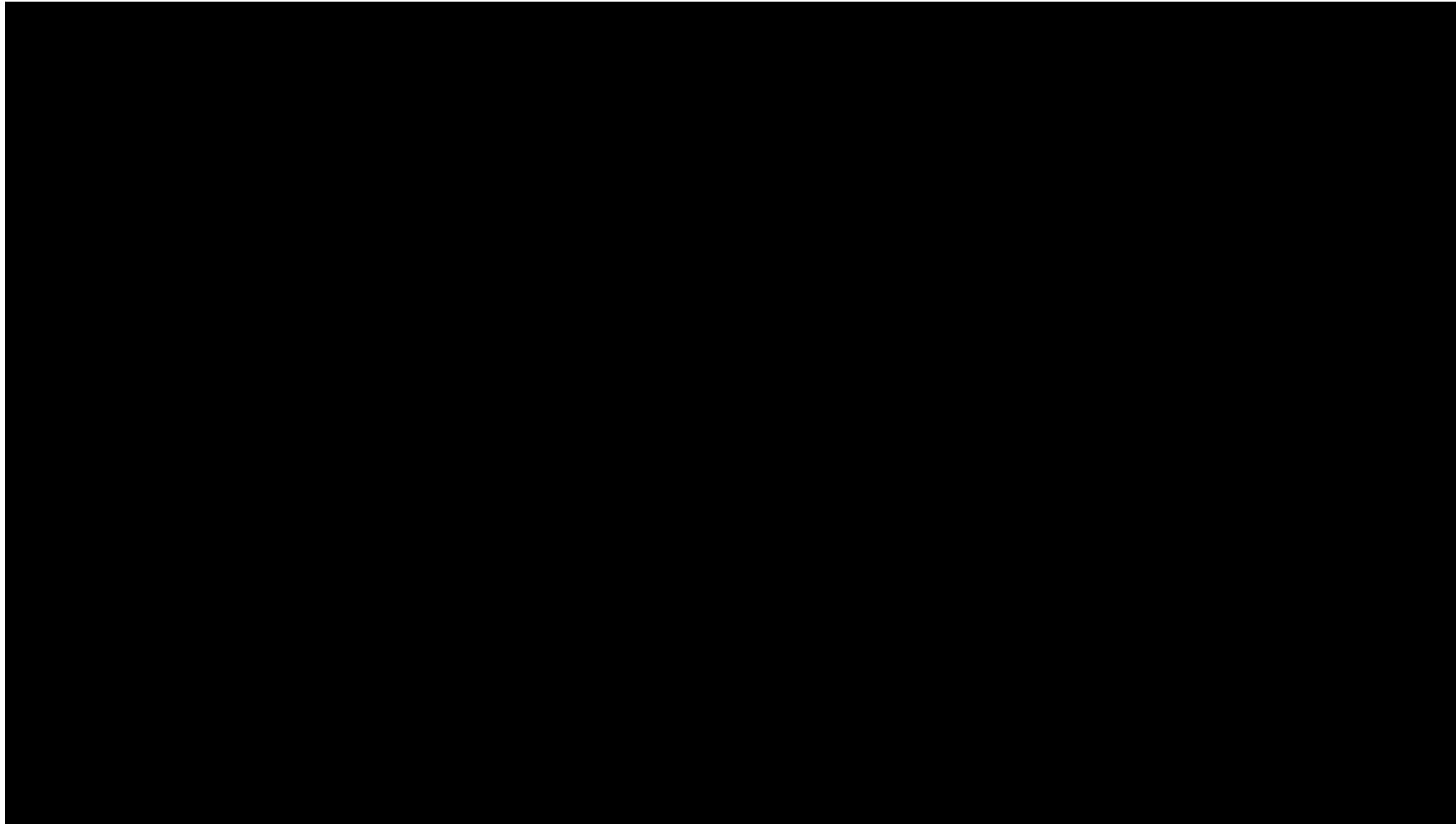


In STEMI thrombin-activated platelets interact with neutrophils to release NETs, via secretion of inorganic polyP

H



Dynamic reorganization of neutrophil domains and receptors allows simultaneous interactions with both the vascular wall and activated platelets in the circulation early during inflammation



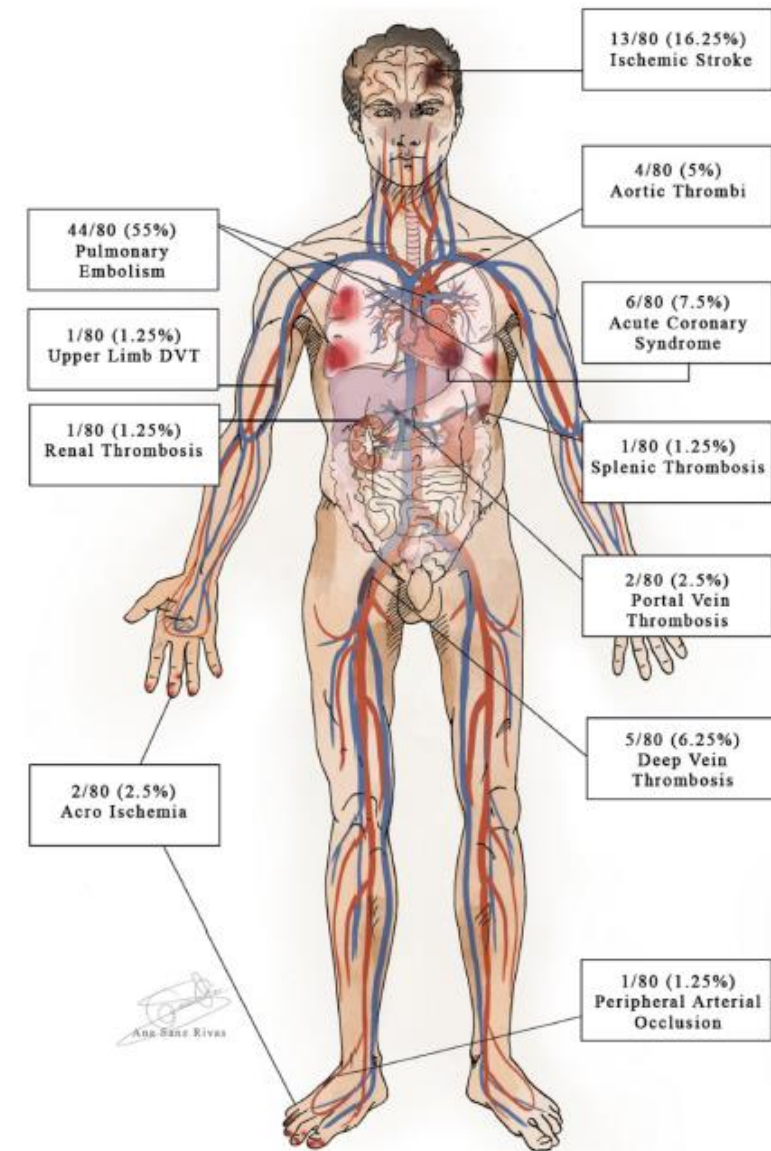
Sreeramkumar, V. et al. **Neutrophils scan for activated platelets to initiate inflammation.** Science 2014

How COVID-19 pandemic recalls old stories.....

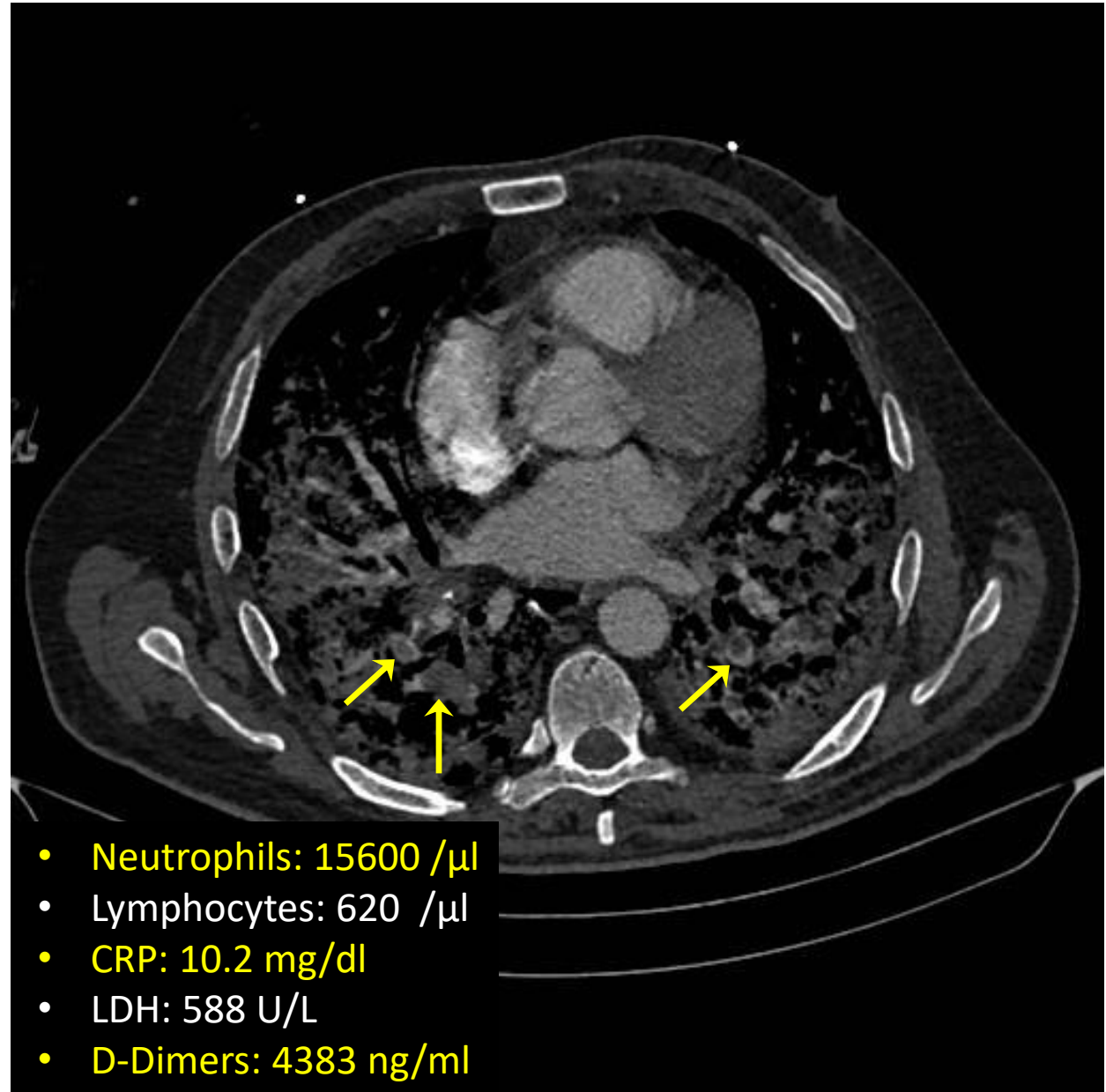
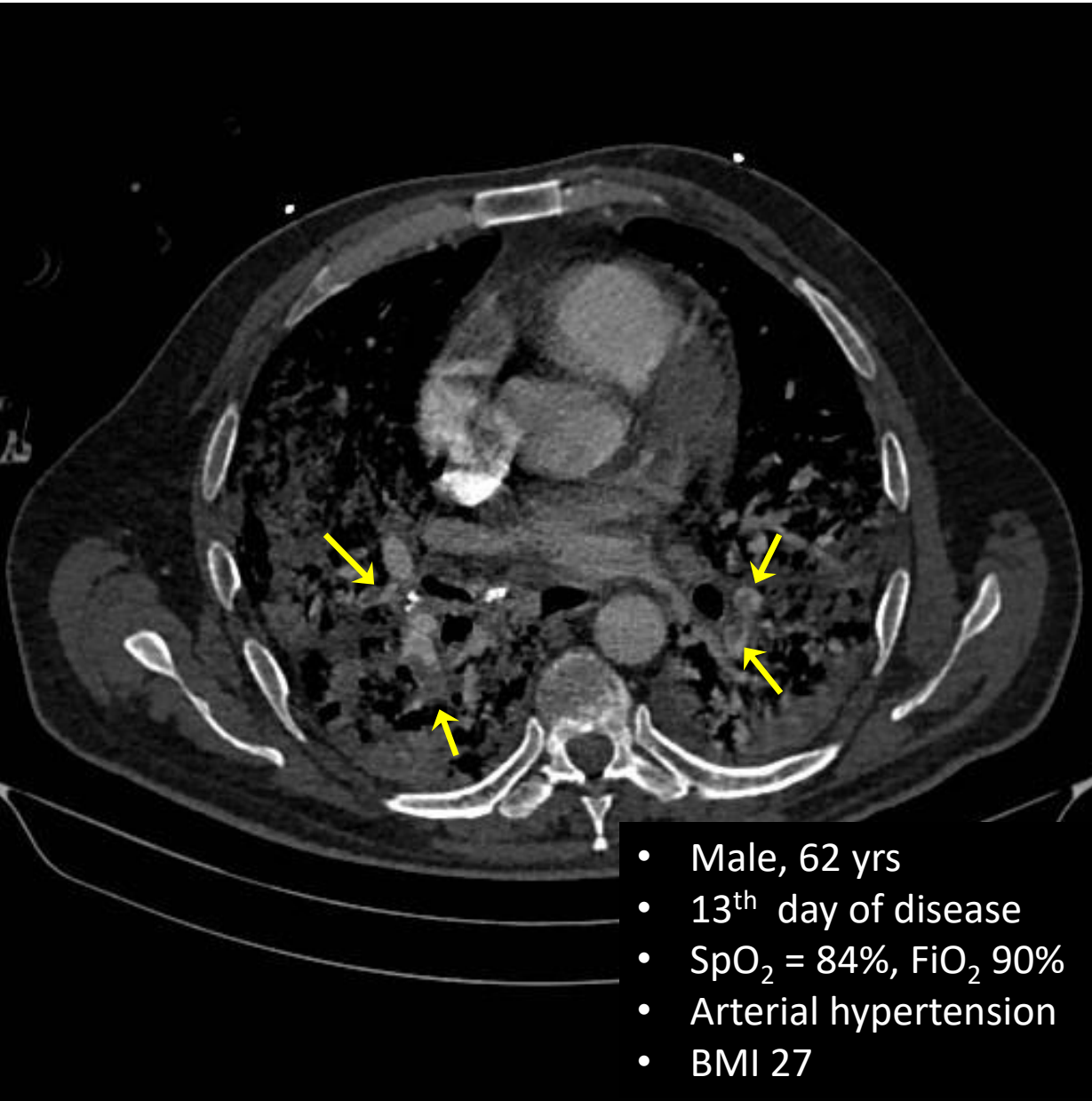
Clinical lessons of COVID-19 coagulopathy

- COVID-19 is associated with **venous and arterial thrombosis, stroke, pulmonary embolism**, and increased rates of **cardiac complications**
- Phenotype similar to **Thrombotic Microangiopathy (TMA)** and/or **Antiphospholipid Syndrome/CAPS**
- **Very high cumulative incidence** of thrombotic complications in hospitalized patients with COVID-19 pneumonia (**20-50%**)
- Many patients with thrombosis have been in intensive care units (ICUs), however **less seriously ill patients are also at significant risk of thromboembolic complications**
- Thrombotic events **may be the initial presenting symptom** of COVID-19

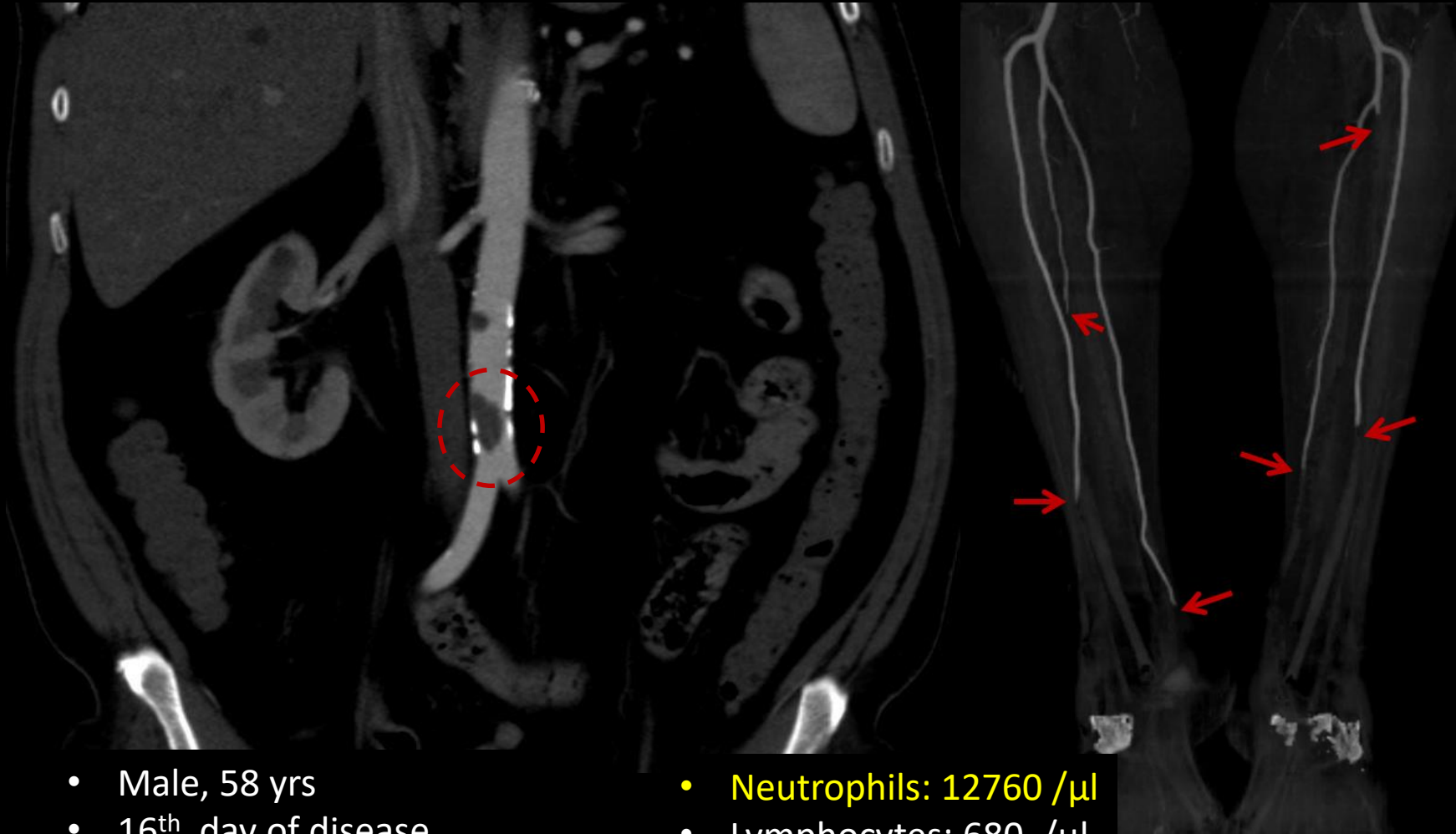
- Guo T et al. *JAMA Cardiol.* 2020
- Ackermann M, et al. *N Engl J Med.* 2020
- Fox SE et al. *Lancet Respir Med* 2020
- Poissy J et al. *Circulation.* 2020
- Zhang Y et al *N Engl J Med.* 2020
- Muñoz-Rivas N et al. *Thromb Res.* 2021



Pulmonary embolism in a severe COVID-19 patient



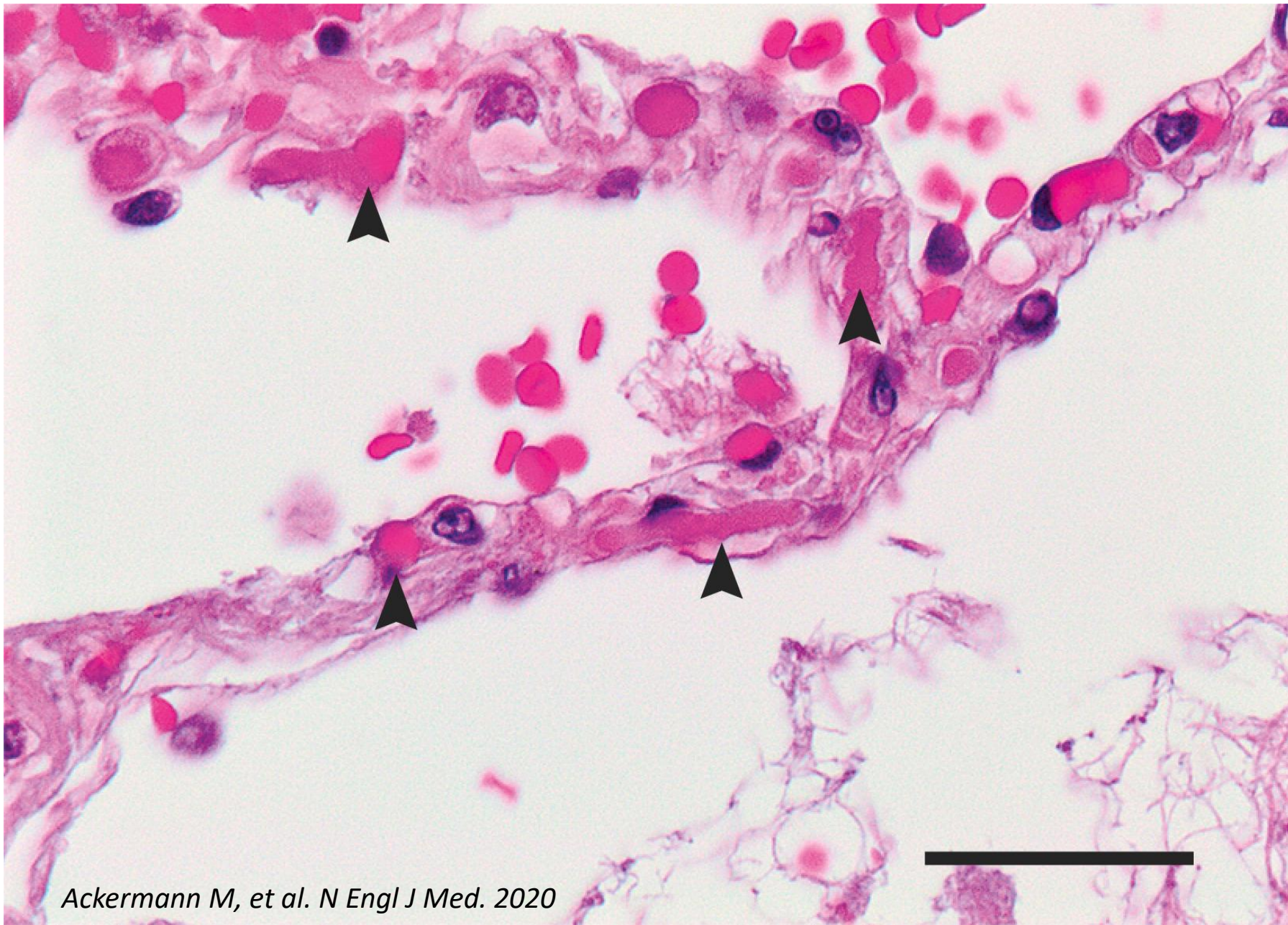
Severe thrombotic complication in a COVID-19 patient



- Male, 58 yrs
- 16th day of disease
- SpO₂ = 97%, FiO₂ 35%
- No smoking, BMI 25
- Well-controlled hypertension
- No history of CVD event

- **Neutrophils: 12760 / μ l**
- **Lymphocytes: 680 / μ l**
- **CRP: 7.71 mg/dl**
- **LDH: 1057 U/L**
- **D-Dimers: 976 ng/ml**

COVID-19 2nd Wards, First Department of Internal Medicine, University Hospital of Alexandroupolis



Micro-CLOTs

**Microthrombi in the
alveolar capillaries
(arrowheads)**

Ackermann M, et al. N Engl J Med. 2020



Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: <https://www.journals.elsevier.com/eclinicalmedicine>

Research Paper

Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis

Mahmoud B. Malas^{1,*}, Isaac N. Naazie¹, Nadin Elsayed, Asma Mathlouthi, Rebecca Marmor, Bryan Clary

Department of Surgery, University of California San Diego Health System, San Diego, CA 92093, United States

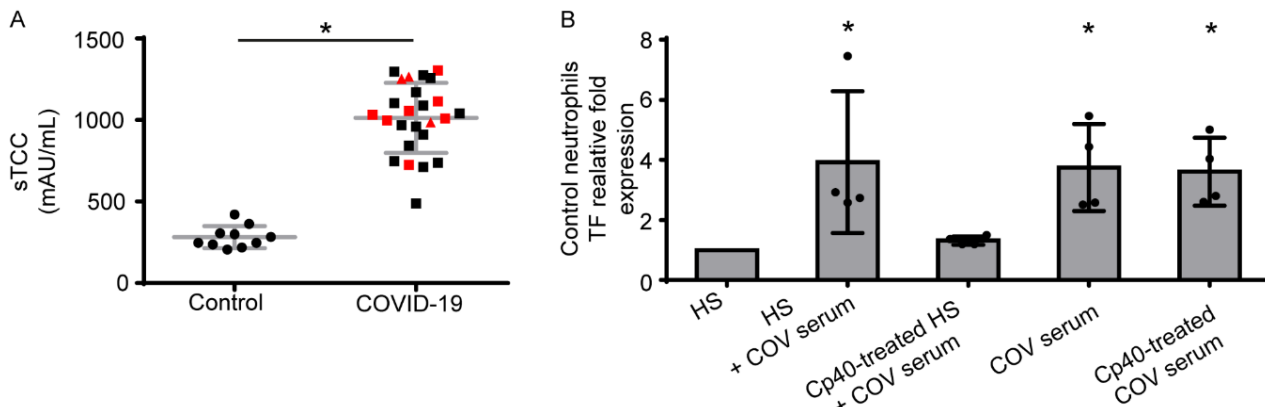
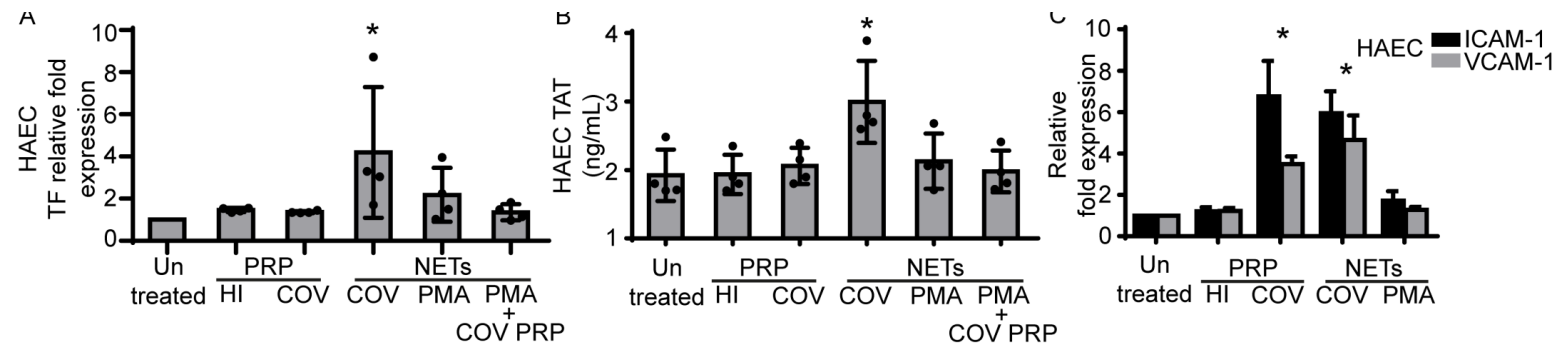
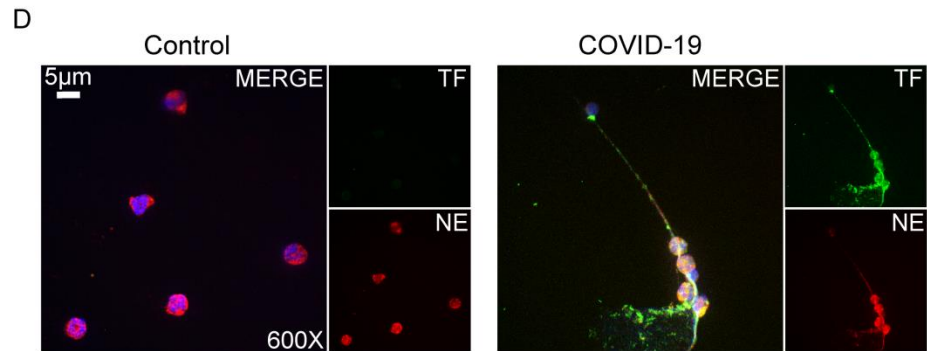
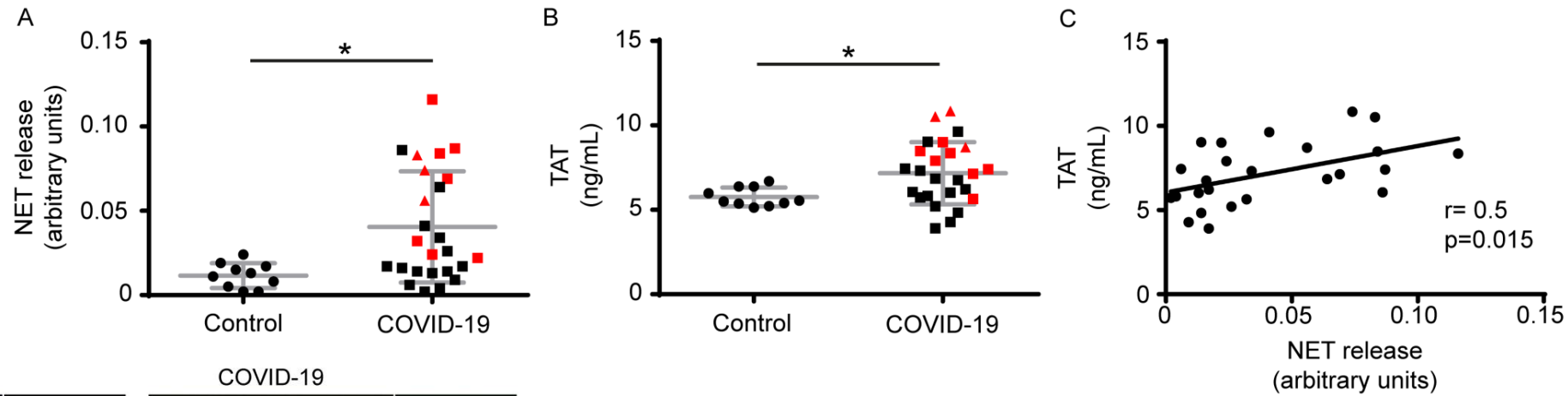
42 studies/8271 patients

Findings: Of 425 studies identified, 42 studies enrolling 8271 patients were included in the meta-analysis. Overall venous TE rate was 21% (95% CI:17–26%): ICU, 31% (95% CI: 23–39%). Overall deep vein thrombosis rate was 20% (95% CI: 13–28%): ICU, 28% (95% CI: 16–41%); postmortem, 35% (95% CI:15–57%). Overall pulmonary embolism rate was 13% (95% CI: 11–16%): ICU, 19% (95% CI:14–25%); postmortem, 22% (95% CI:16–28%). Overall arterial TE rate was 2% (95% CI: 1–4%): ICU, 5% (95%CI: 3–7%). Pooled mortality rate among patients with TE was 23% (95%CI:14–32%) and 13% (95% CI:6–22%) among patients without TE. The pooled odds of mortality were 74% higher among patients who developed TE compared to those who did not (OR, 1.74; 95%CI, 1.01–2.98; $P = 0.04$).

Understanding the immunothrombotic mechanisms in COVID-19 constitutes a significant medical challenge today



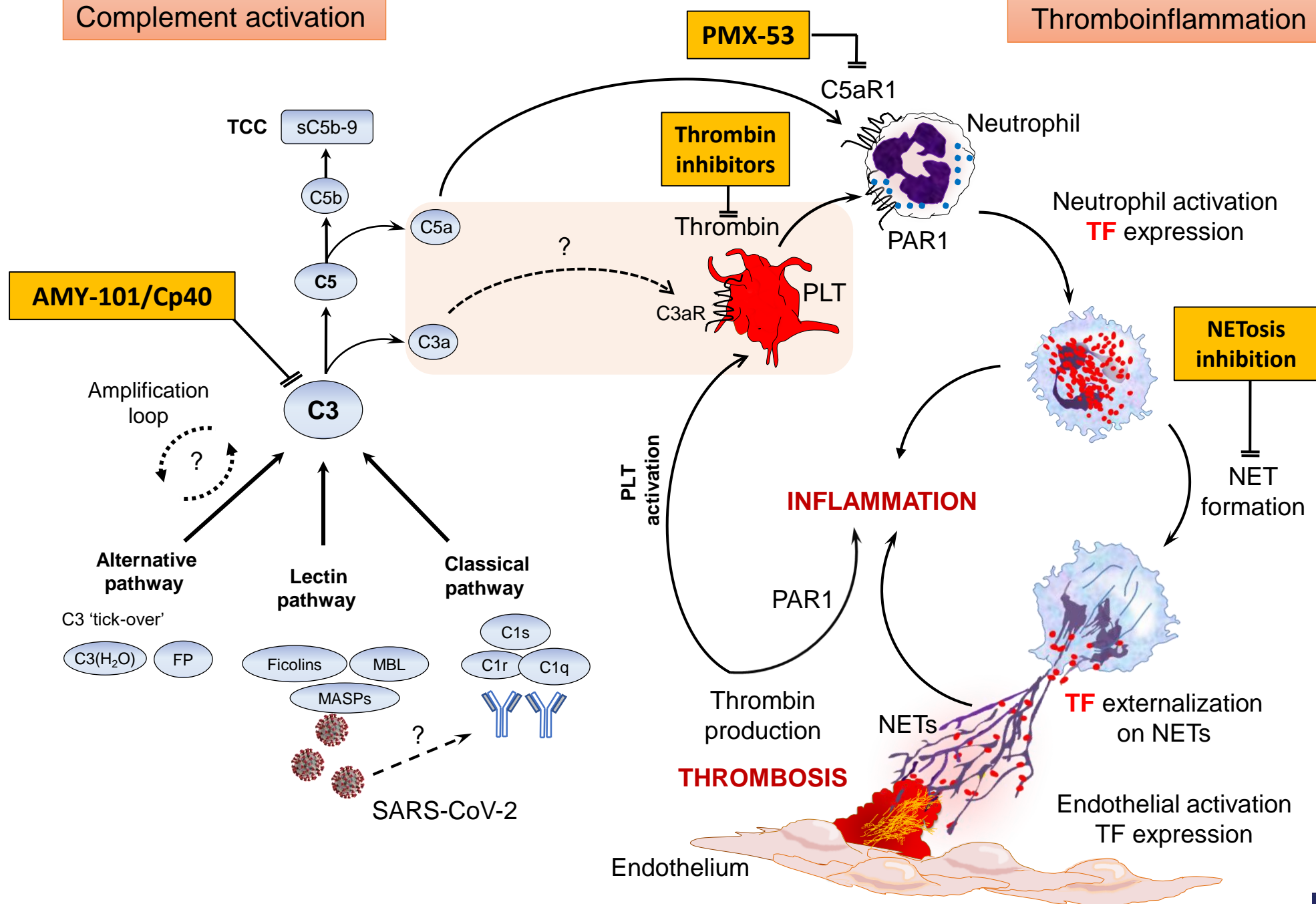
Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis



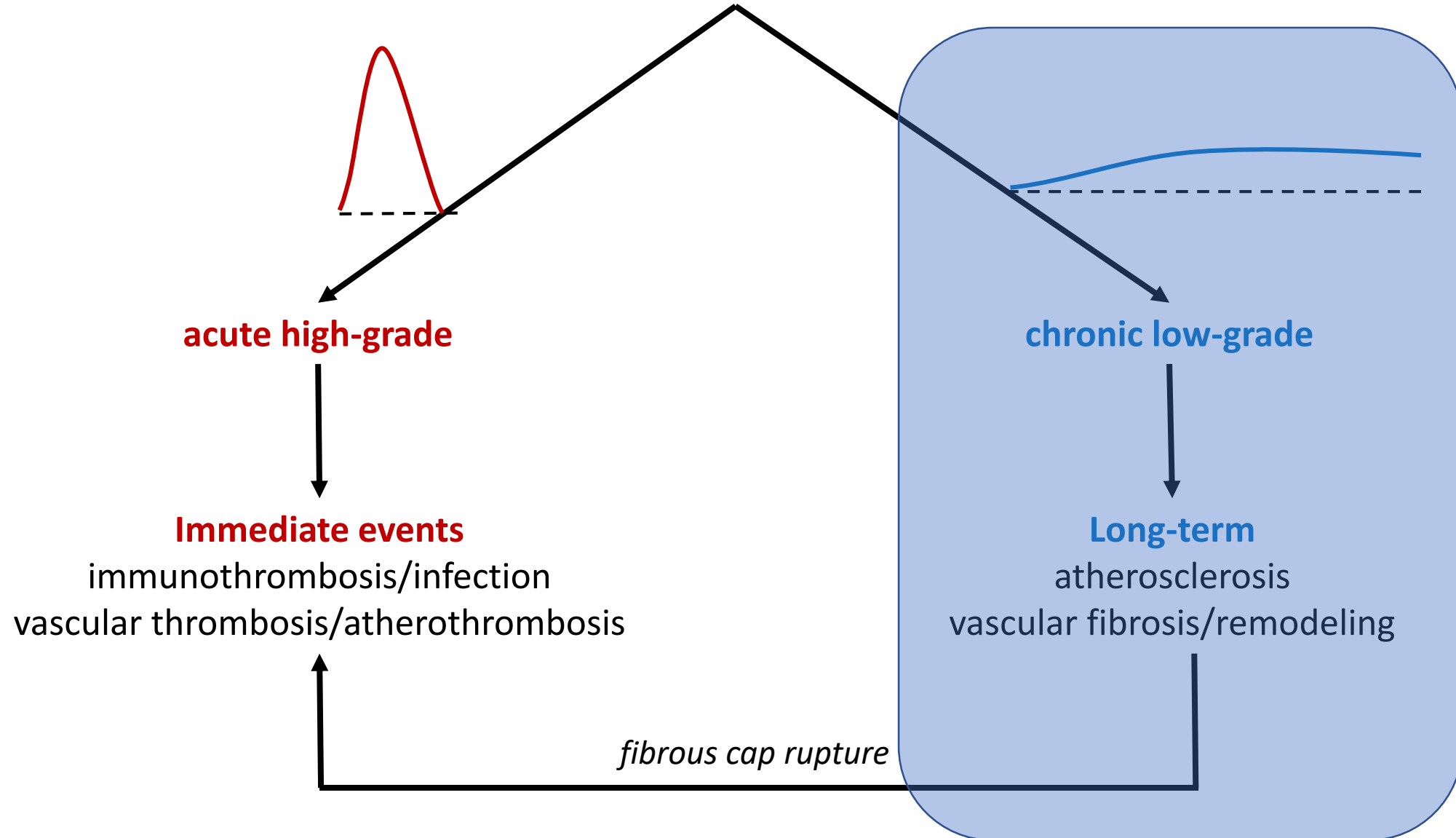
**Complement/neutrophil-mediated
endothelial activation and
thrombogenicity**

Complement activation

Thromboinflammation

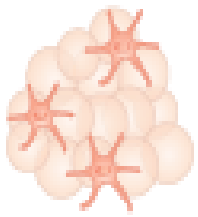


Thromboinflammation



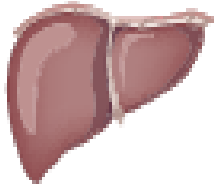
Consequences of Nlrp3 inflammasome activation

Adipose tissue



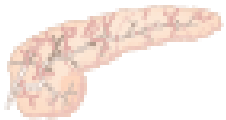
- Inflammation
- Decreased adipocyte differentiation and insulin resistance
- Decreased adipose tissue mass

Liver



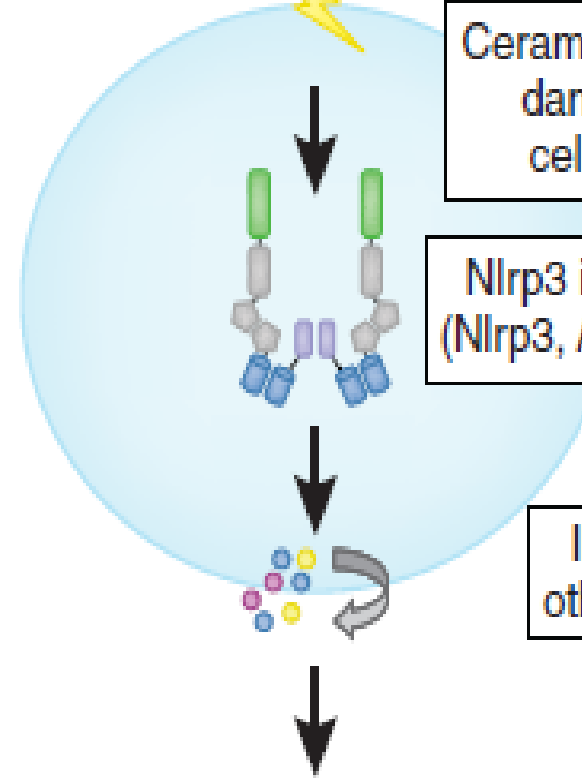
- Insulin resistance
- Altered lipid metabolism
- Inflammation

Pancreas



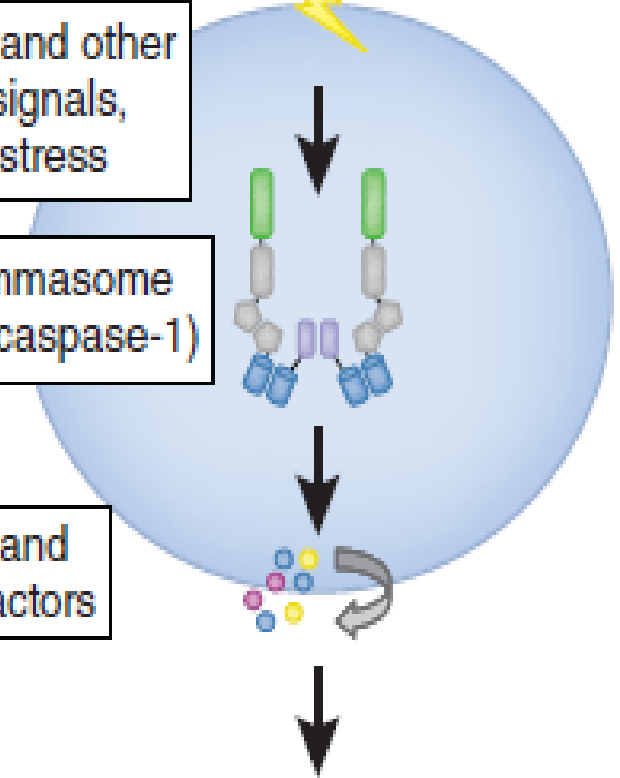
- Cytotoxicity of pancreatic beta cells

Macrophage



Macrophage activation,
chronic inflammation

Adipocyte



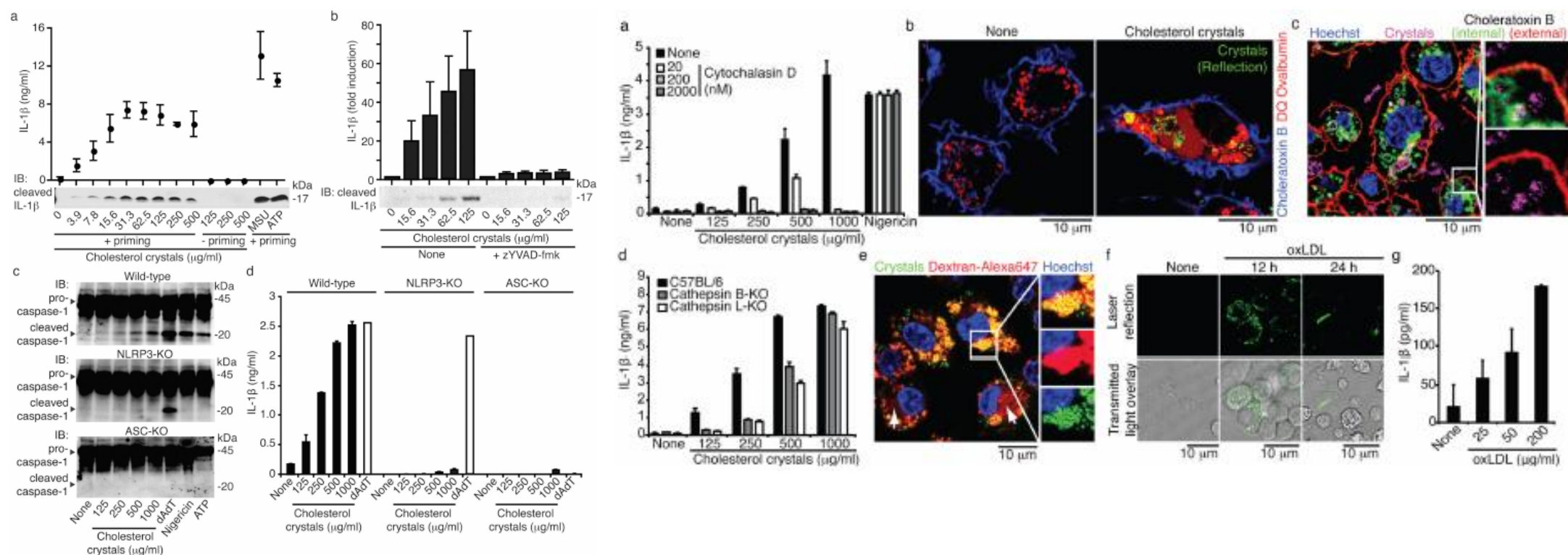
Adipocyte differentiation,
insulin resistance, inflammation

The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance

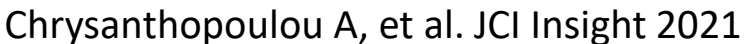
Vandanmagsar et al *Nature Medicine* VOL 17 ; 2 | FEBRUARY, 2011

NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals that form early in disease

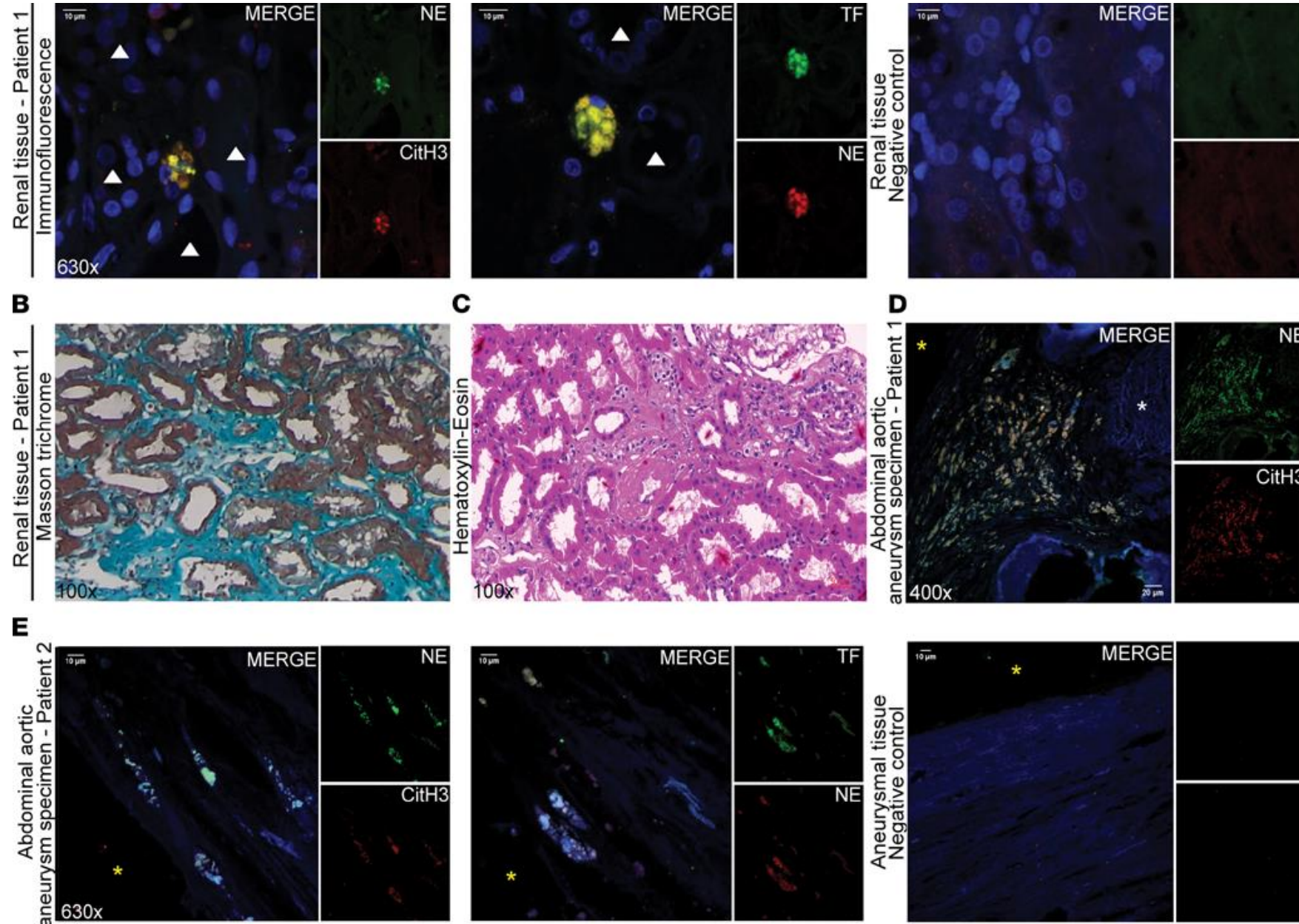
Peter Duewell^{1,3,*}, Hajime Kono^{2,*}, Katey J. Rayner^{4,5}, Cherilyn M. Sirois¹, Gregory Vladimer¹, Franz G. Bauernfeind⁶, George S. Abela⁹, Luigi Franchi⁸, Gabriel Nuñez⁸, Max Schnurr³, Terje Espevik¹⁰, Egil Lien¹, Katherine A Fitzgerald¹, Kenneth L. Rock², Kathryn J. Moore^{4,5}, Samuel D Wright¹¹, Veit Hornung^{5,*}, and Eicke Latz^{1,7,10,*}



essential hypertension patients



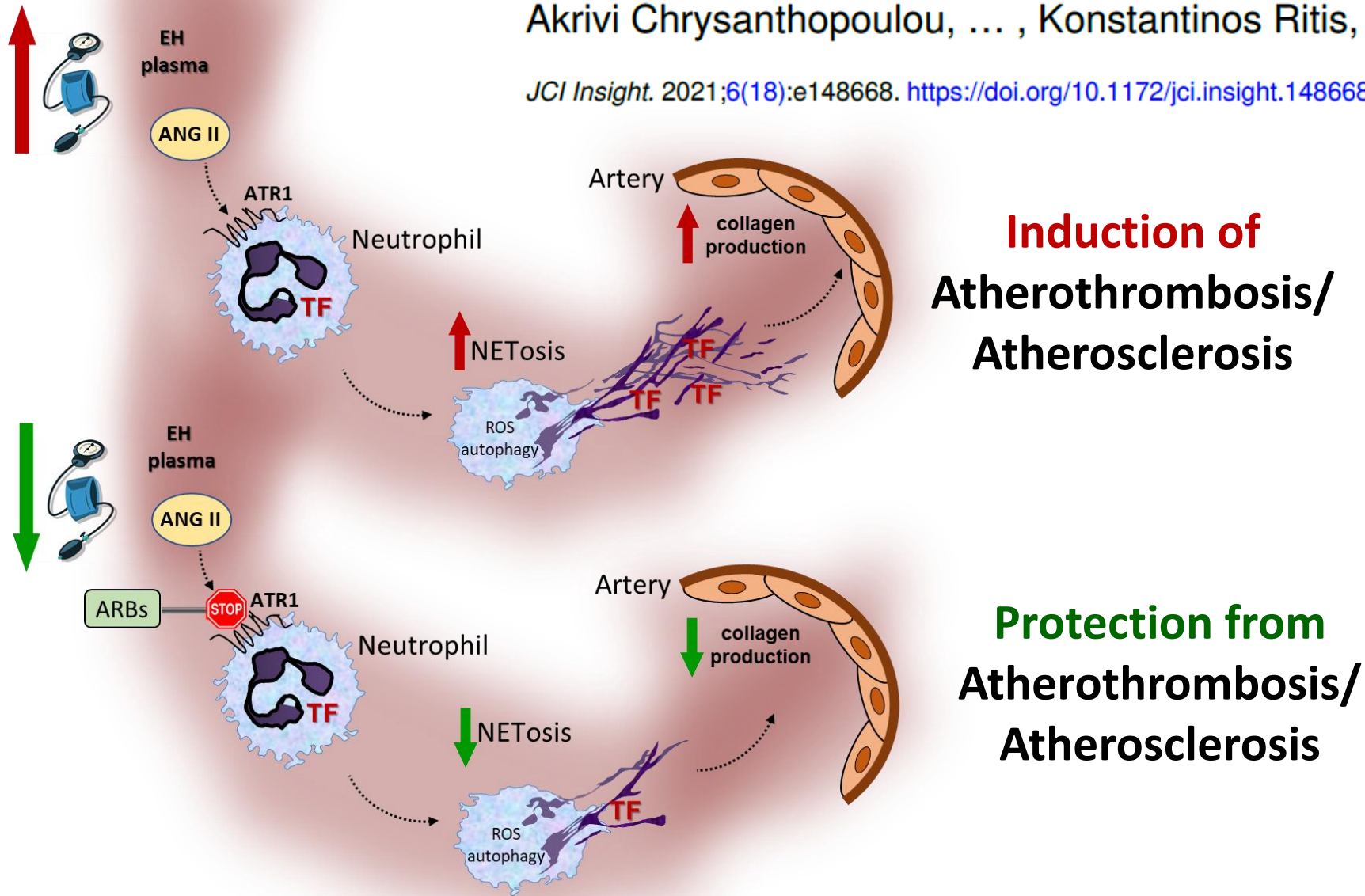
Presence of NETotic neutrophils expressing TF in the fibrotic renal and aneurysmal aortic tissue of patients with essential hypertension



Angiotensin II triggers release of neutrophil extracellular traps, linking thromboinflammation with essential hypertension

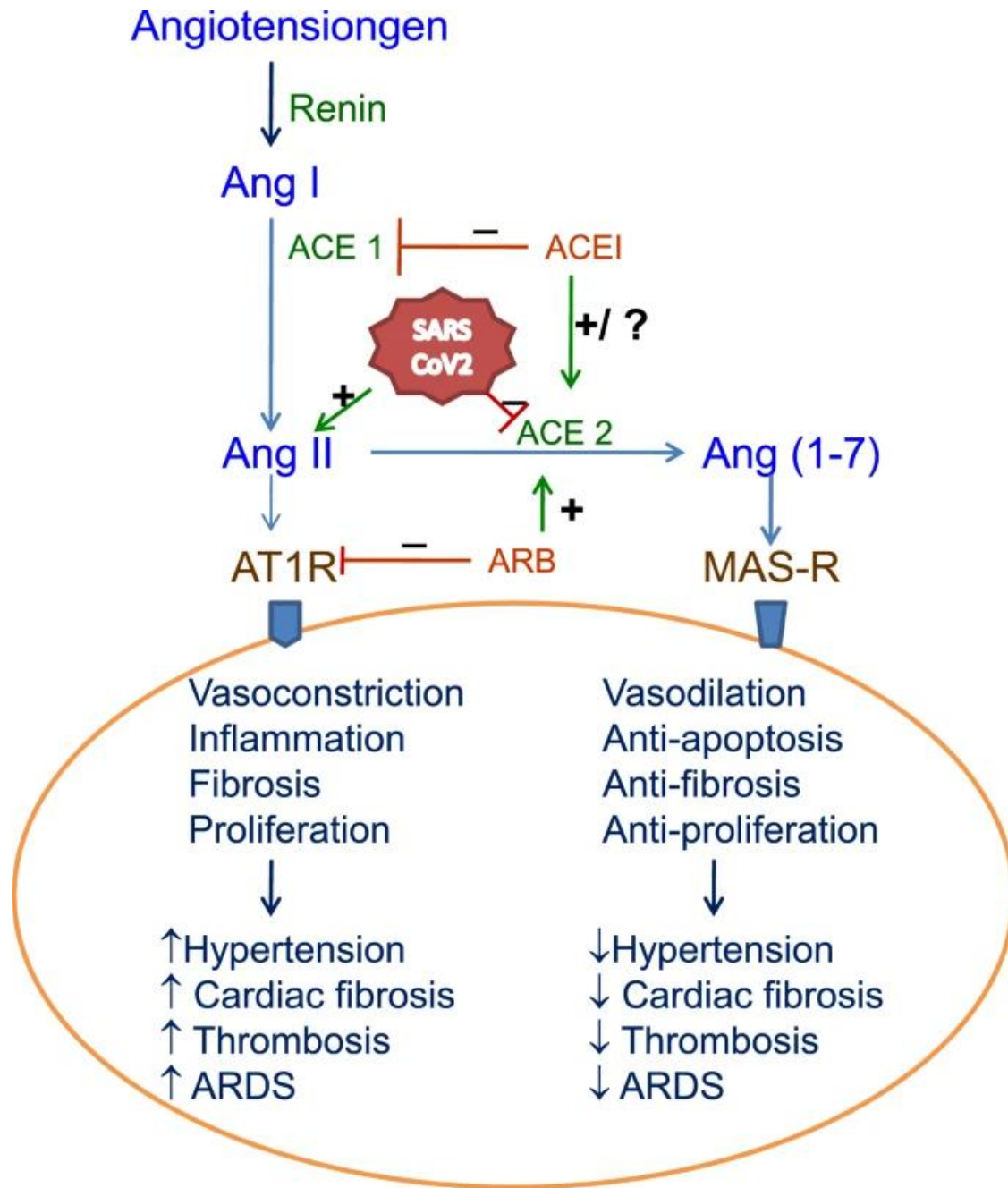
Akrivi Chrysanthopoulou, ... , Konstantinos Ritis, Panagiotis Skendros

JCI Insight. 2021;6(18):e148668. <https://doi.org/10.1172/jci.insight.148668>.

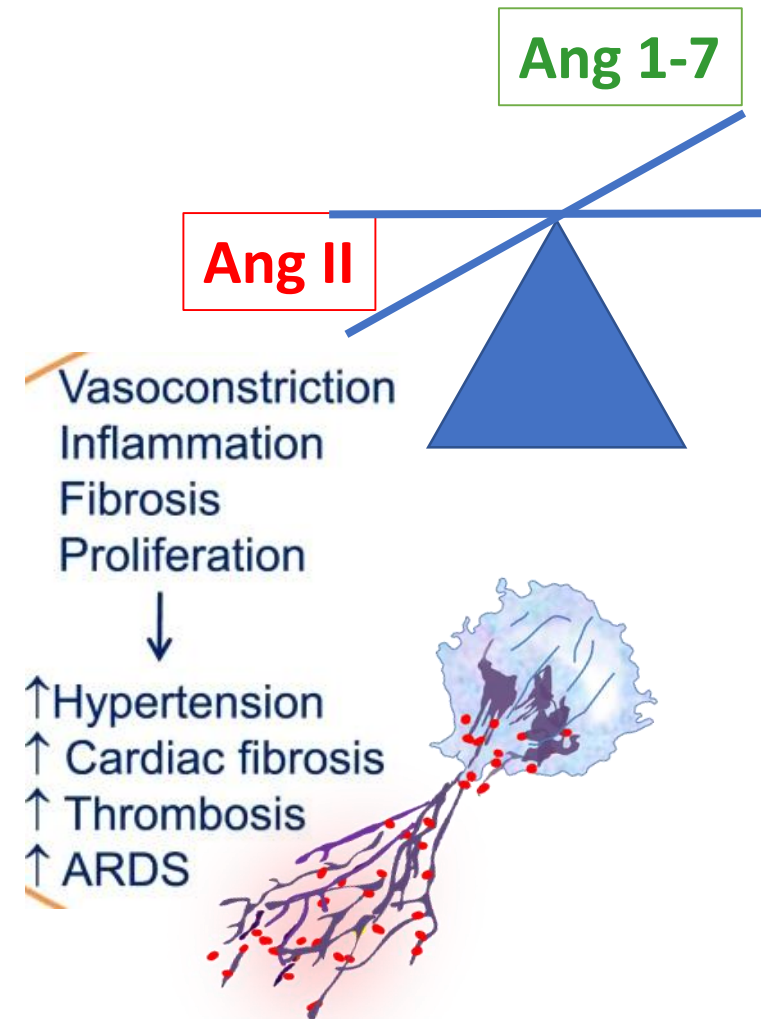


Is there any link between this mechanism in hypertension and COVID-19 immunothrombosis?

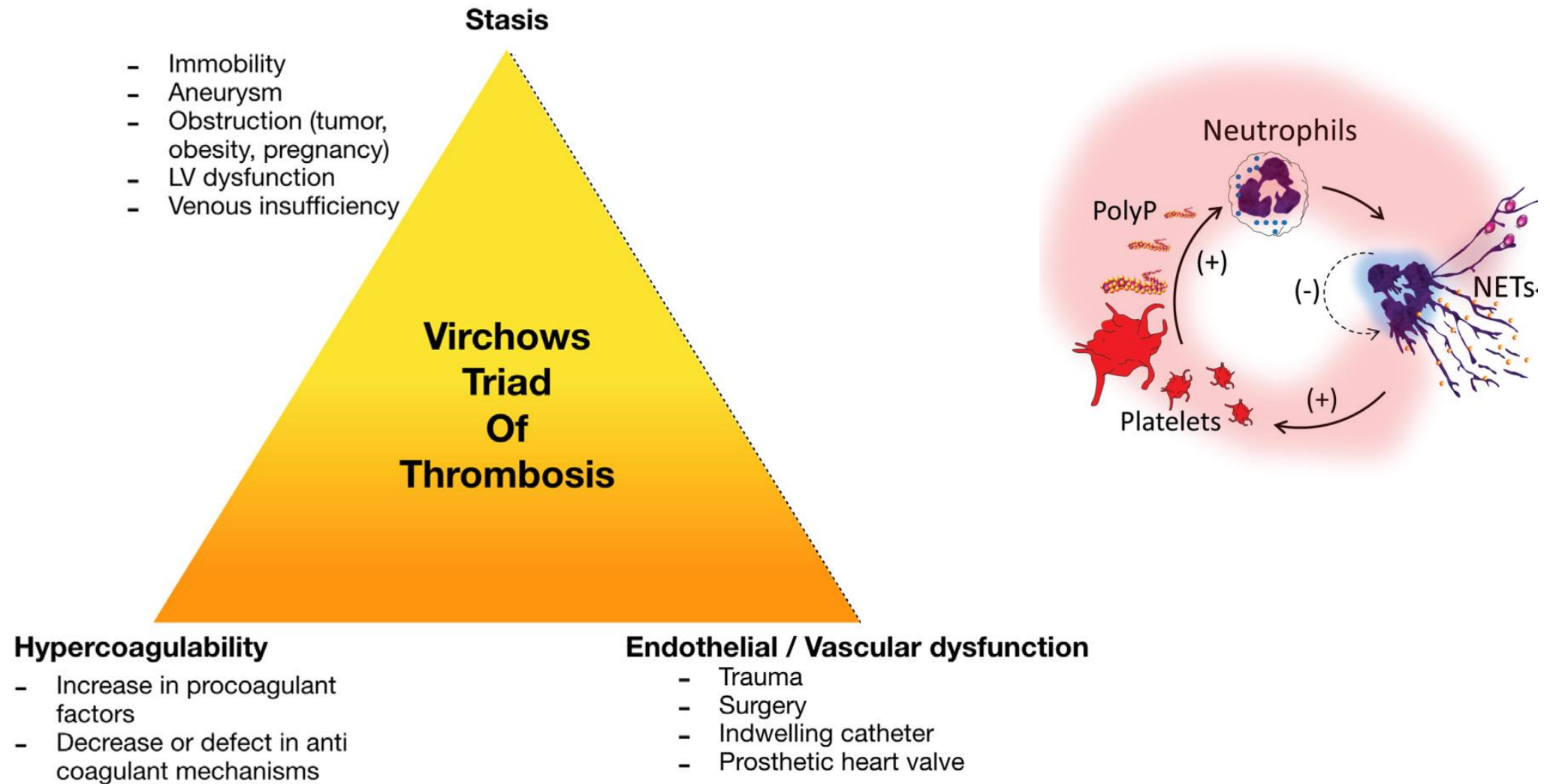




Deregulation of RAS in COVID-19



Immunothrombosis/thromboinflammation concept



Immunothrombosis: a conserved mechanism of host defence

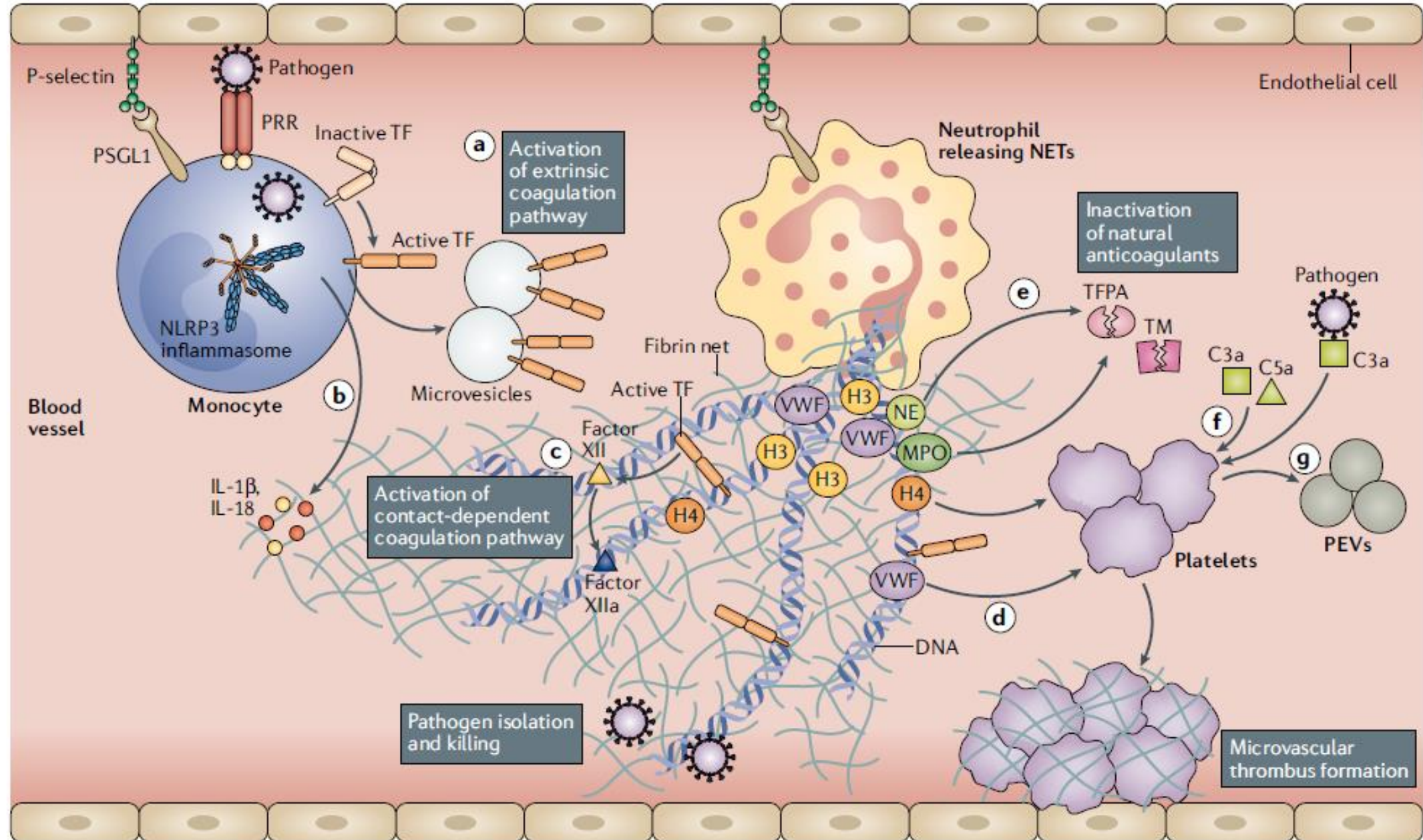


Table 2 | **New anti-inflammatory approaches for the prevention of atherosclerosis and thrombosis**

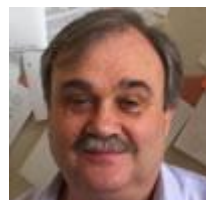
Study name (year)	Medications	Clinical setting	Ischaemic events	Infections	All-cause mortality
CANTOS (2017)	Canakinumab (150 mg) versus placebo	Secondary prevention of MI	↓ Non-fatal MI, non-fatal stroke or cardiovascular death: HR 0.85, 95% CI 0.74–0.98, <i>P</i> = 0.021; MI: HR 0.76, 95% CI 0.62–0.92; any stroke: HR 0.98, 95% CI 0.71–1.35	↑ Fatal infections and sepsis	↔ HR 0.92, 95% CI 0.78–1.09
CIRT (2019)	Low-dose methotrexate versus placebo	Secondary prevention of MI or multivessel coronary artery disease	↔ Non-fatal MI, non-fatal stroke, cardiovascular death or hospitalization for unstable angina that led to urgent revascularization: HR 0.96, 95% CI 0.79–1.16, <i>P</i> = 0.67	↔ Serious infection events	↔ HR 1.16, 95% CI 0.87–1.56
COLCOT (2019)	Low-dose colchicine versus placebo	Treatment within 30 days of an MI	↓ MI: HR 0.91, 95% CI 0.68–1.21; stroke: HR 0.26, 95% CI 0.10–0.70; VTE: HR 1.43, 95% CI 0.54–3.75	↑ Pneumonia	↔ HR 0.98, 95% CI 0.64–1.49
LoDoCo2 (2020)	Low-dose colchicine versus placebo	Chronic coronary artery disease	↓ Cardiovascular death, MI, ischaemic stroke or ischaemia-driven coronary revascularization: HR 0.69, 95% CI 0.57–0.83; cardiovascular death, MI or ischaemic stroke: HR 0.72, 95% CI 0.57–0.92, <i>P</i> = 0.007; MI: HR 0.70, 95% CI 0.53–0.93; ischaemic stroke: HR 0.66, 95% CI 0.35–1.25; VTE: HR 1.06, 95% CI 0.53–2.10	↔ Hospitalizations for infection	↔ HR 1.21, 95% CI 0.86–1.71

Table 1 | **Anti-inflammatory effects of antithrombotic medications**

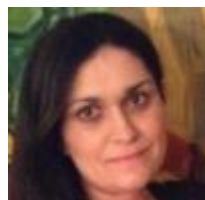
Medication	Antithrombotic effects	Anti-inflammatory effects
Heparin	Inhibition of coagulation	Disruption of neutrophil extracellular traps
		Neutralization of histones
Low-dose aspirin	Inhibition of platelet activation	Increased synthesis of the pro-resolution mediator 15-epi-lipoxin A4
P2Y ₁₂ receptor inhibitors	Inhibition of platelet activation	Decreased pro-inflammatory mediator release
Direct-acting oral anticoagulants	Inhibition of coagulation	Inhibition of protease-activated receptors, which induce the expression of chemokines, cytokines and adhesion molecules



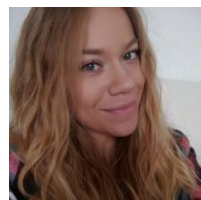
- ✓ **Dysregulated innate immunity leading to immunothrombosis is involved in the whole spectrum of cardiovascular pathology**
- ✓ **Inflammation emerges as a promising candidate therapeutic target in addition to optimizing risk factors and targeting platelets and the coagulation system**



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