Thrombosis and Sickle Cell Anemia

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Sickle Cell Disease SCD

Genetic disease

Red Blood Cell disorder

Complex vascular disorder

- Micro-vessel disease
- Large-vessel disease
  - Cummulative incidence about 25%
  - Deep Vein thrombosis
  - Pulmonary Embolism

J Thromb Hemost 2017; 15: 1307-16 // Int J Mol Sci 2020; 21: 5279

Clinical risk for VTE in SCD (African Americans)

30% lifetime risk for an overt cerebrovascular accident

- Increased risk if SS-genotype, high WBC, low HbF
- Lower risk (18%) if under RBC transfusions

Risk for VTE in SCD

- 2.9% in children
- 25% in adults

Blood Adv 2020; 4 (9): 1978-86

Current issues of Sickle Cell Disease SCD

Pathophysiology of SCD

Pathophysiology of thrombosis in SCD

Clinical risk factors

Laboratory risk factors

Genetic risk factors

Guidelines

Take home message

Pathophysiology of Thrombosis in SCD

Phospatidylserine on the surface of red cells

Tissue factor TF on endothelial cells and circulation

Endothelial dysfunction

Depletion of protein C and S

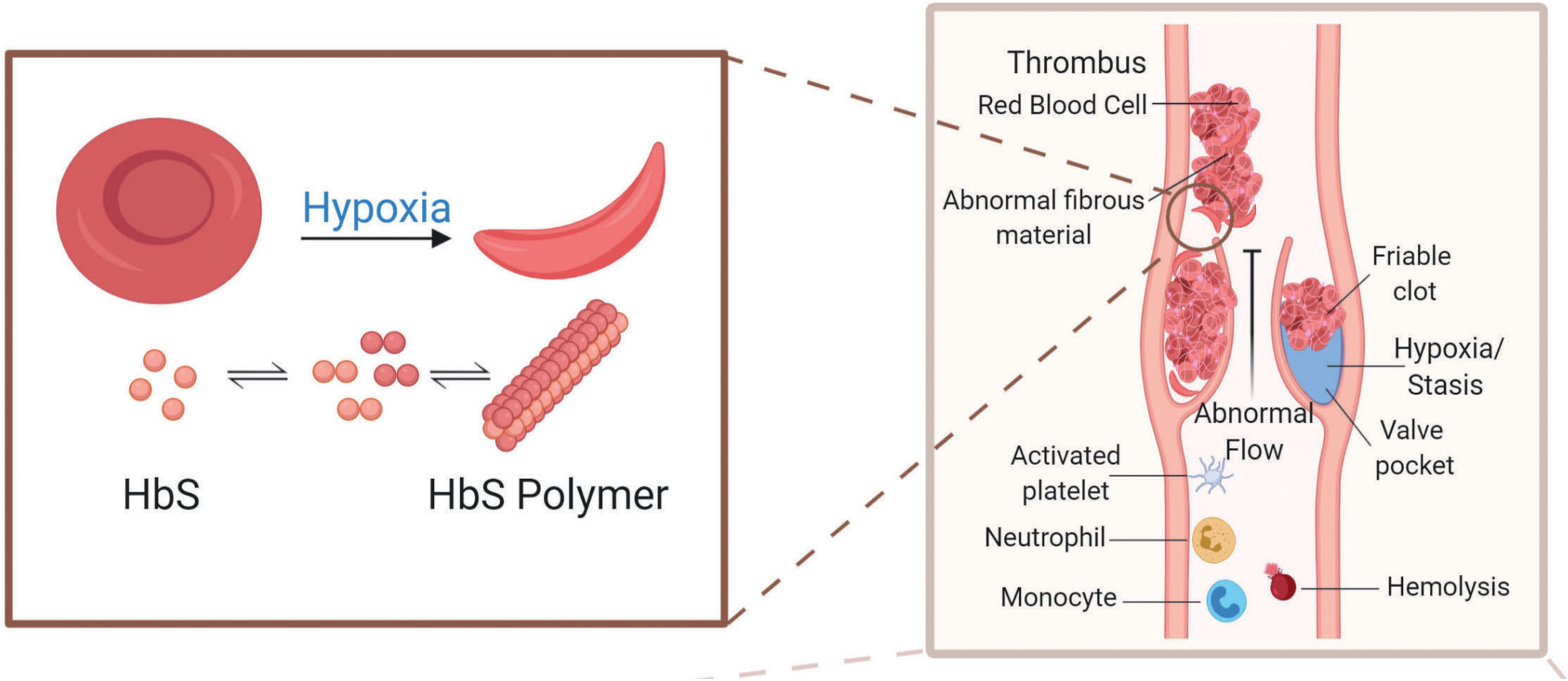
Circulating activated platelets

Inflammasomes NETs

Blood Adv 2020; 4 (9): 1978-86

Thrombo-iflammatory processes in SCD

A



Haematologica 2020; 105 (10): 2368-79

Platelet membrane and phospholipids

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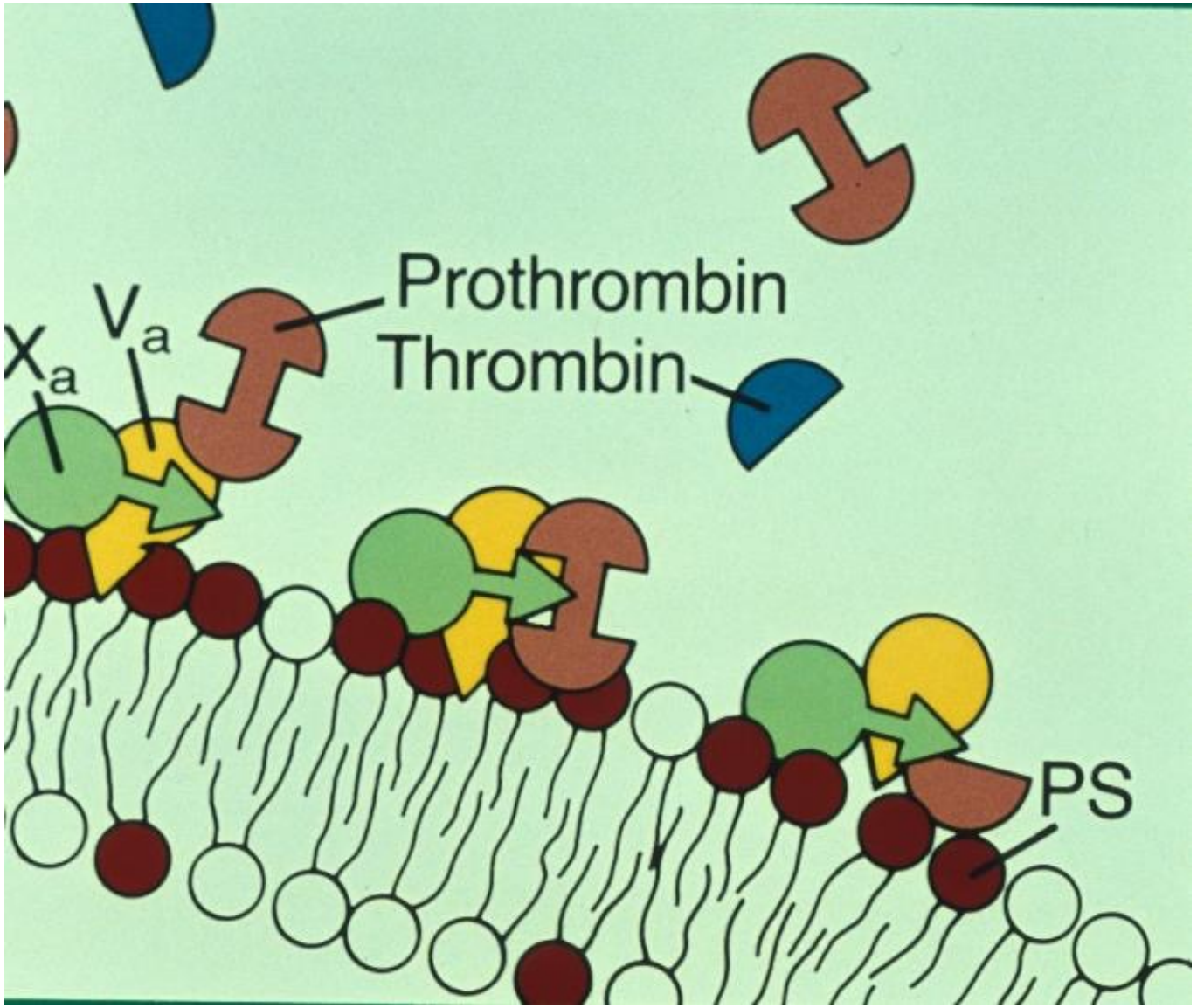

Thrombo-iflammatory processes in SCD

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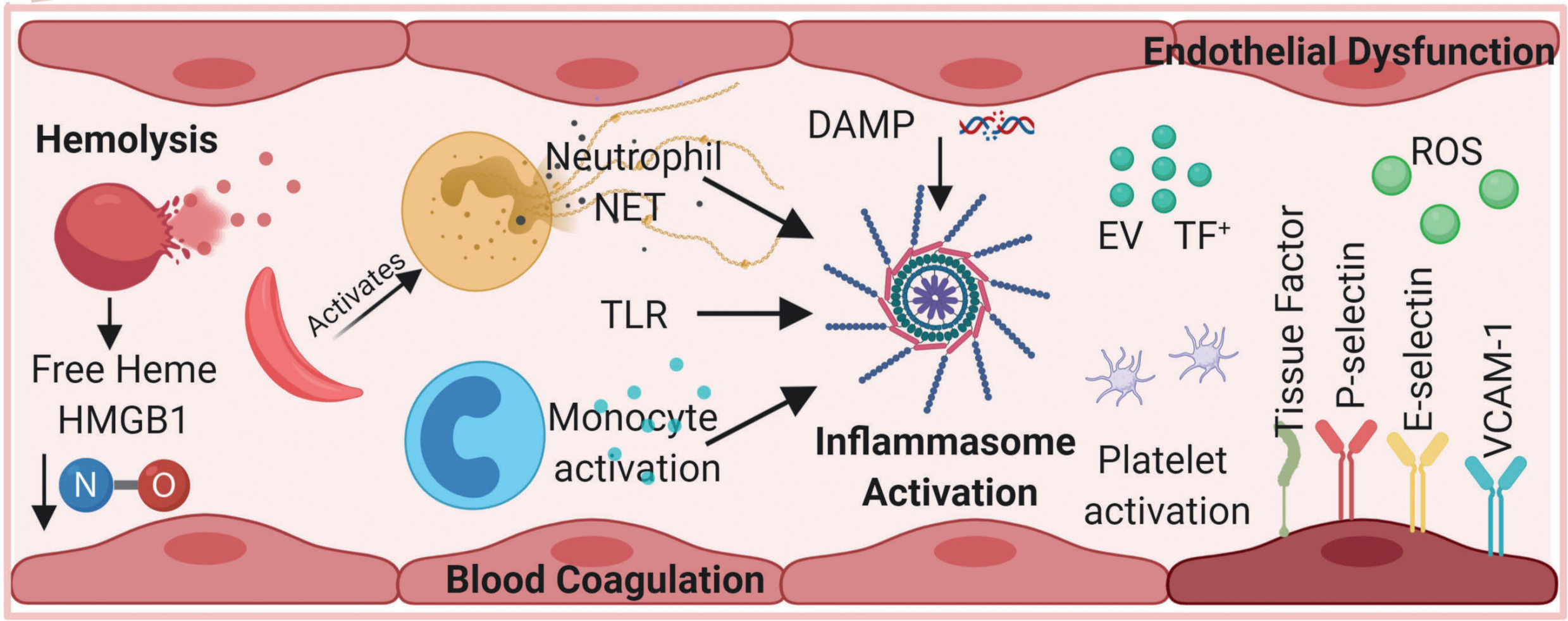

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Coagulation in SCD

Increased thrombin generation

Role of tissue factor generation

- Correlates with hemolysis
- Focus on endothelial TF
- Inhibition of TF attenuates coagulation AND inflammation
- Inhibition of FXa attenuates IL-6 Inflammation

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Role of TF in SCD

Whole blood TF

Endothelial cell TF

Monocyte TF

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Thrombin generation in SCD

Related to TF

Thrombin activates EC to express P-Selectin

P-Selectin mediates cell adhesion on EC

MoAbs against P-Selectin ameliorates VOC

Role of fibrinogen

- Protects from inflammation ?
- Buffers thrombin excess ?

J Thromb Hemost 2017; 15: 1307-16 // Int J Mol Sci 2020; 21: 5279

Platelets in SCD

Increased platelet numbers

Circulating activated platelets (P-Selectin, CD40L)

Antiplatelet drugs (Aspirin, Eptifibatid, Prasugrel)

- Reduce biomarkers of platelet activation
- Do not reduce painful crisis
- Do not reduce VOC

J Thromb Hemost 2017; 15: 1307-16 // Int J Mol Sci 2020; 21: 5279

Microparticles in SCD

Increased RBC, endothelial, platelet, monocyte MPs

- Contribute to thrombin generation
- Contribute to inflammation, entrapped heme

J Thromb Hemost 2017; 15: 1307-16 // Int J Mol Sci 2020; 21: 5279

Contact activation of coagulation in SCD

FXI deficiency or inhibition no effect on thrombin generation

FXII deficiency attenuated thrombin generation in mice

Increased thrombin generation in VOC is due to activation of the contact pathway

Glycated Hb can activate FXII

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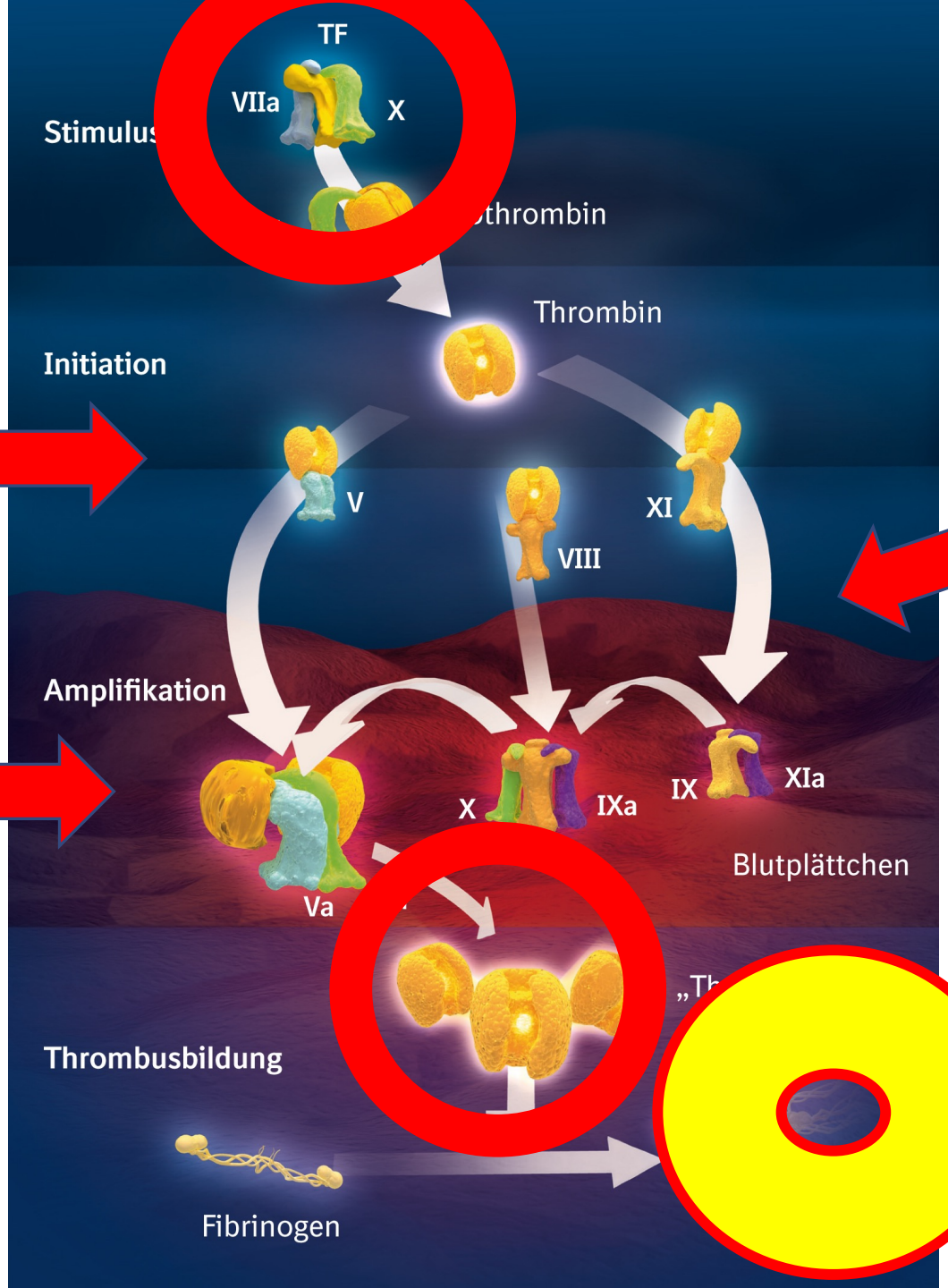
Cell-based Hemostasis

Coagulation factors

Cell membranes PS



Contact phase
Complement
NETs

Fibrin Clot

Results of pathophysiology triggers in SCD

Ischemia/reperfusion injury due to vasoocclusion

- Oxidative stress
- Vascular inflammation

Increased Hemolysis and free heme in circulation

- Free hemoglobin and heme
- Decreased NO bioavailability
- Proinflammatory changes of endothelial cells
- Respiratory burst of neutrophils, NETs

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Time dynamic of SCD

Most of the time in „steady state“

Periods of accelerated sickling

- Acute-on-chronic hemolysis
- Vaso-occlusion crisis VOC
- Multiorgan damage
  - SCD nephropathy
  - Ischemic stroke
  - Pulmonary hypertension
  - Cardiac dysfunction
  - Osteonecrosis

J Thromb Hemost 2017; 15: 1307-16

Vaso-occlusive events

Vaso-occlusion and ischemic tissue damage

Splenic sequestration and infarction

Ischemic stroke

Silent cerebral infarcts

Risk factors for VTE in SCD

Sickle genotypes HbSS and $S\beta^0$-thalassemia

- Frequent with HbSS and/or $S\beta^0$-thal
- Less with HbSC and/or $S\beta^+$-thal

Female sex

>3 hospital admissions per year

Splenectomy

Presence of indwelling catheters

Blood 2018; 132 (17): 1761-9

Biomarkers of Vaso-occlusive Phenotype

Higher WBC count

Lower HbF level

Older age

Coexisting alpha-thalassemia trait

Iron overload (secondary to transfusions)

Vessel flow resistance related to deoxygenation

Darbari et al. J Pediatr. 2012;160:286–90 // Wood et al. Sci Transl Med. 2012;4:123ra26

Anticoagulants in SCD

Heparins

Antiplatelet agents

Vitamin K antagonists

Direct oral anticoagulants

Targeted anti-FXII

ASH Guideline for Treatment of thromboembolism in SCD as of May 2021

Thrombosis	Anticoagulation
First unprovoked VTE	Indefinite anticoagulation
First provoked VTE (surgical or non-surgical)	Defined antikoagulation 3-6 months Continue if risk factors persist (e.g. CVL)
Recurrent provoked VTE	Indefinite anticoagulation
	Regular re-evaluation, shared decision making Patient values and preferences
	Choose anticoagulant according to comorbidities and bleeding risk

Blood Adv. 2019 Dec 10. 3 (23):3867-3897

ASH Guideline for primary stroke prevention in children with SCD as of May 2021

Prevention	
Annual transcranial Doppler (TCD) screening for children aged 2-16 years with hemoglobin SS (HbSS) or HbSβ^0 thalassemia	
Regular blood transfusions for a minimum of 1 year for children aged 2-16 years with HbSS or HbSβ^0 thalassemia who have abnormal TCD velocities	typically every 3-4 weeks, to maintain the maximum HbS level below 30% and the hemoglobin level above 9.0 g/dL

Blood Adv. 2020 Apr 28. 4 (8):1554-1588

ASH Guideline for stroke treatment in children with SCD as of May 2021

Management of suspected or confirmed ischemic stroke or TIA	Screening for silent cerebral infarcts in children and adults with HbSS or HbSβ^0
Prompt blood transfusion is recommended for children or adults with SCD who have acute neurologic deficits, including transient ischemic attack (TIA)	At least a one-time magnetic resonance imaging (MRI) screening, without sedation, is recommended to detect silent cerebral infarcts in early school-aged children
For children with HbSS or HbSβ^0 thalassemia and a history of prior ischemic stroke, blood transfusion goals for secondary stroke prevention are to increase the hemoglobin level above 9 g/dL at all times and maintain the HbS level at < 30% of total hemoglobin until the time of the next transfusion	

Blood Adv. 2020 Apr 28. 4 (8):1554-1588

Drugs in treatment of SCD

Antimetabolites

Analgesics

Antibiotics

Vaccines

Nutritional agents

Other

Other Drugs in treatment of SCD

Glutamine

Voxelotor (HbS polymerization inhibitor)

Crizanlizumab (P-Selectin-Inhibitor)

PDE5-Inhibitors (Sildenafil, Tadalafil)

Endothelin receptor antagonists (Bosentan)

Other experimental HbS polymerization inhibitors

- PFE-001, Mitapivat, Etavopivat, IMR-687

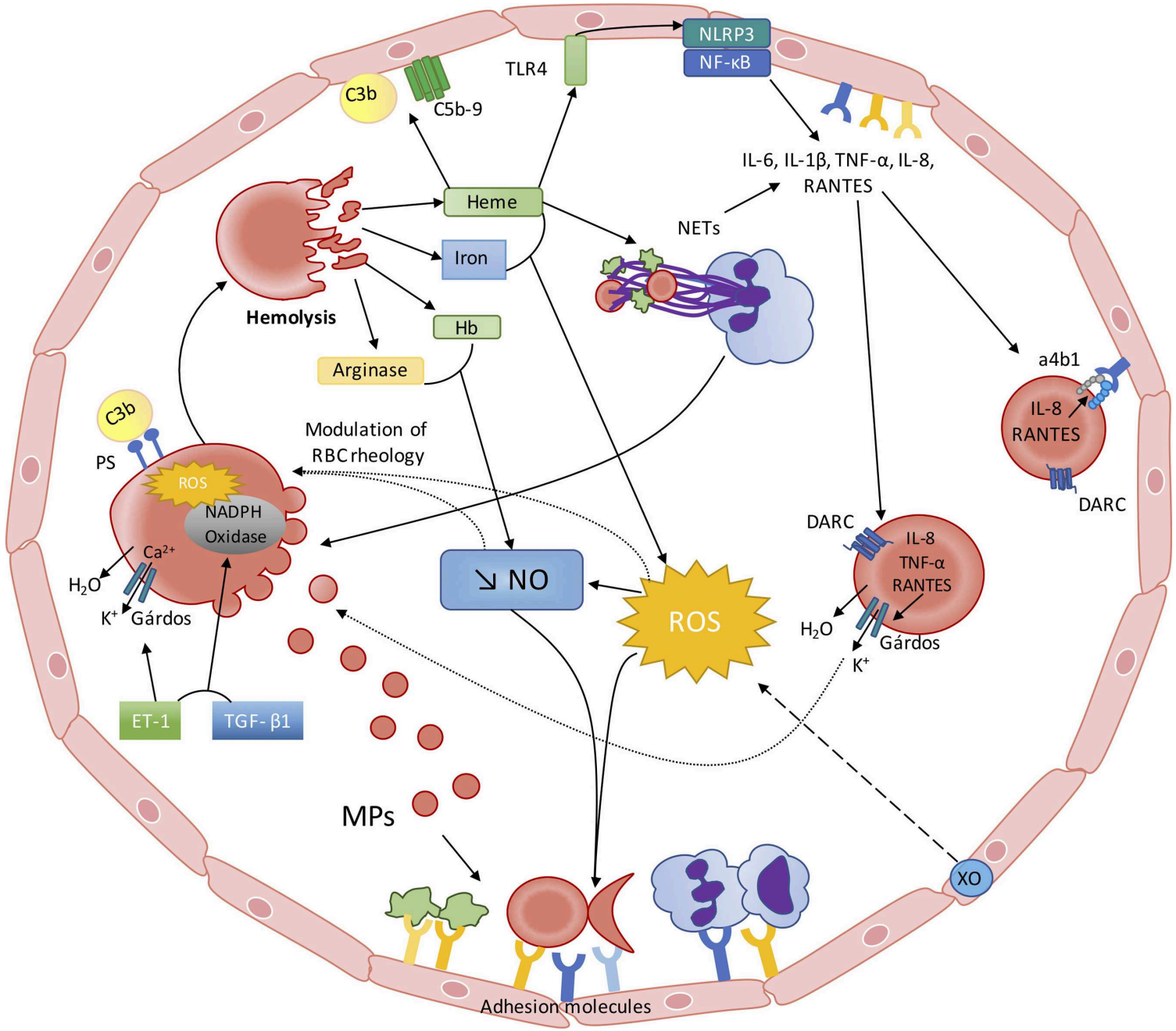
Treatment of VTE in SCD

Treatment decisions are extrapolated from guidelines for VTE management in the general population

Heparin, vitamin K antagonists, and DOACs are all effective agents in the treatment of VTE in SCD patients

Standard duration of anticoagulation is three months; the decision to extend anticoagulation must weigh the risk of recurrent VTE with the risk of major bleeding

Thank you !



Front Immunol 2020; 11: 454