



# The Biology of Trauma Induced Coagulopathy-

## *Early Phase Response*

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Assistant Professor of Laboratory Medicine

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Hospital and Trauma Center



# Disclosures

- Funding:
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  - University of Maryland
  - BARDA
  - Gamma Diagnostics

# TIC



BONFILS  BLOOD CENTER

**EE Moore**  
**Denver Health / University of Colorado Denver**

Disclosure : Haemonetics, Instrumentation Laboratory, Stago  
& Prytime Research Support / Haemonetics Shared IP  
Co-founder Thrombo Therapeutics Inc  
NIH P50 / T32 / UMI & DOD Grants



# TIC

in 114 slides....



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**Date:** Wednesday, May 11, 2022 at 1:23:54 PM Pacific Daylight Time  
**From:** Neal, Matthew D  
**To:** Spinella, Philip Charles, Hoydich, Zachariah, Kornblith, Lucy  
**Attachments:** Outlook-4eryh1bn.png

**This Message Is From an External Sender**

This message came from outside your organization.

Lucy will cover: The Biology of Trauma Induced Coagulopathy - Early phase response (Lucy you can change the title if you want)

I will do The Biology of Trauma Induced Coagulopathy - Late phase response

Matthew D. Neal, MD FACS  
Roberta G. Simmons Associate Professor of Surgery  
Co-Director, Pittsburgh Trauma and Transfusion Medicine Research Center  
Associate Program Director, Acute Care Surgery Fellowship  
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# Objectives and overview of *early* TIC

- History and epidemiology
- Definitions
- Drivers
- Mechanisms and biologic endotypes
- Treatments
- Controversies

# History and epidemiology of TIC

- Early preventable deaths after injury in civilian and military due to uncontrolled hemorrhage
- Impaired coagulation following injury observed for centuries
  - Cannon WB 1917; Hardaway RM 1962; Simmons RL 1969

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Tisherman, S. A. et al. Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the Resuscitation Outcomes Consortium. *Ann. Surg.* 261, 586–590 (2015).

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# History and epidemiology of TIC

- Early preventable deaths after injury in civilian and military due to uncontrolled hemorrhage
- Impaired coagulation following injury observed for centuries
  - Cannon WB 1917; Hardaway RM 1962; Simmons RL 1969
- Last 20 years: multiple biologic endotypes
- No standardized definition of TIC
- Hemorrhagic deaths occur early after injury

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Tisherman, S. A. et al. Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the Resuscitation Outcomes Consortium. *Ann. Surg.* 261, 586–590 (2015).

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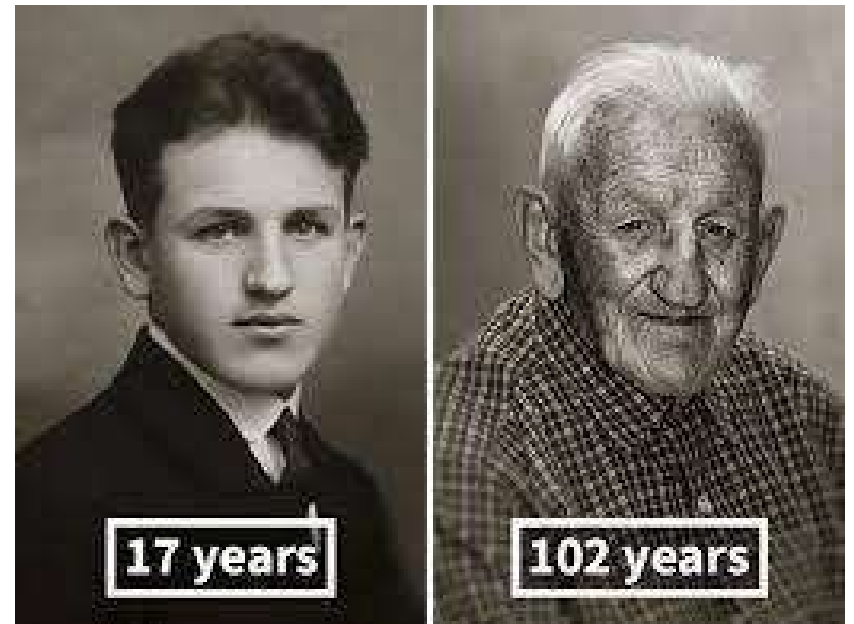
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## 2 important concepts

- 1. *Early vs. Later* TIC is not a concept of time

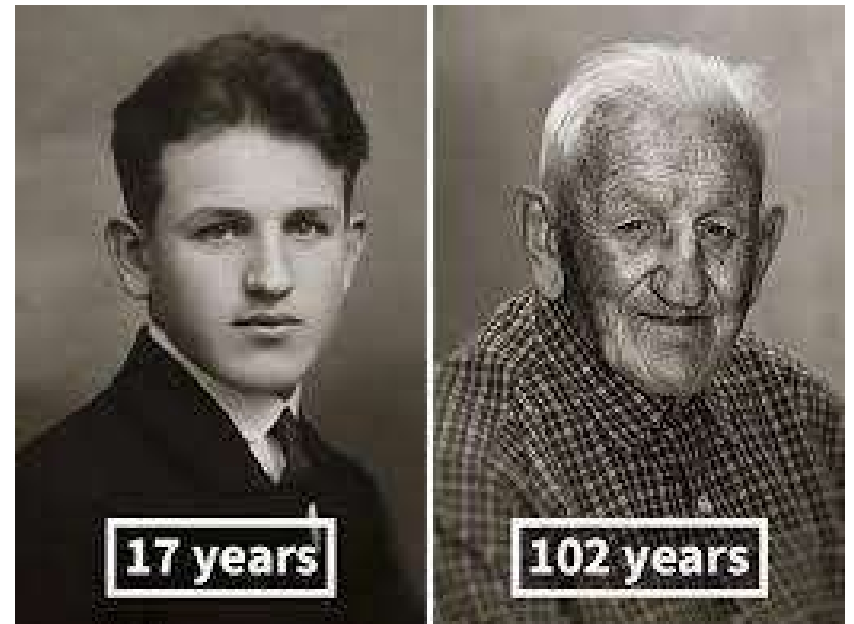
# Definition of *early*

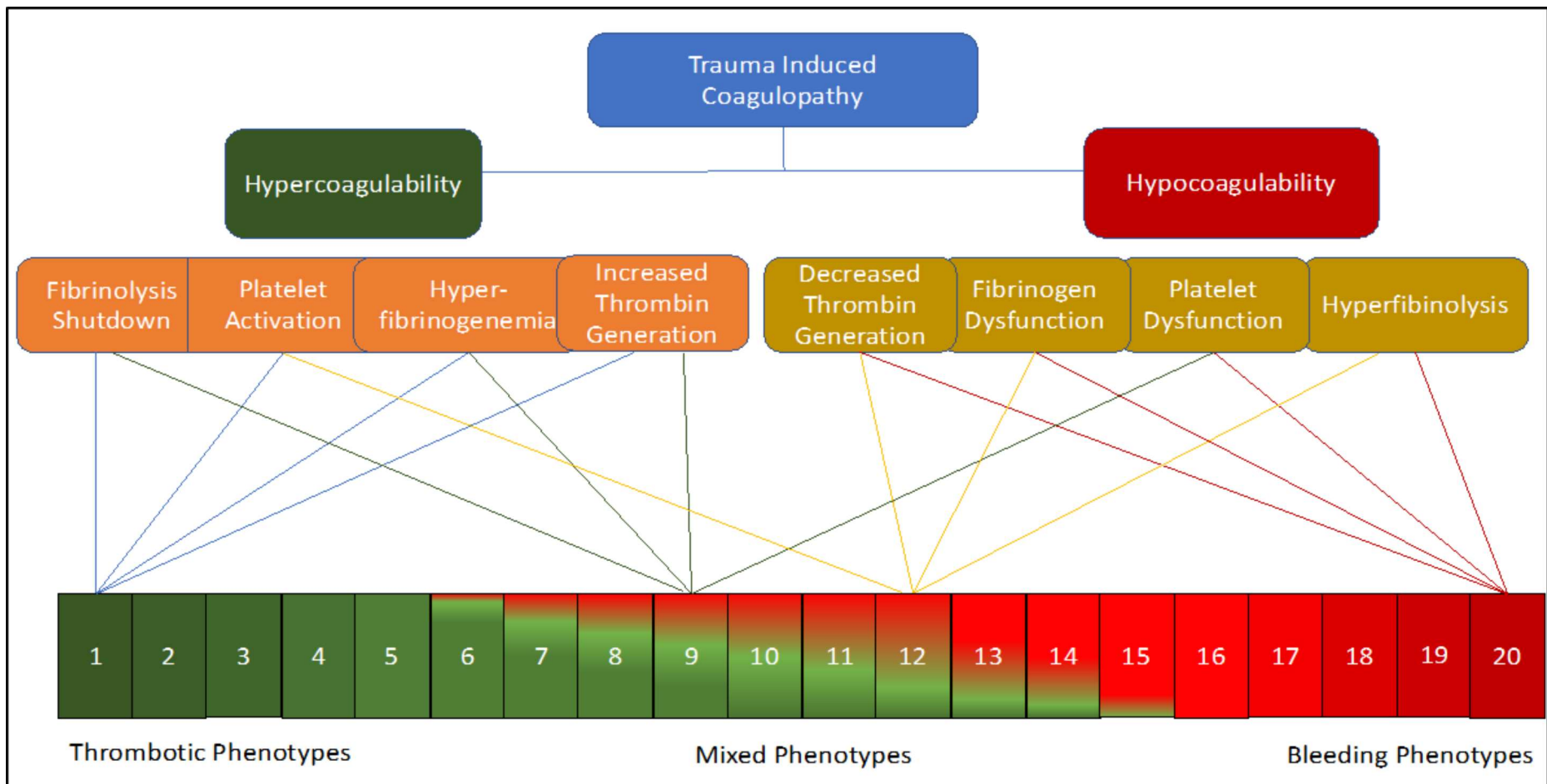
- There isn't a good time definition
- The transition from a hypocoagulable to a hypercoagulable biology



# Definition of *early*

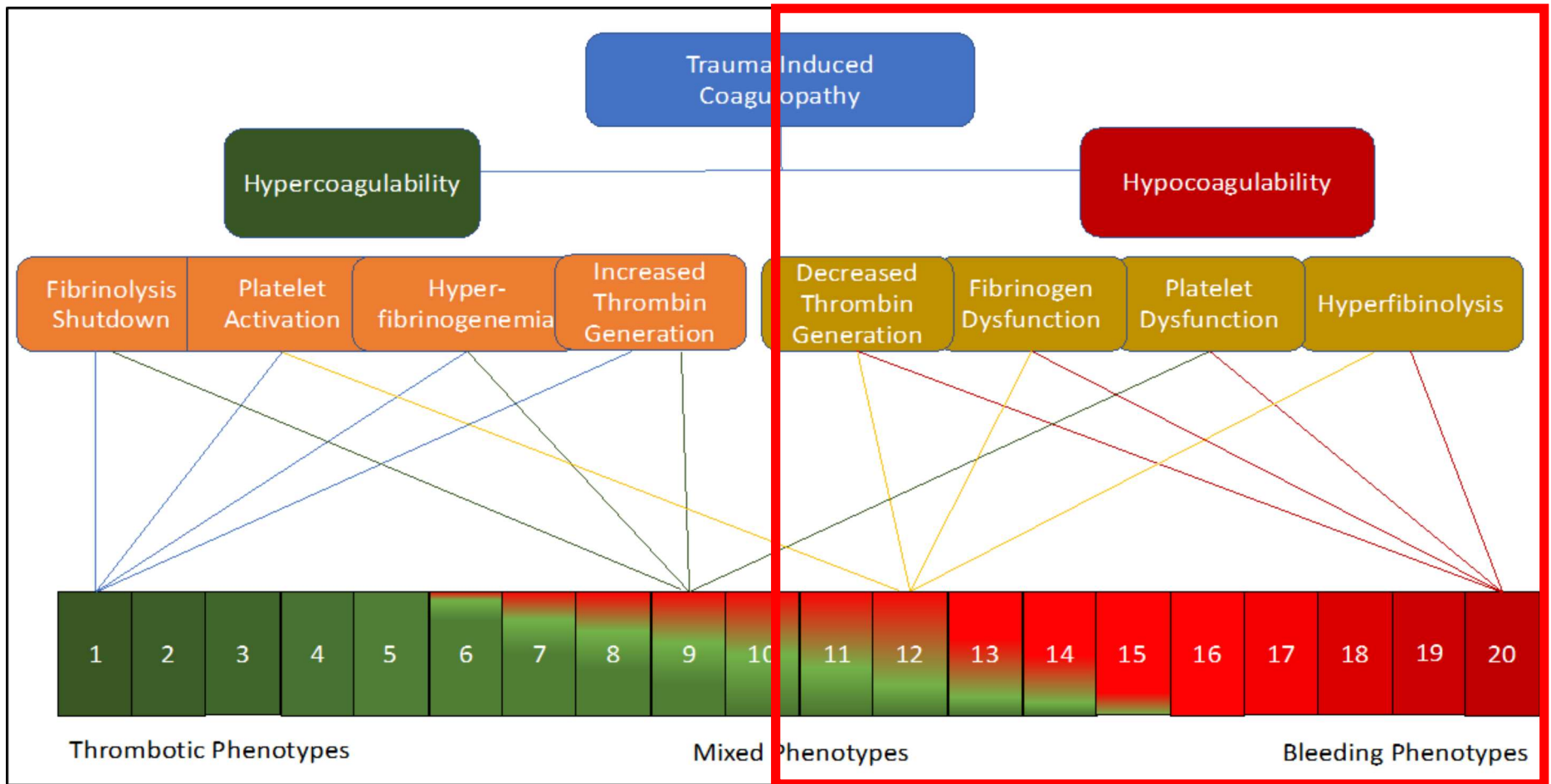
- It is probably VERY early
- It is possible it may start immediately
- It is probably a continuum



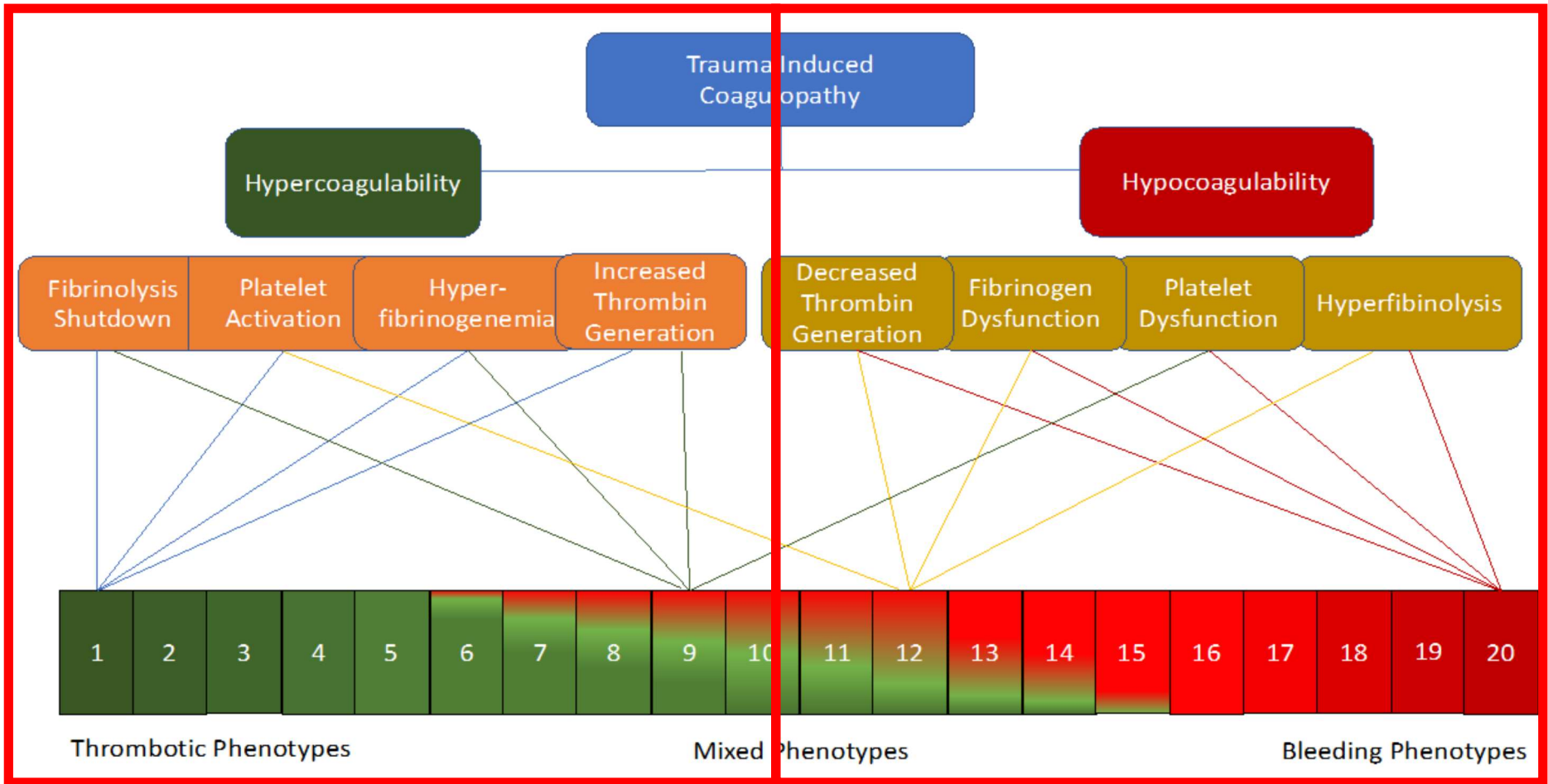


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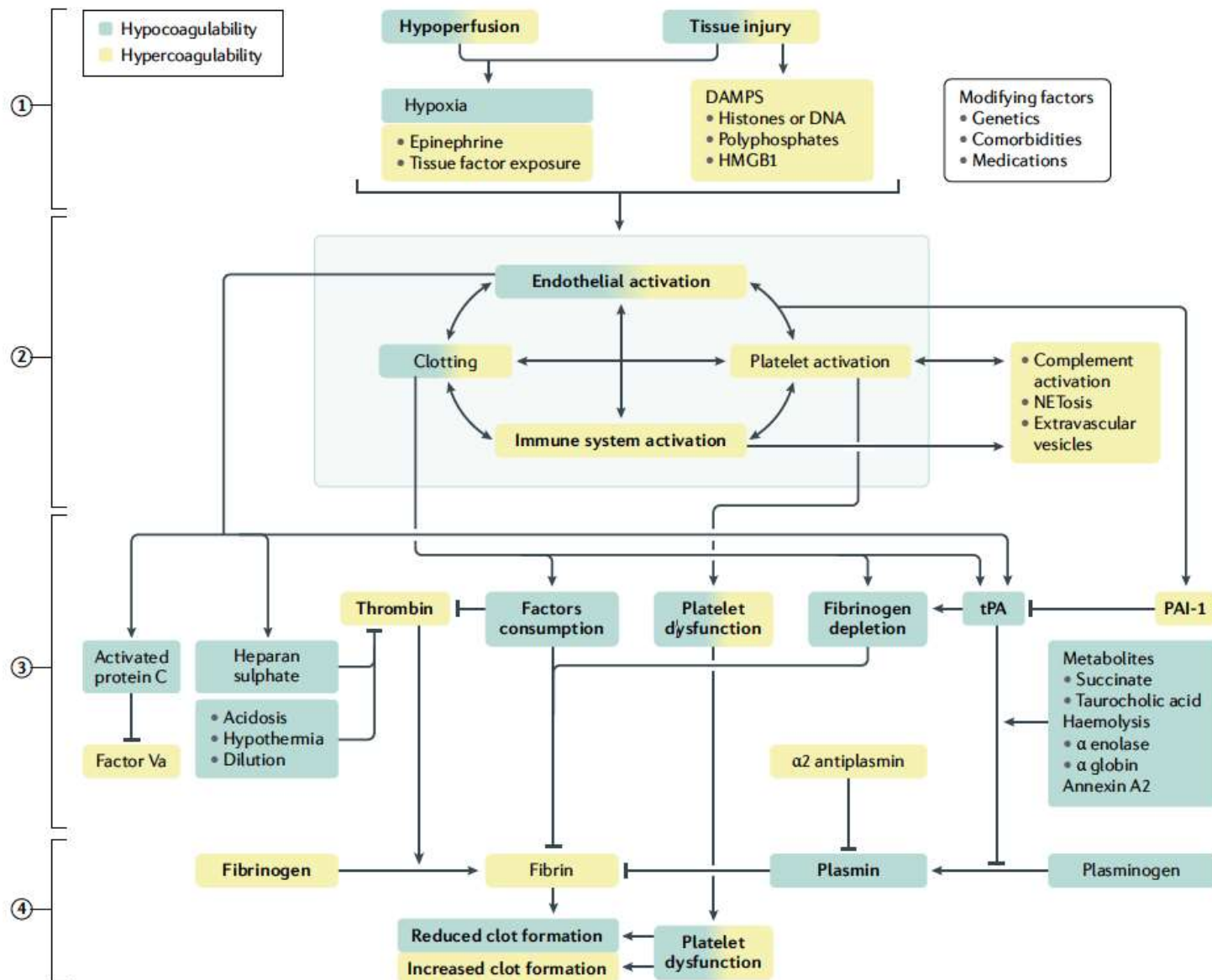
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## 2 important concepts

- 1. *Early vs. Late* TIC is not a concept of time
- 2. There is no unifying single driver or mechanism



**Figure:**

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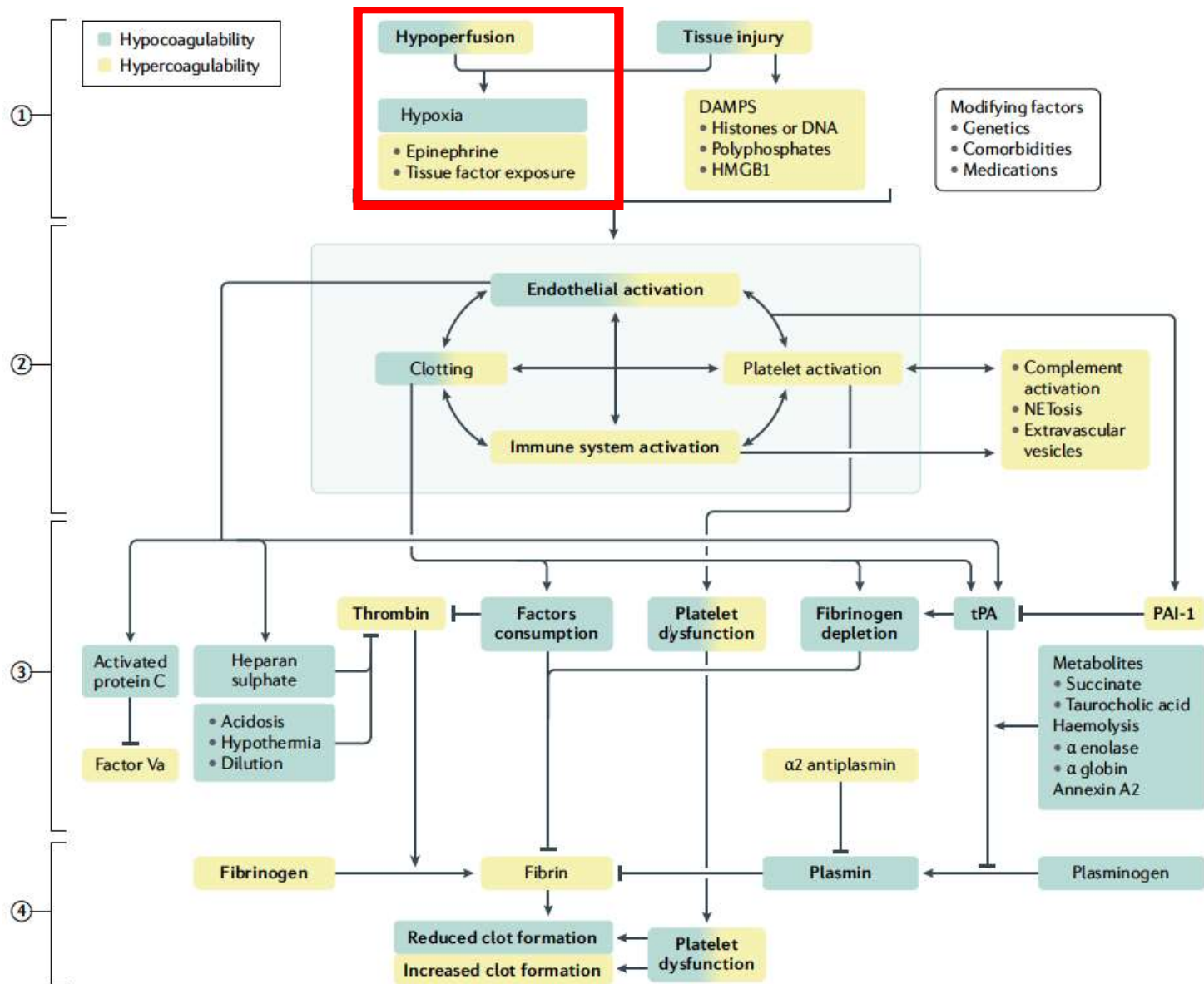
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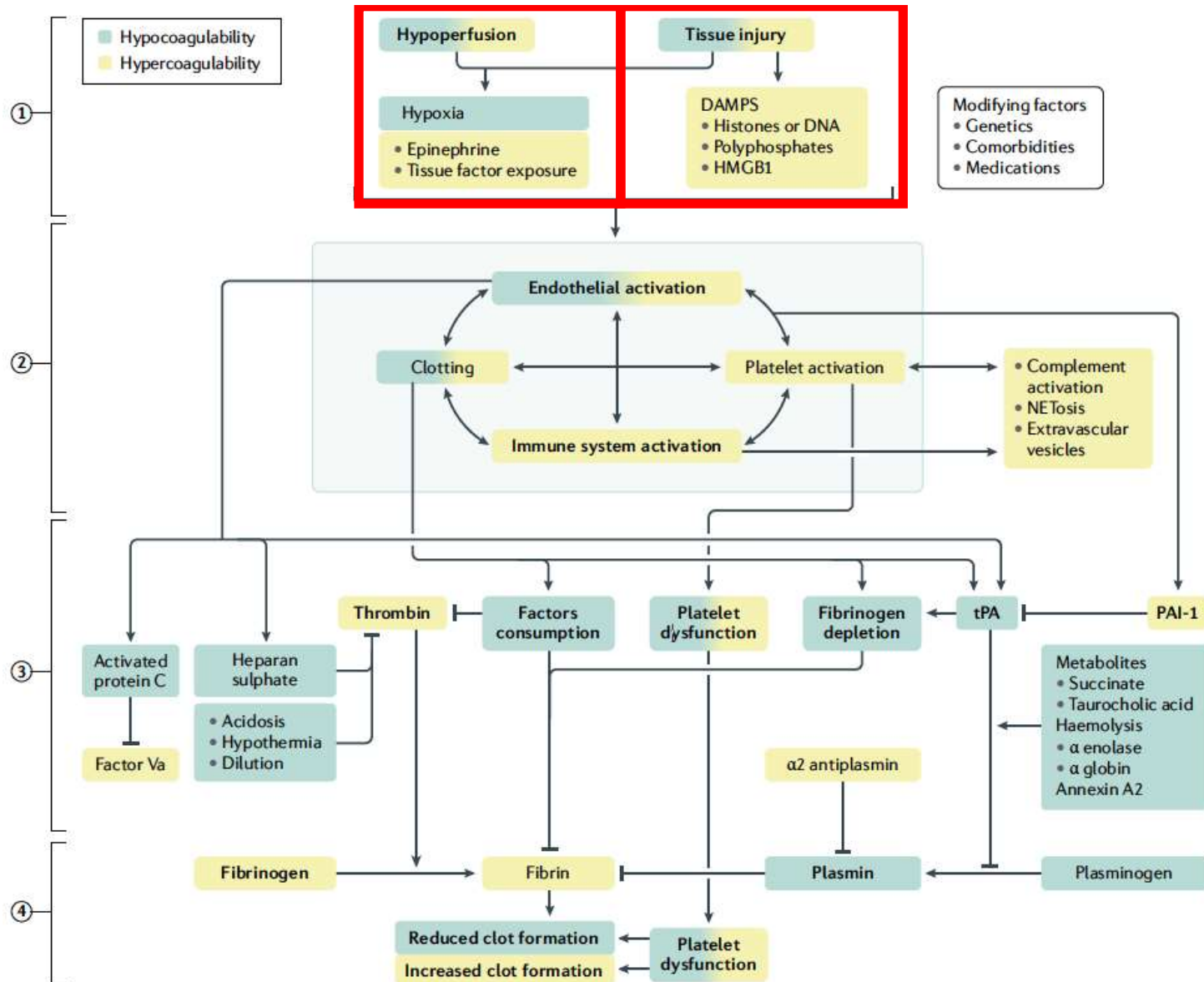
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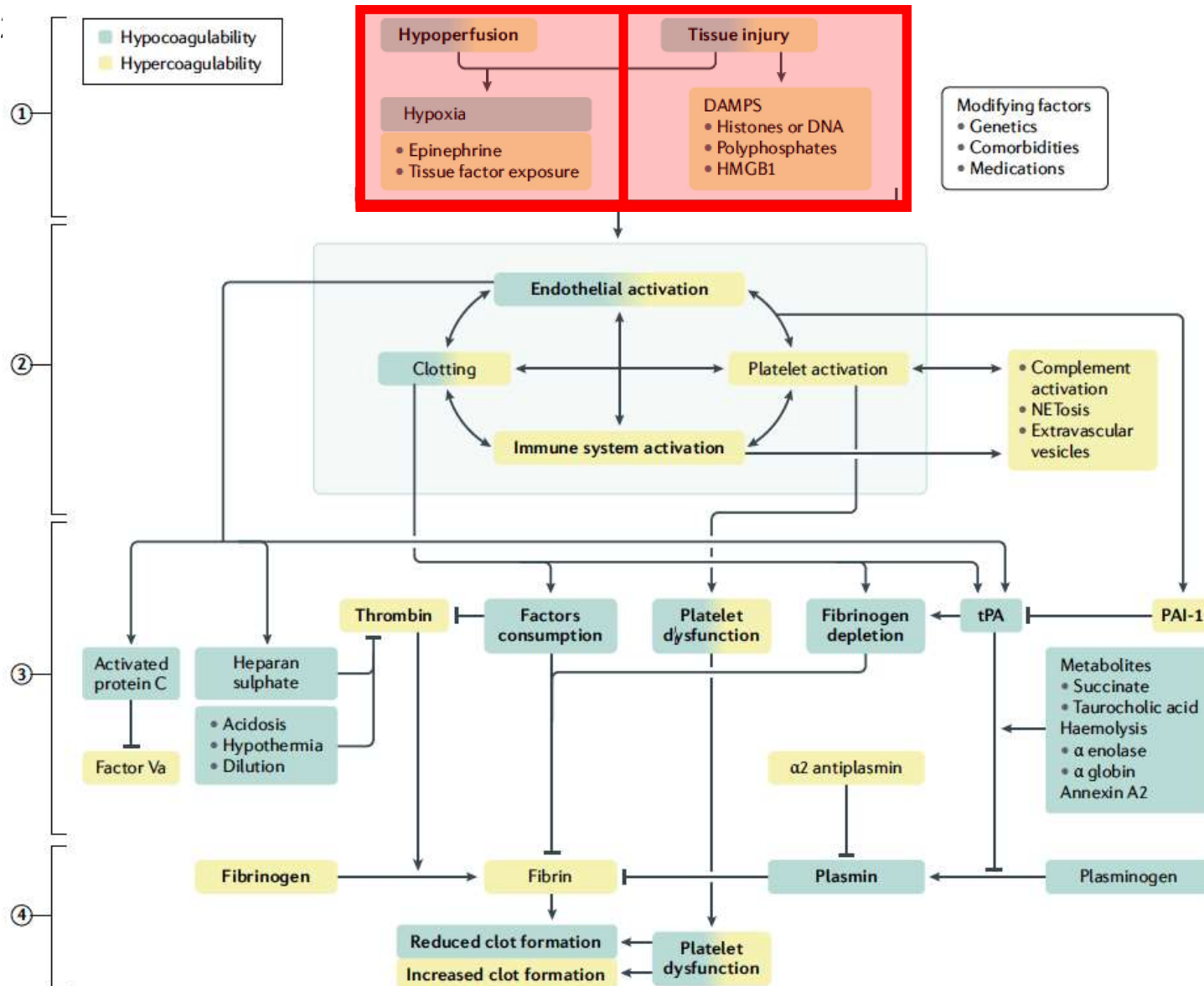
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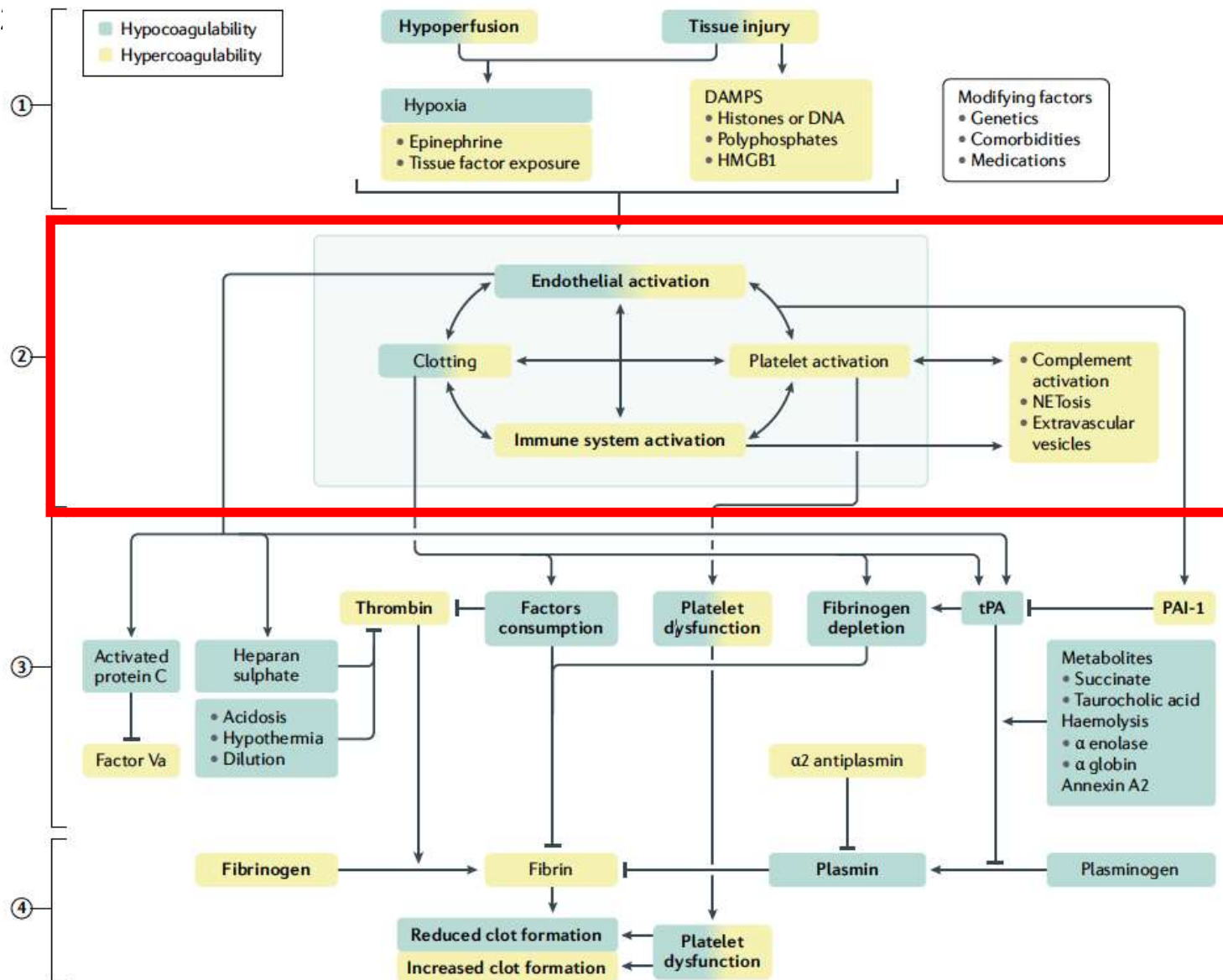
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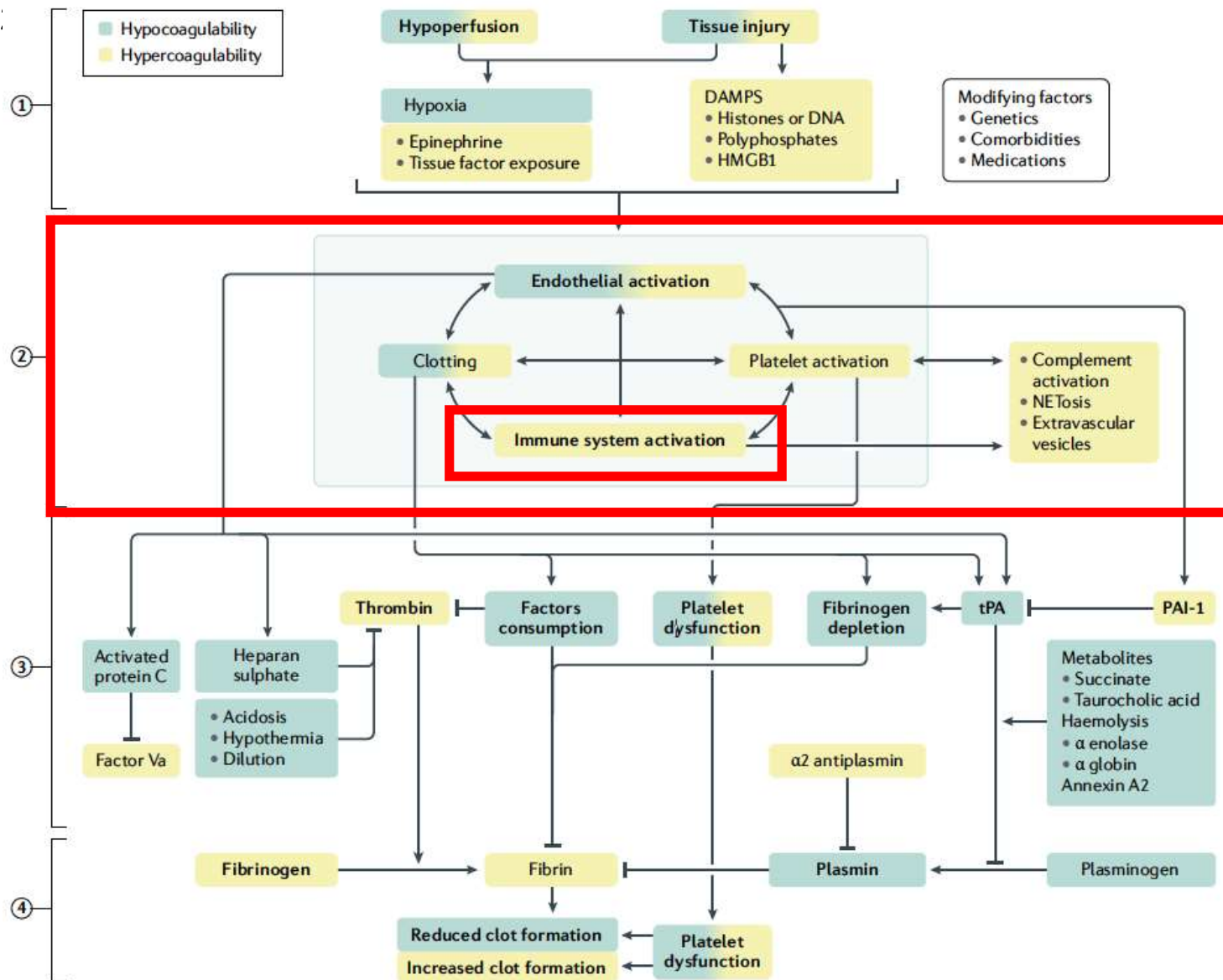
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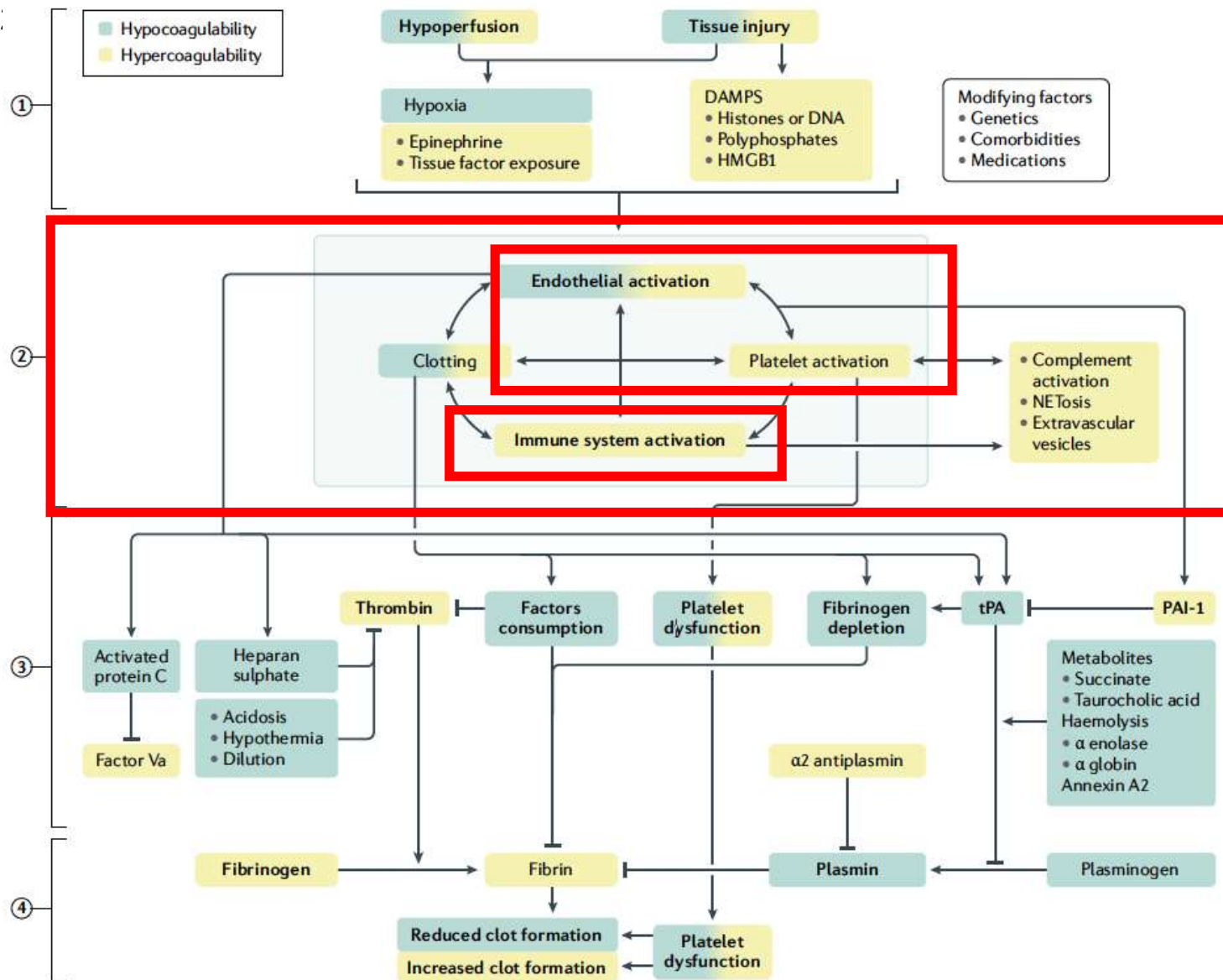
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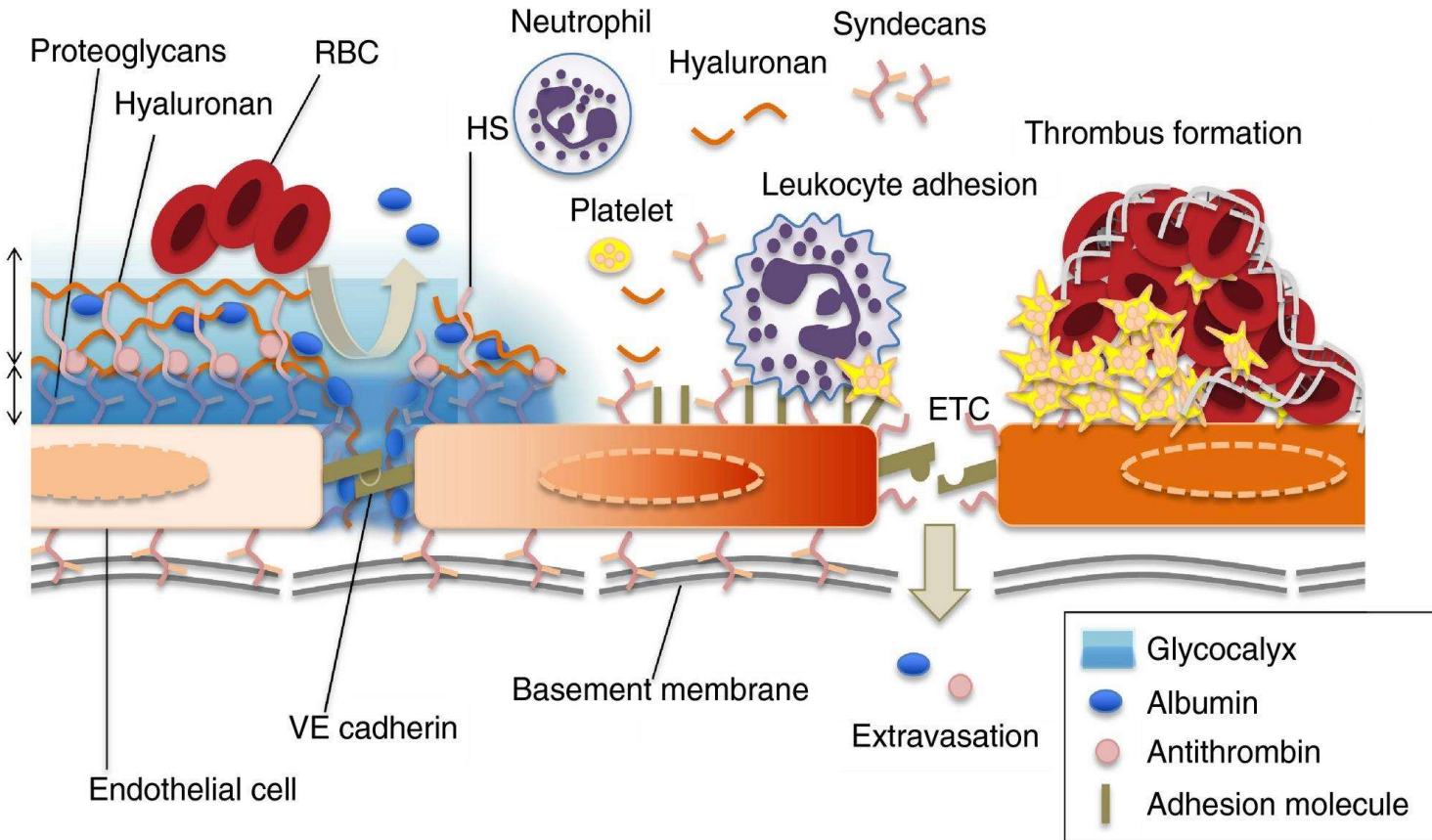
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# Endothelium



**Figure:**

Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. *J Thromb Haemost.* 2019 Feb;17(2):283-294.

**Selected readings:**

Kozar, R. A. & Pati, S. Syndecan-1 restitution by plasma after hemorrhagic shock. *J. Trauma Acute Care Surg.* 78, S83–S86 (2015).

Simão, F. & Feener, E. P. The effects of the contact activation system on hemorrhage. *Front. Med.* 4, 121 (2017).

Johansson, P. I., Stensballe, J., Rasmussen, L. S. & Ostrowski, S. R. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. *Ann. Surg.* 254, 194–200 (2011).

Gonzalez Rodriguez, E. et al. Syndecan-1: a quantitative marker for the endotheliopathy of trauma. *J. Am. Coll. Surg.* 225, 419–427 (2017).

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Ostrowski, S. R. & Johansson, P. I. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. *J. Trauma Acute Care Surg.* 73, 60–66 (2012).

Cohen, M. J. et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann. Surg.* 255, 379–385 (2012).

Pati, S. et al. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. *J. Trauma* 69, S55–S63 (2010).

Kozar, R. A. et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth. Analg.* 112, 1289–1295 (2011).

# Platelets

- Thrombocytopenia associated with bleeding
- Majority with initial normal platelet counts

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Kornblith, L. Z. et al. Fibrinogen and platelet contributions to clot formation: implications for trauma resuscitation and thromboprophylaxis. *J Trauma Acute Care Surg*. 76, 255–256; Discussion 262–263 (2014).

Zipperle, J. et al. Potential role of platelet-leukocyte aggregation in trauma-induced coagulopathy: ex vivo findings. *J Trauma Acute Care Surg*. 82, 921–926 (2017).

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Kornblith, L. Z. et al. Perhaps it's not the platelet: ristocetin uncovers the potential role of von Willebrand factor in impaired platelet aggregation following traumatic brain injury. *J Trauma Acute Care Surg*. 85, 873–880 (2018).

Plautz, W. E. et al. Von Willebrand factor as a thrombotic and inflammatory mediator in critical illness. *Transfusion* 60, S158–S166 (2020).

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# Platelets

- Thrombocytopenia associated with bleeding
- Majority with initial normal platelet counts
- Increased markers of activation
- Increased platelet contribution to clot strength
- Increased pro-coagulant factor release
- Impaired aggregation responses ex-vivo

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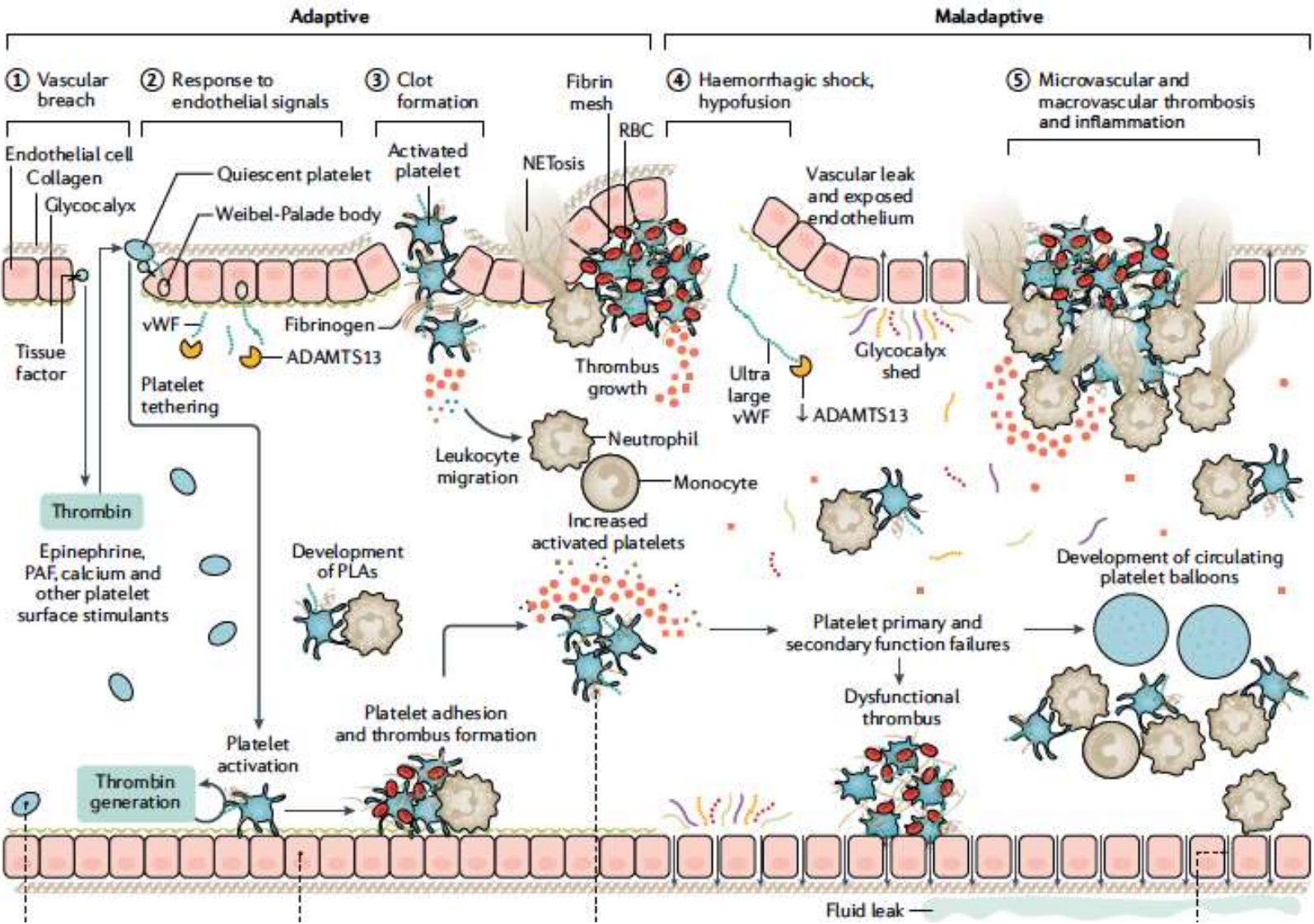
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Ding, N. et al. Toll- like receptor 4 regulates platelet function and contributes to coagulation abnormality and organ injury in hemorrhagic shock and resuscitation. *Circ. Cardiovasc. Genet.* 7, 615–62 (2014).

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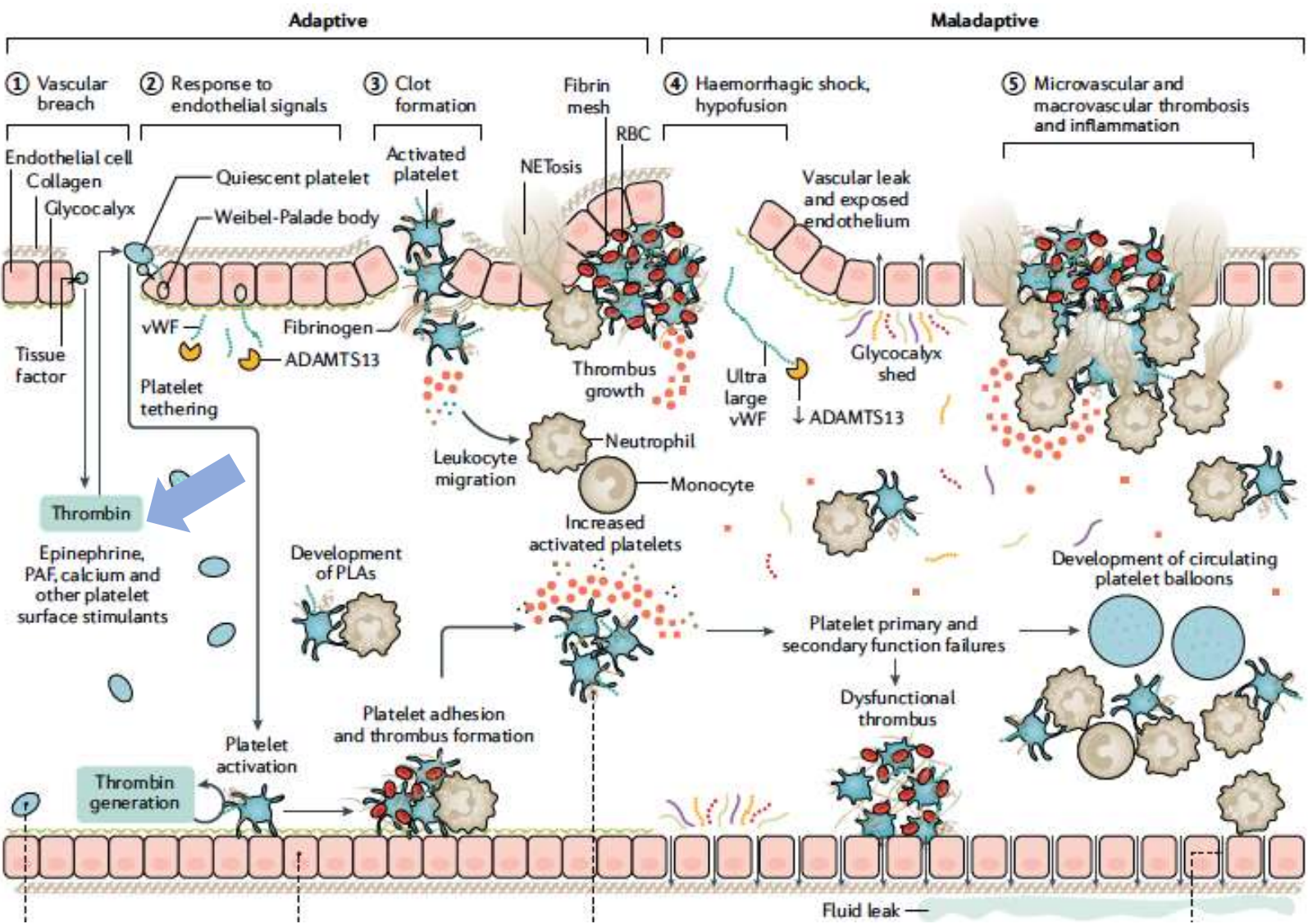
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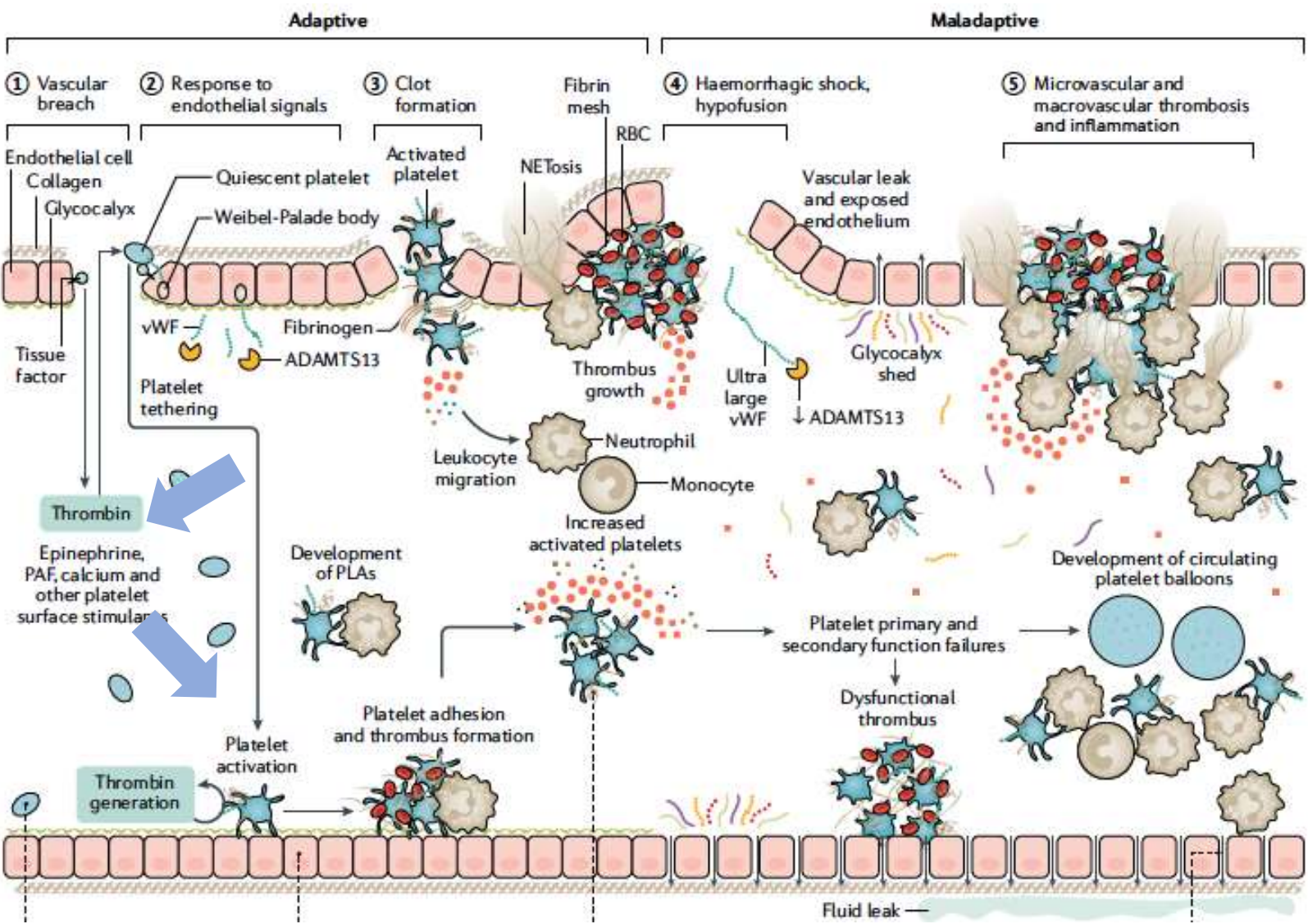
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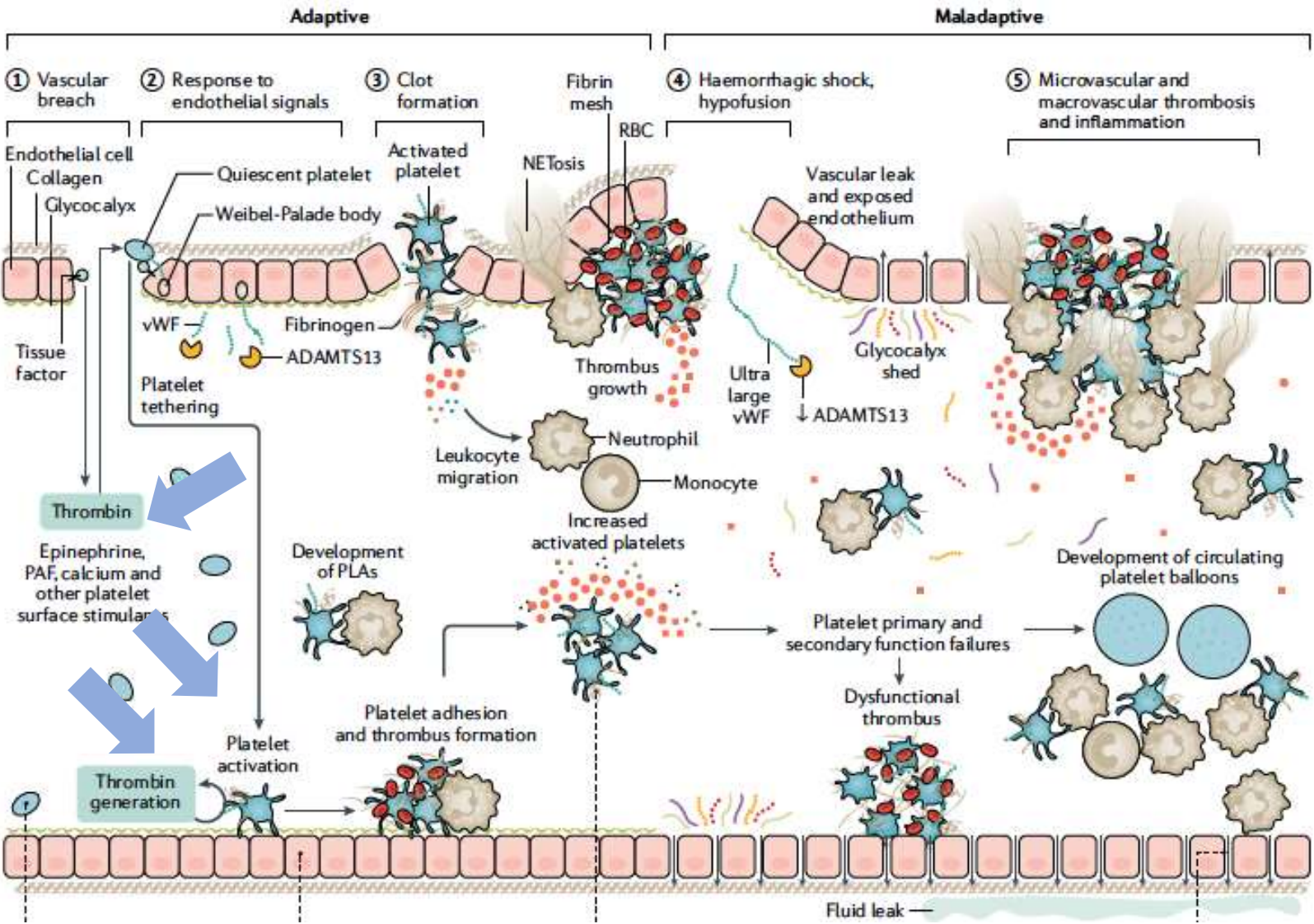
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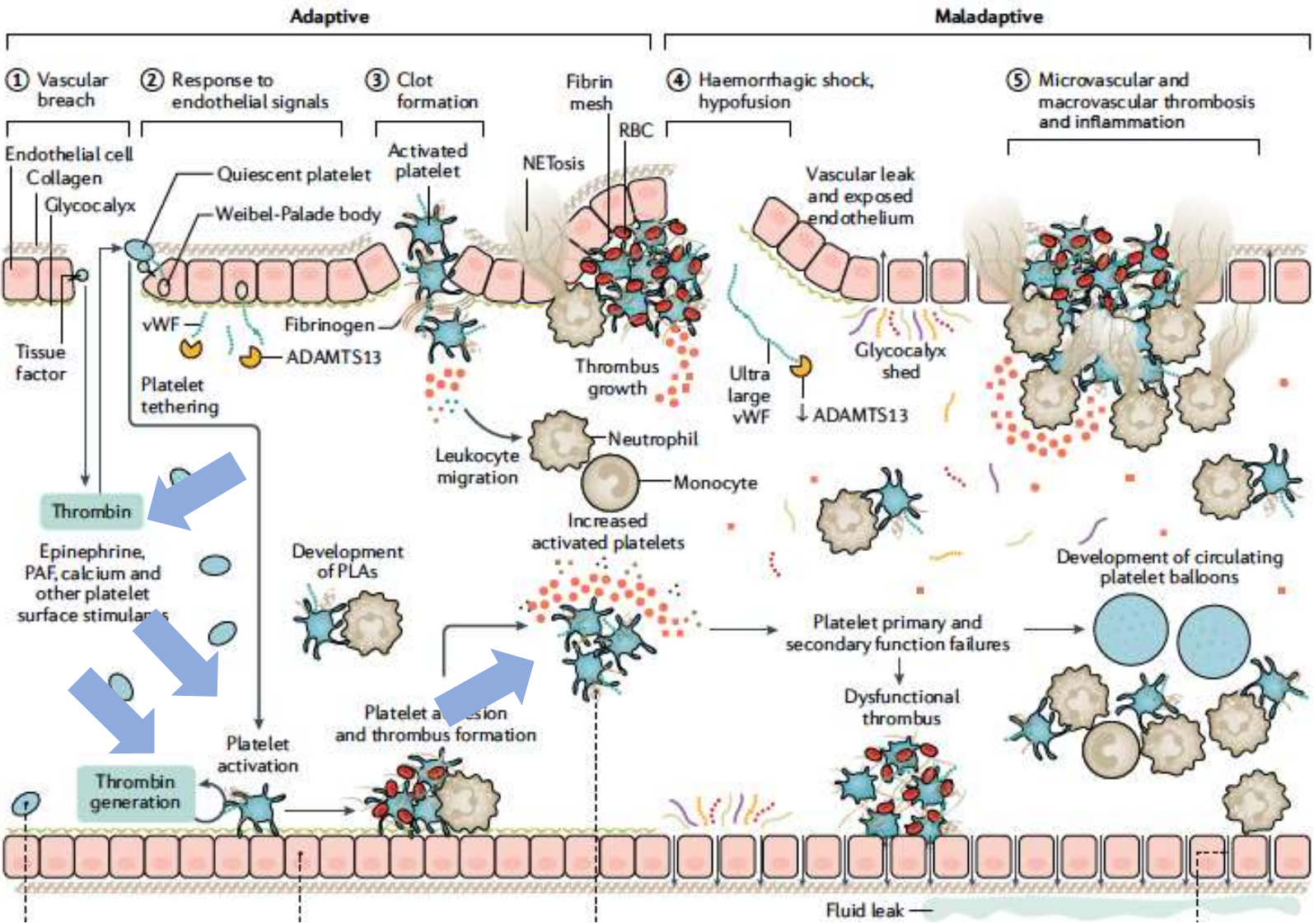
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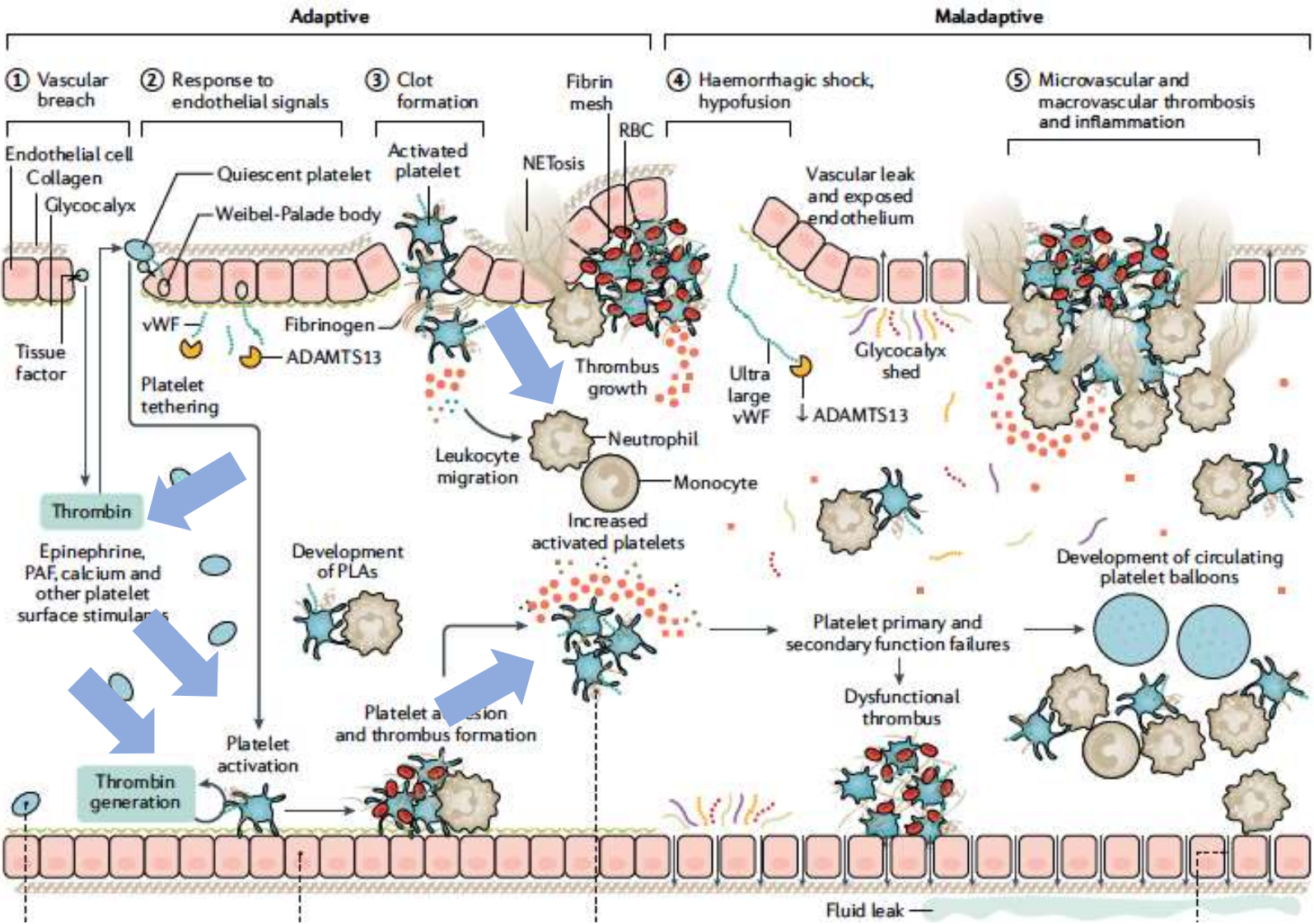
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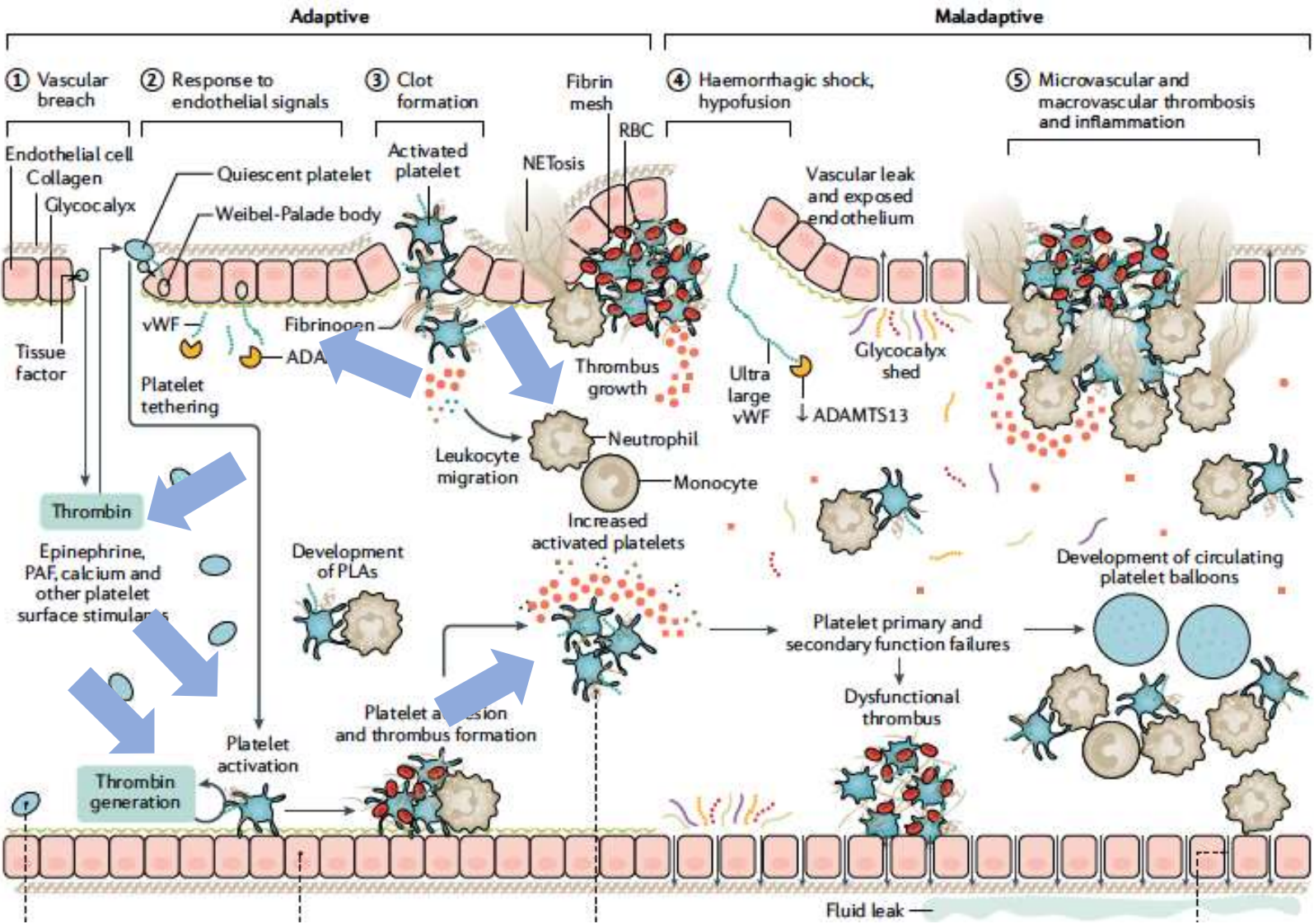
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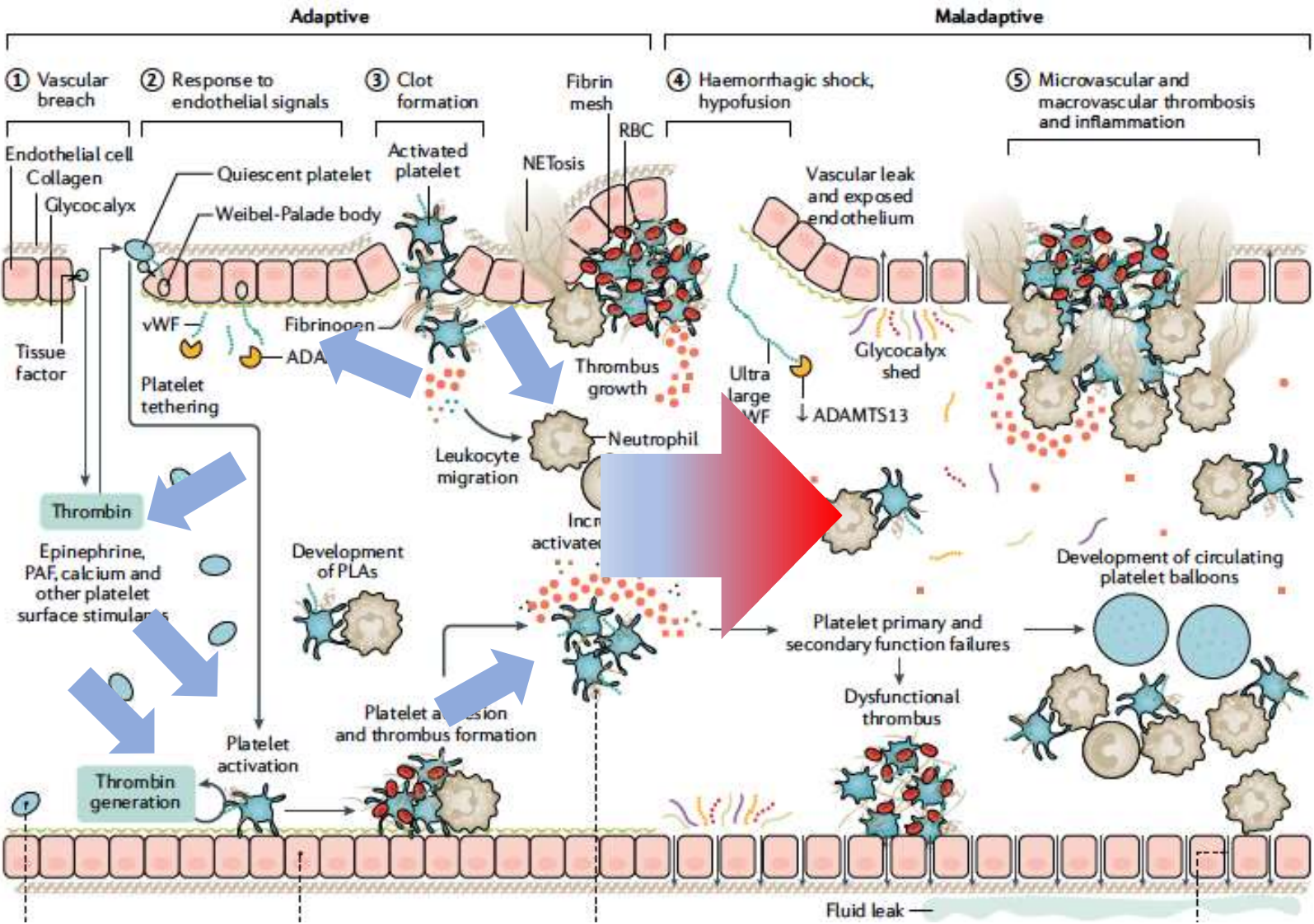
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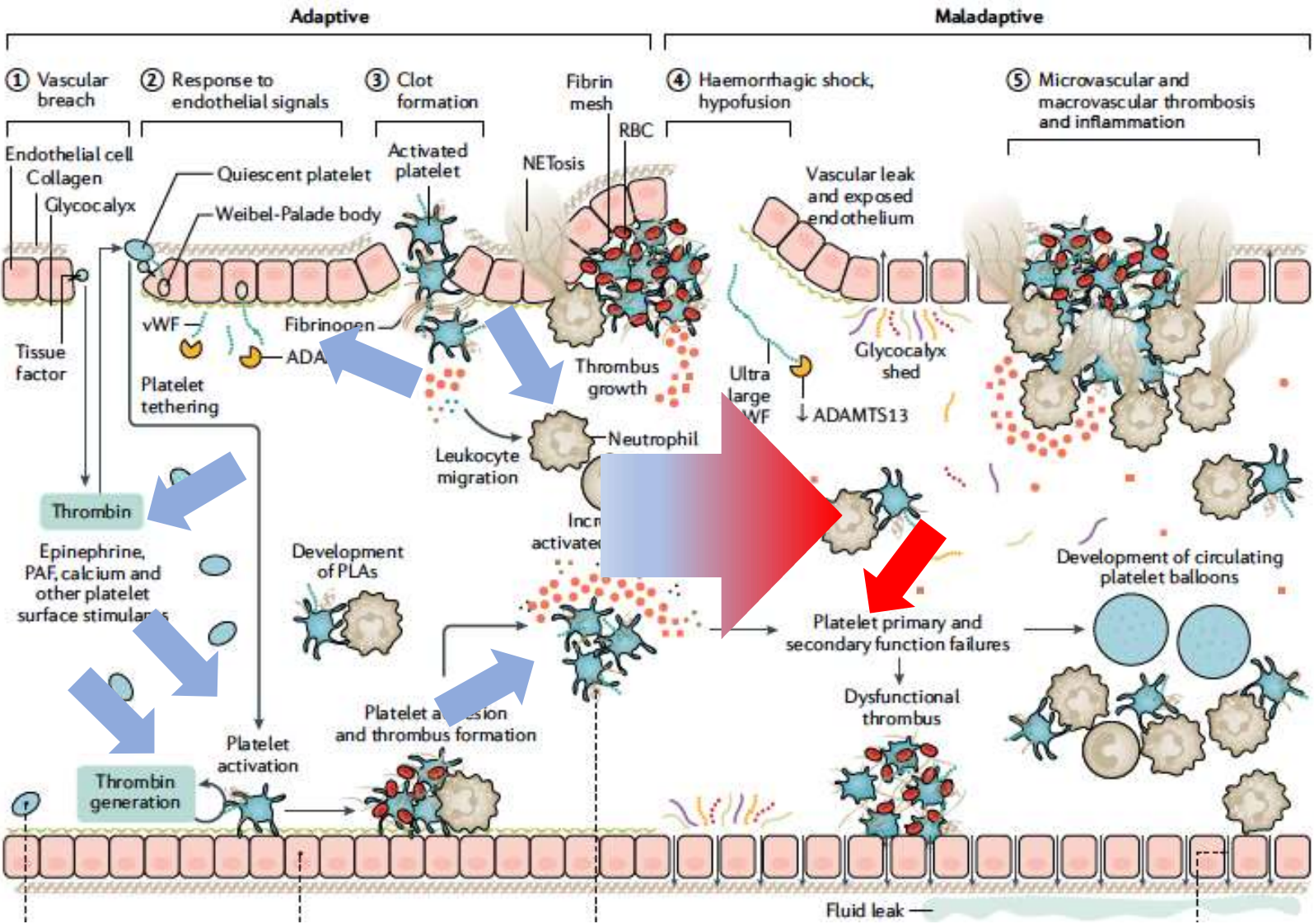
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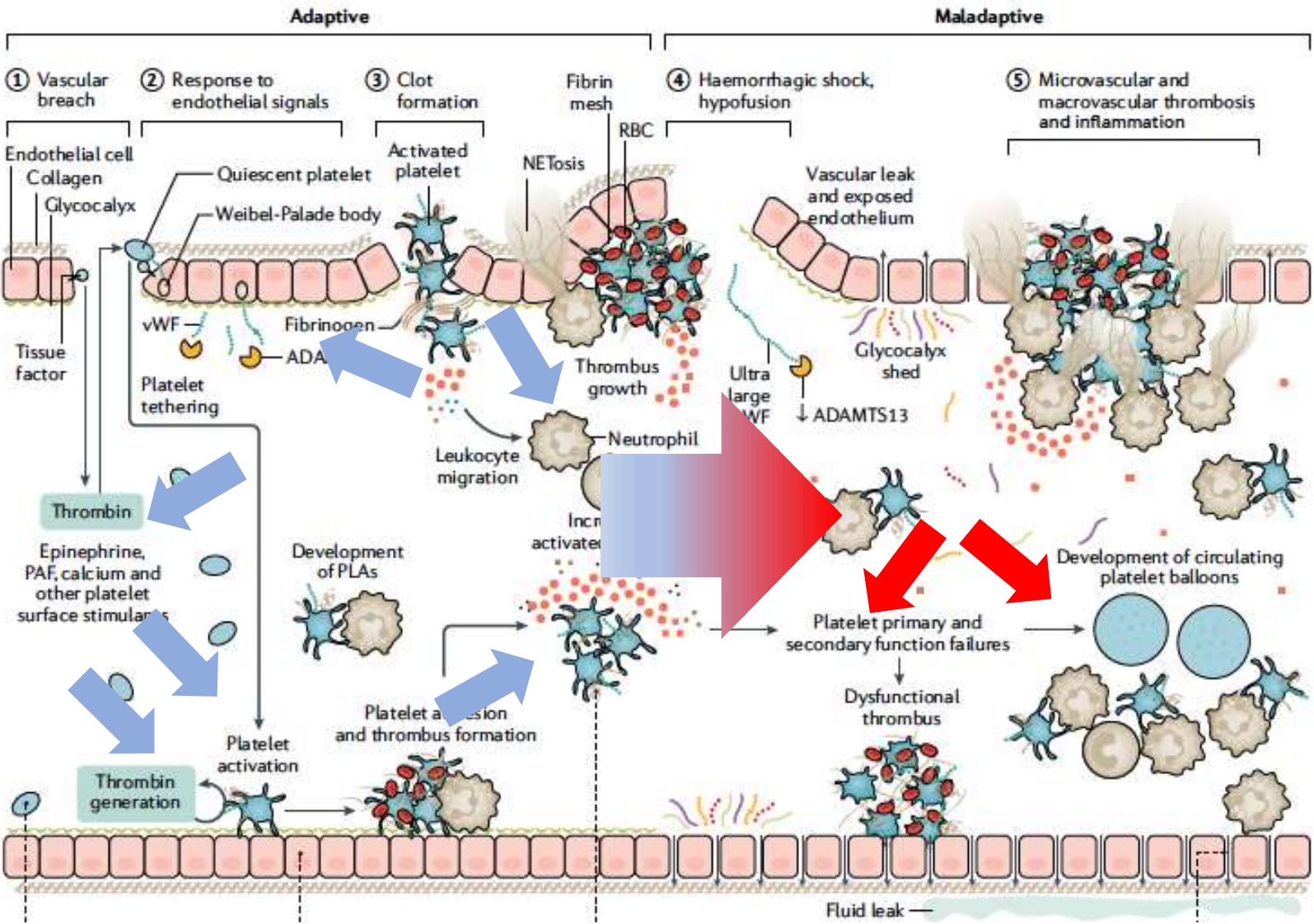
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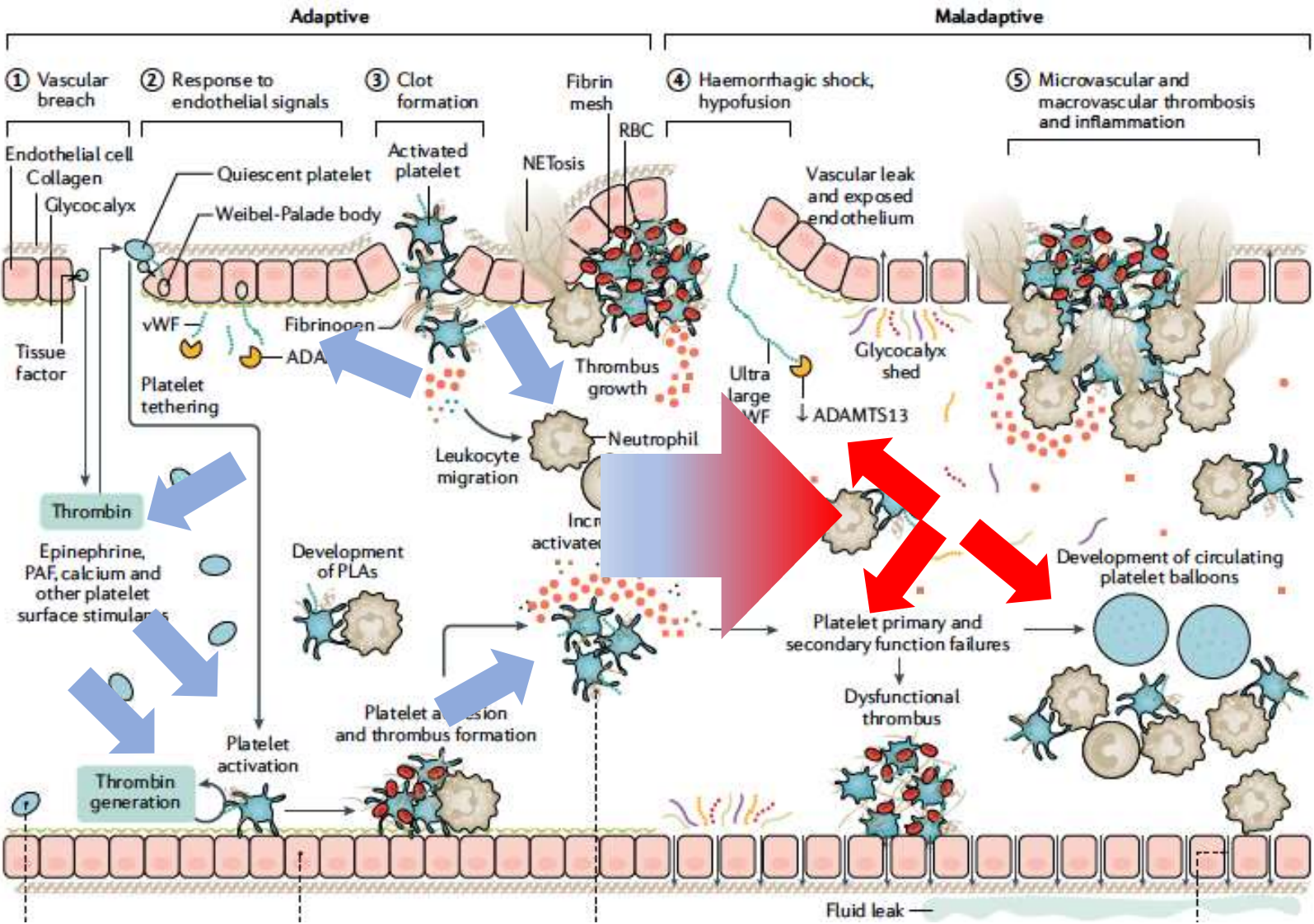
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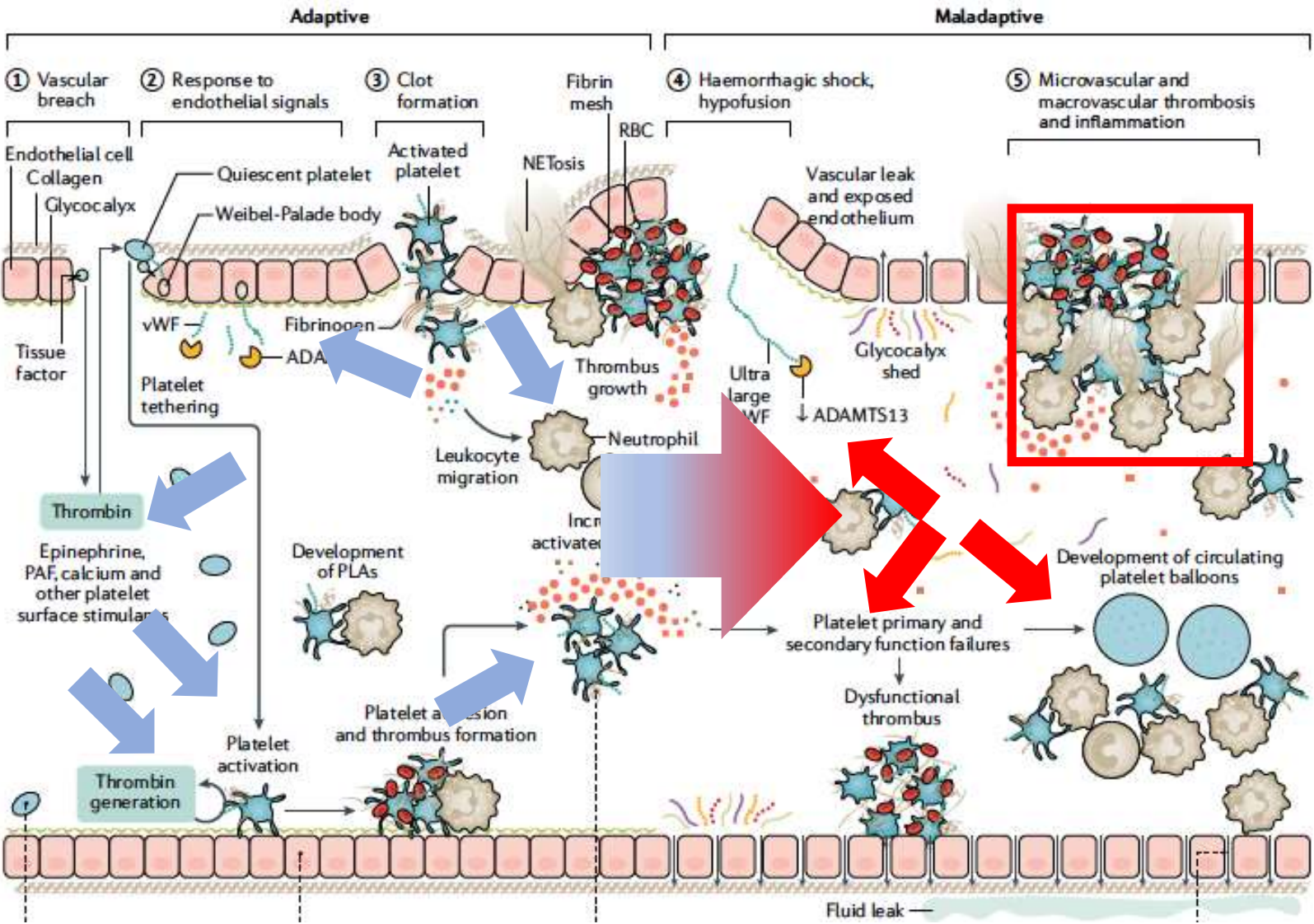
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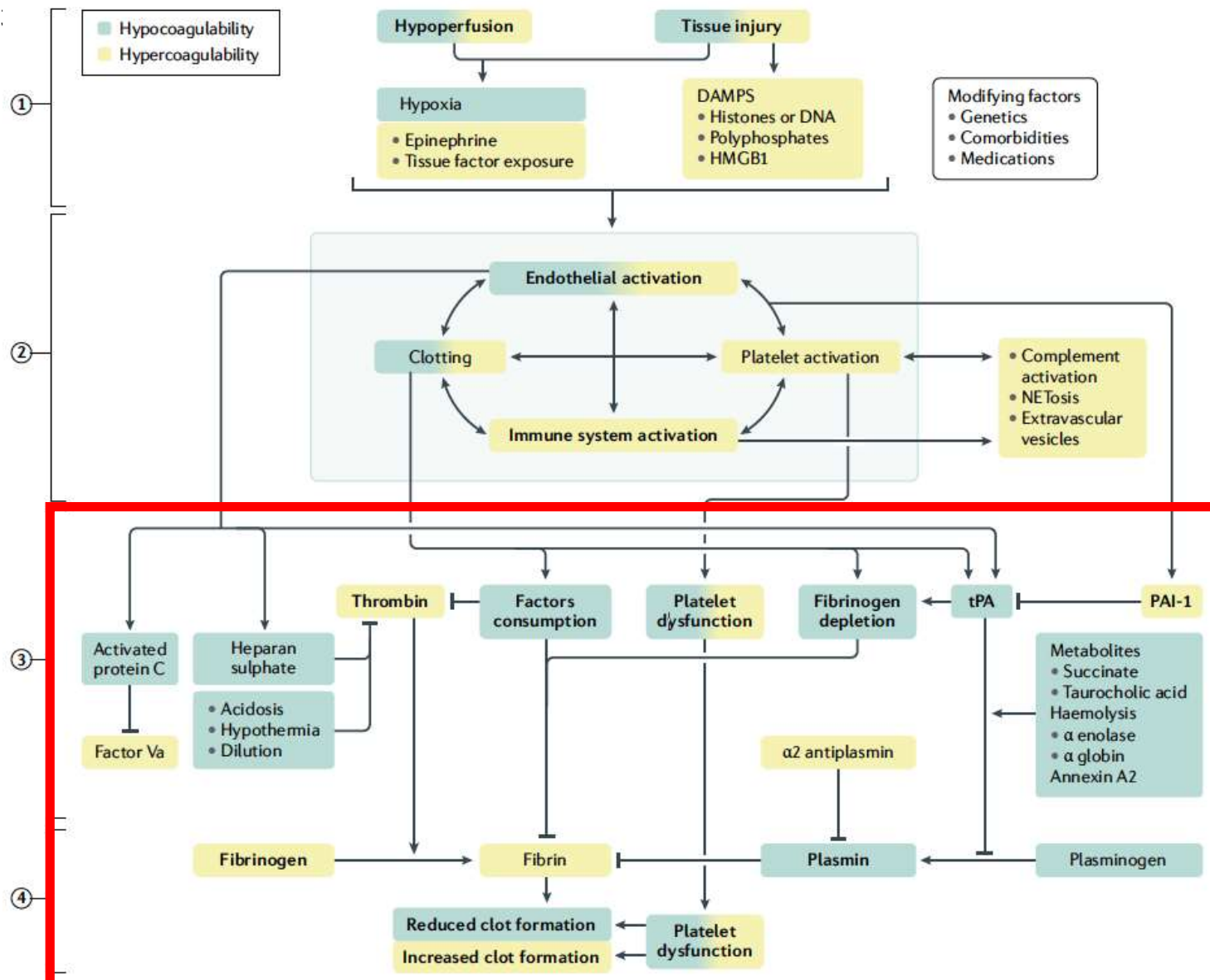
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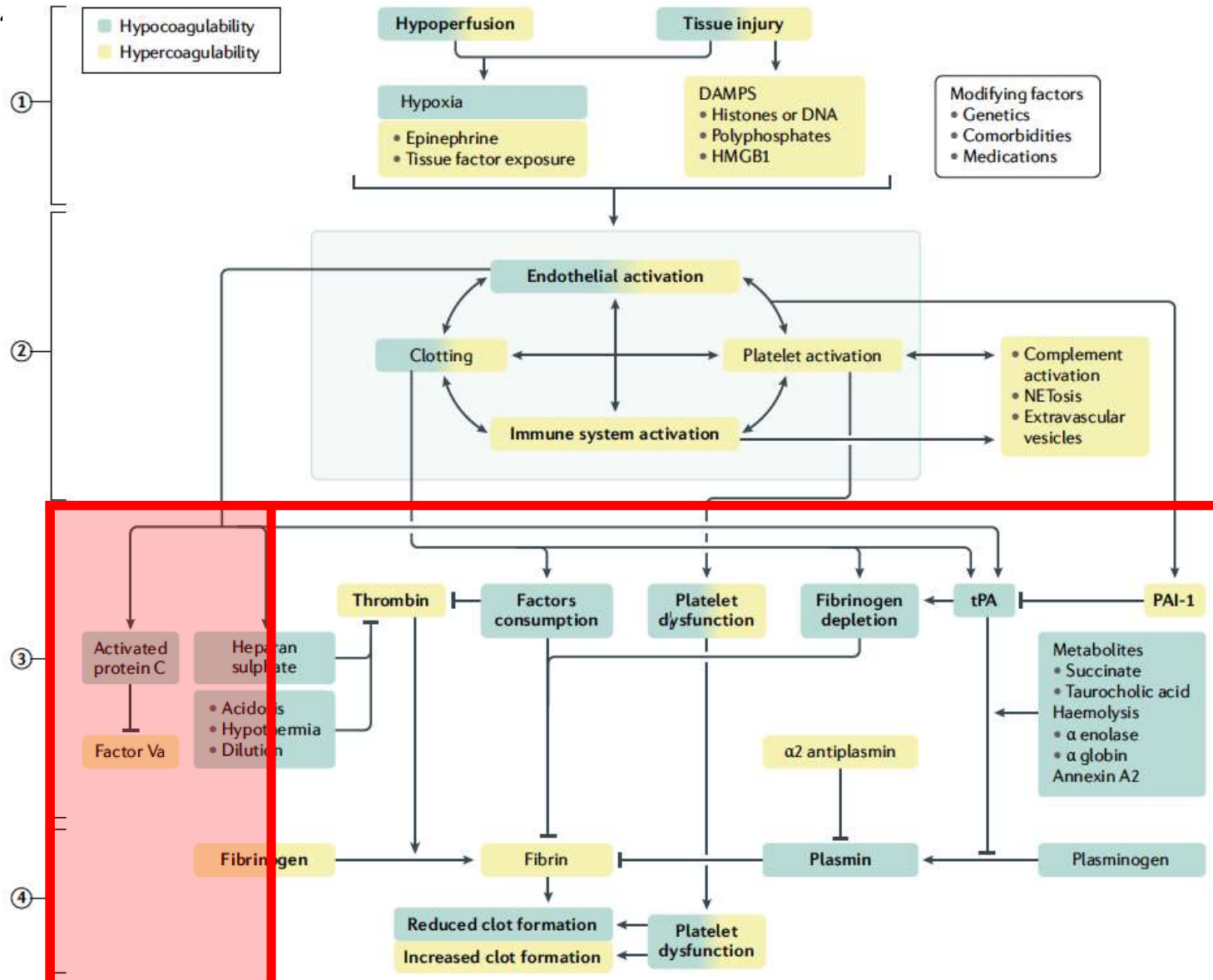
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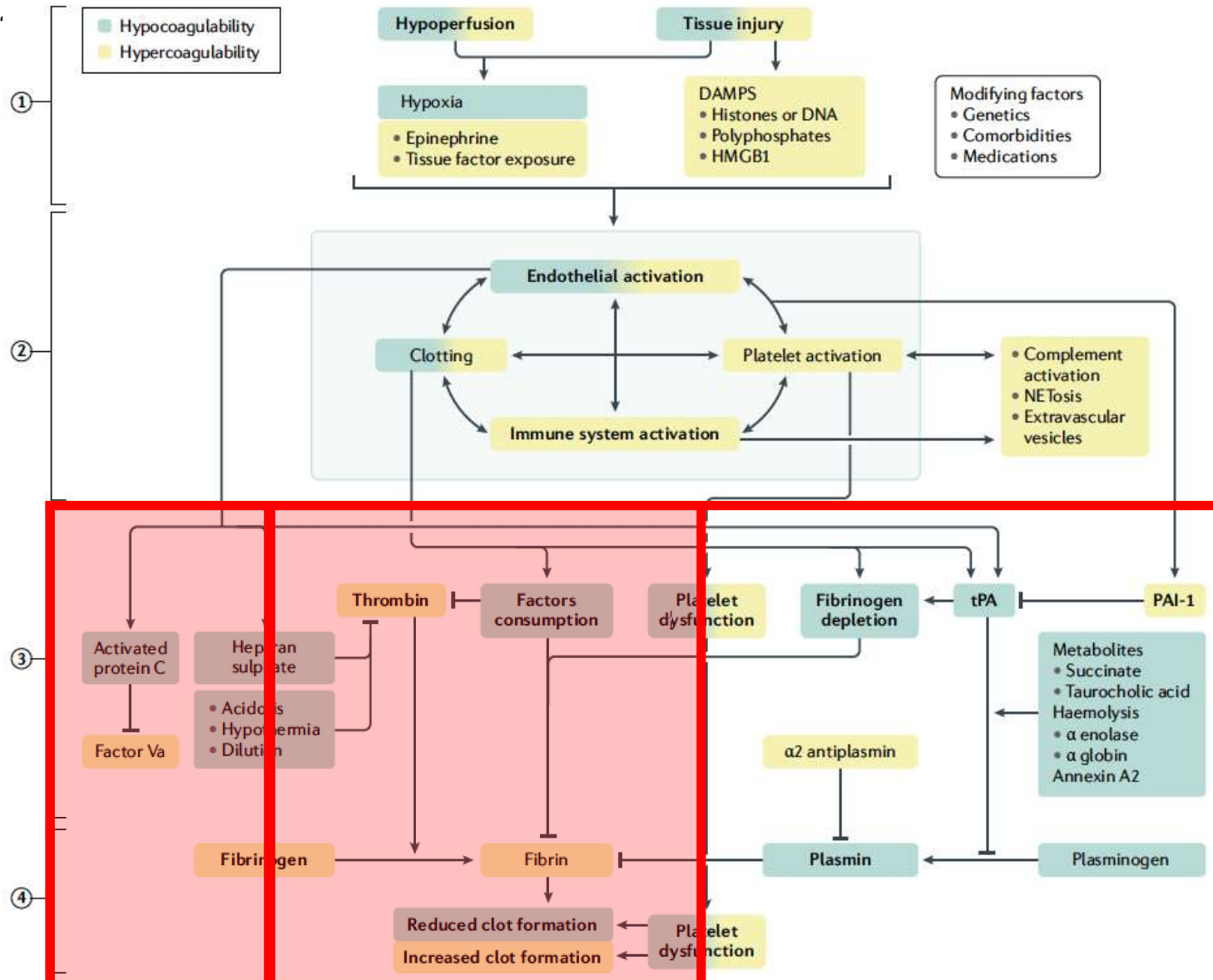
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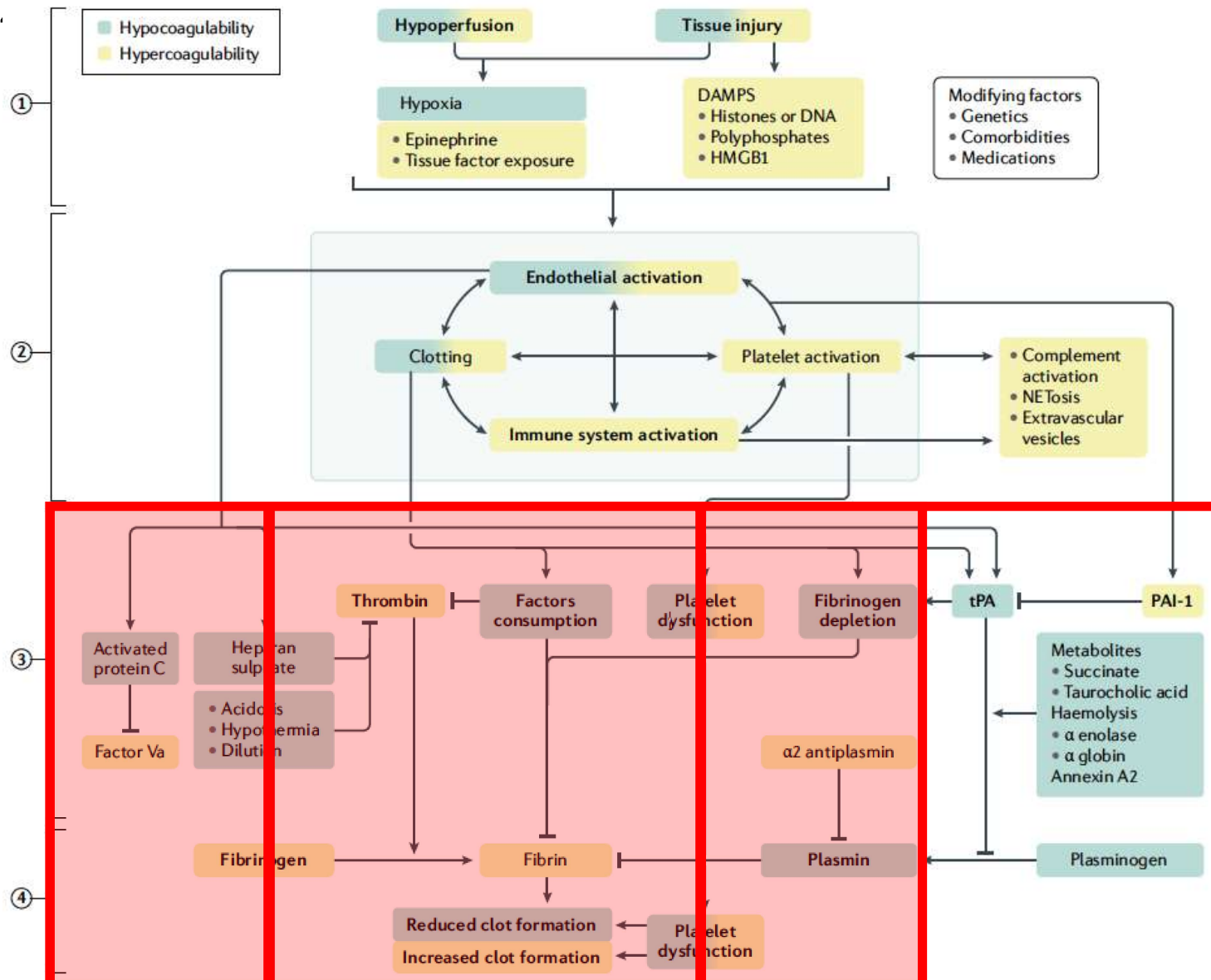
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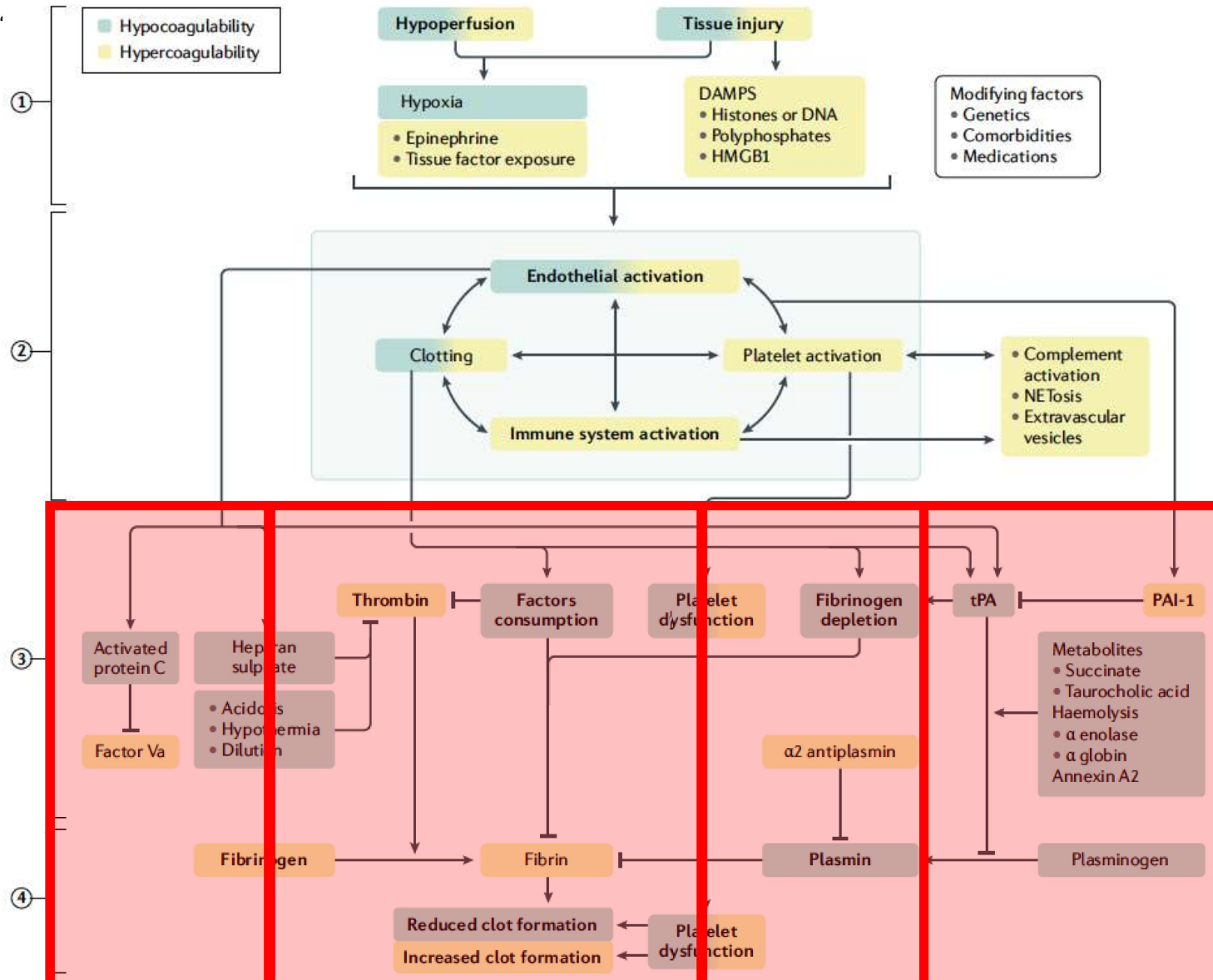
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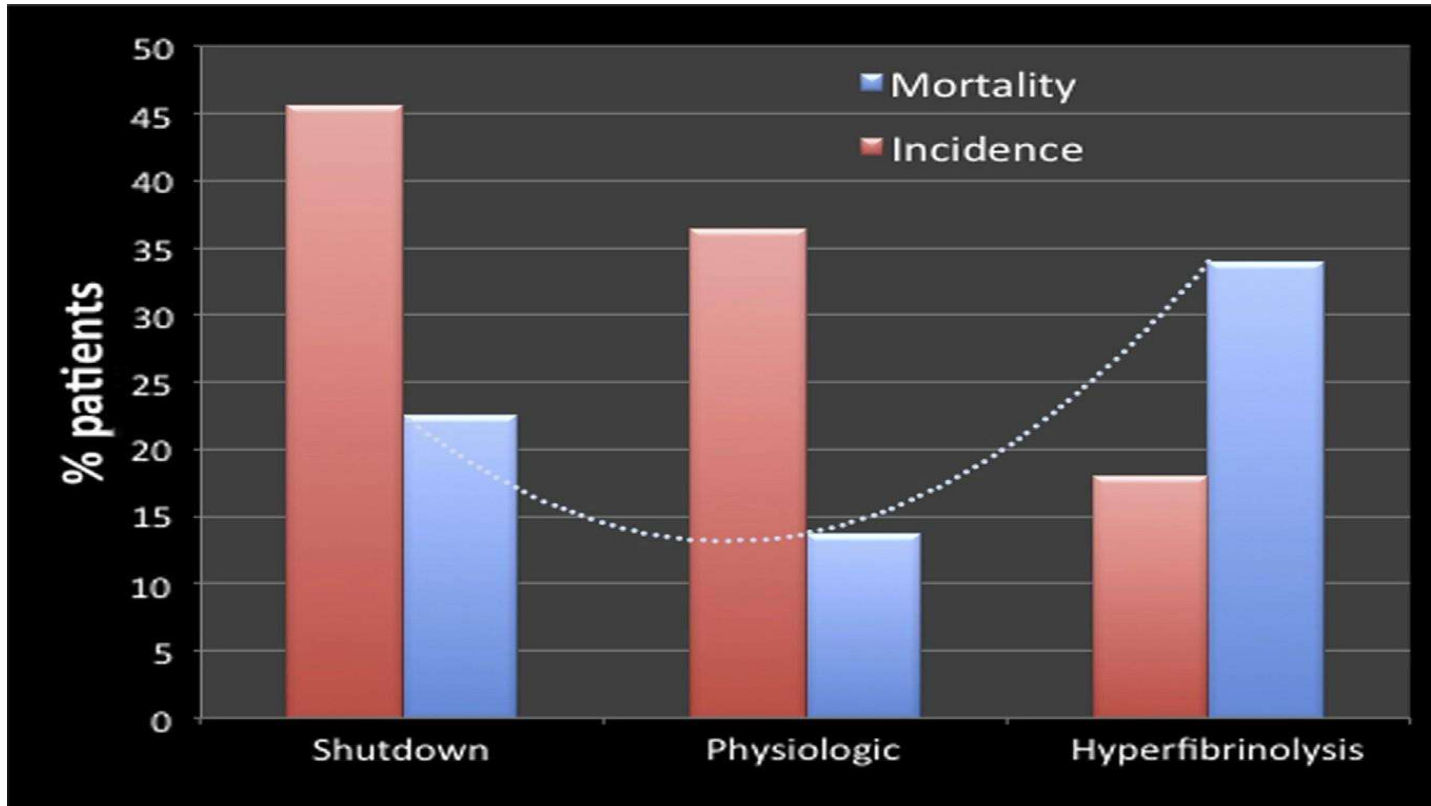
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# Fibrinolysis



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Moore, H. B. et al. Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2,540 severely injured patients. *J. Am. Coll. Surg.* 222, 347–355 (2016).

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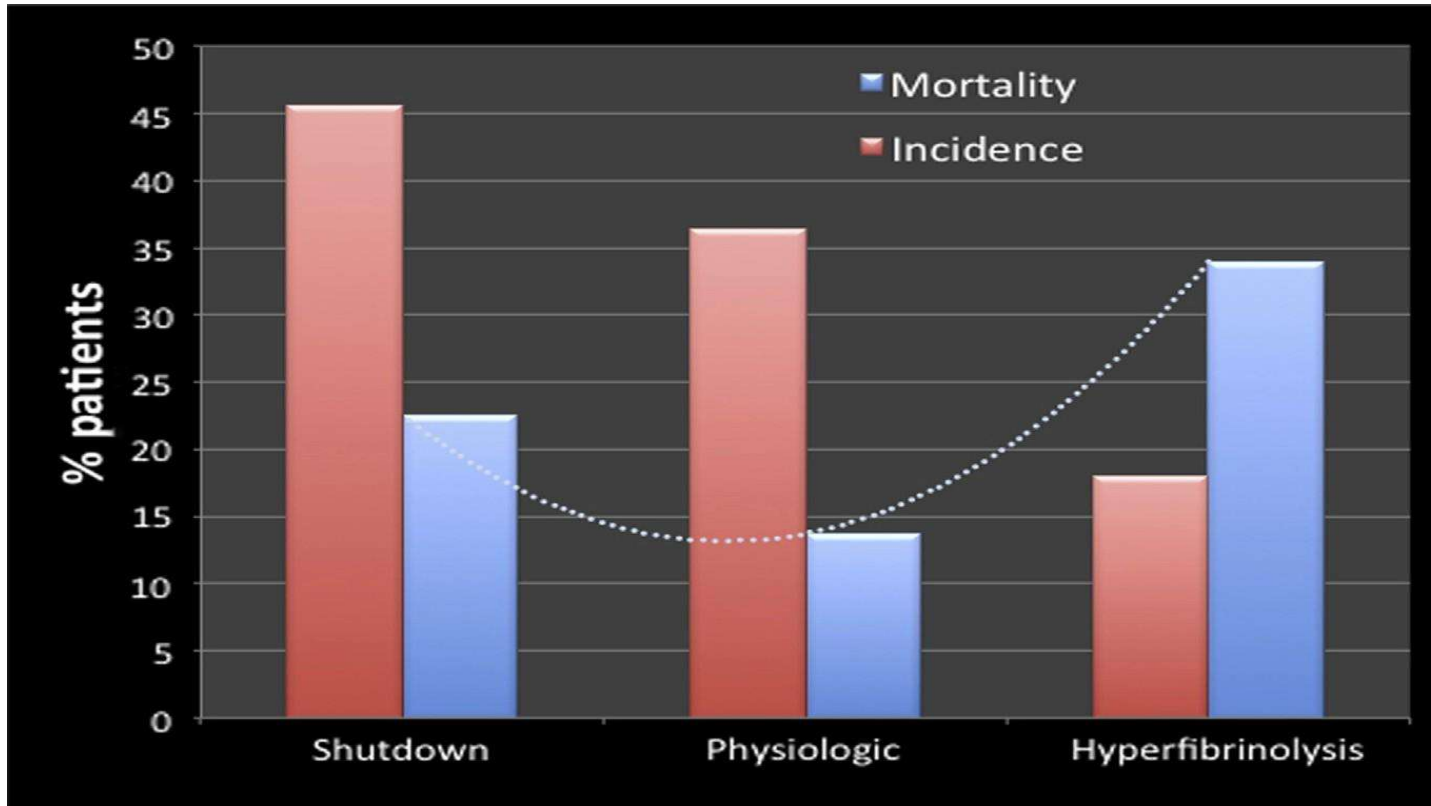
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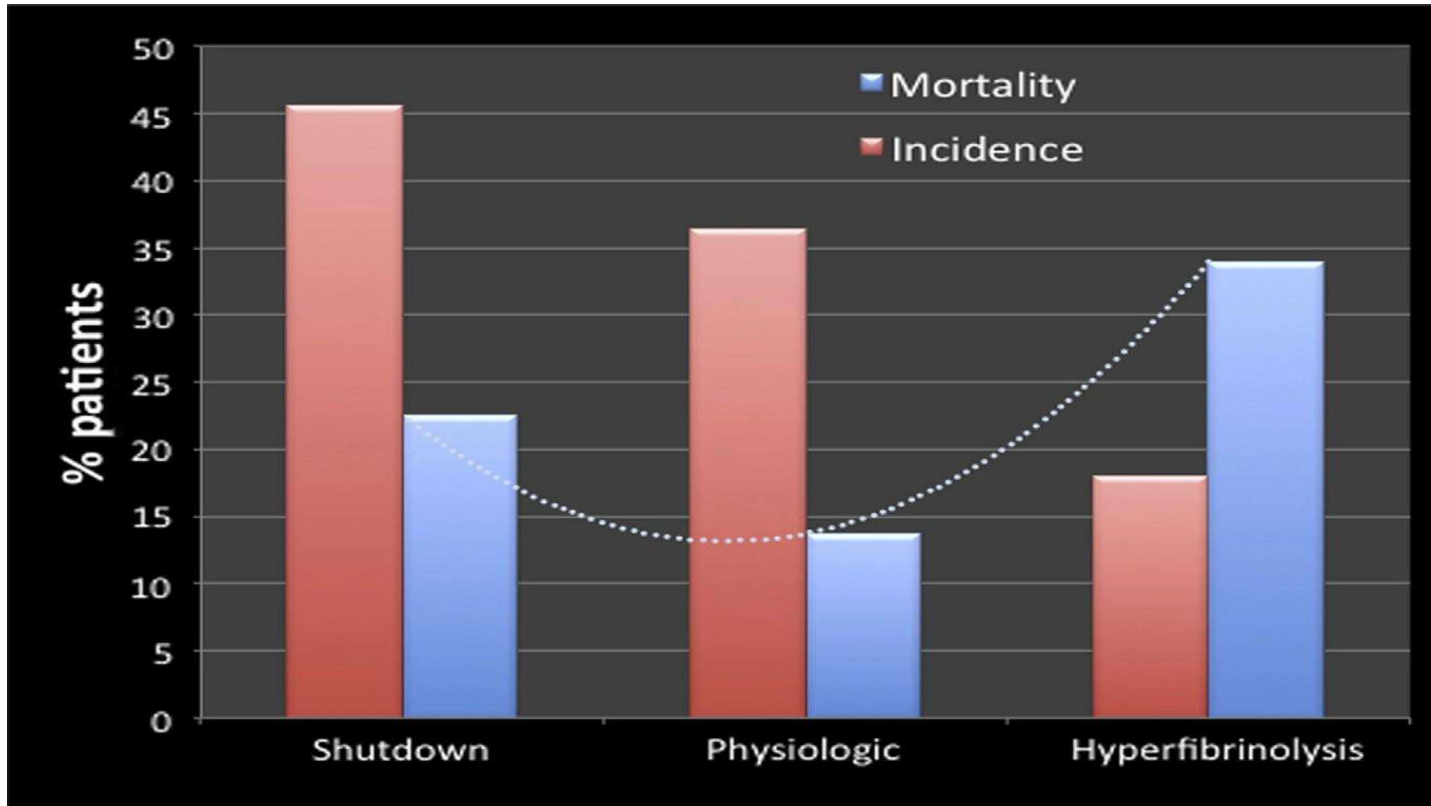
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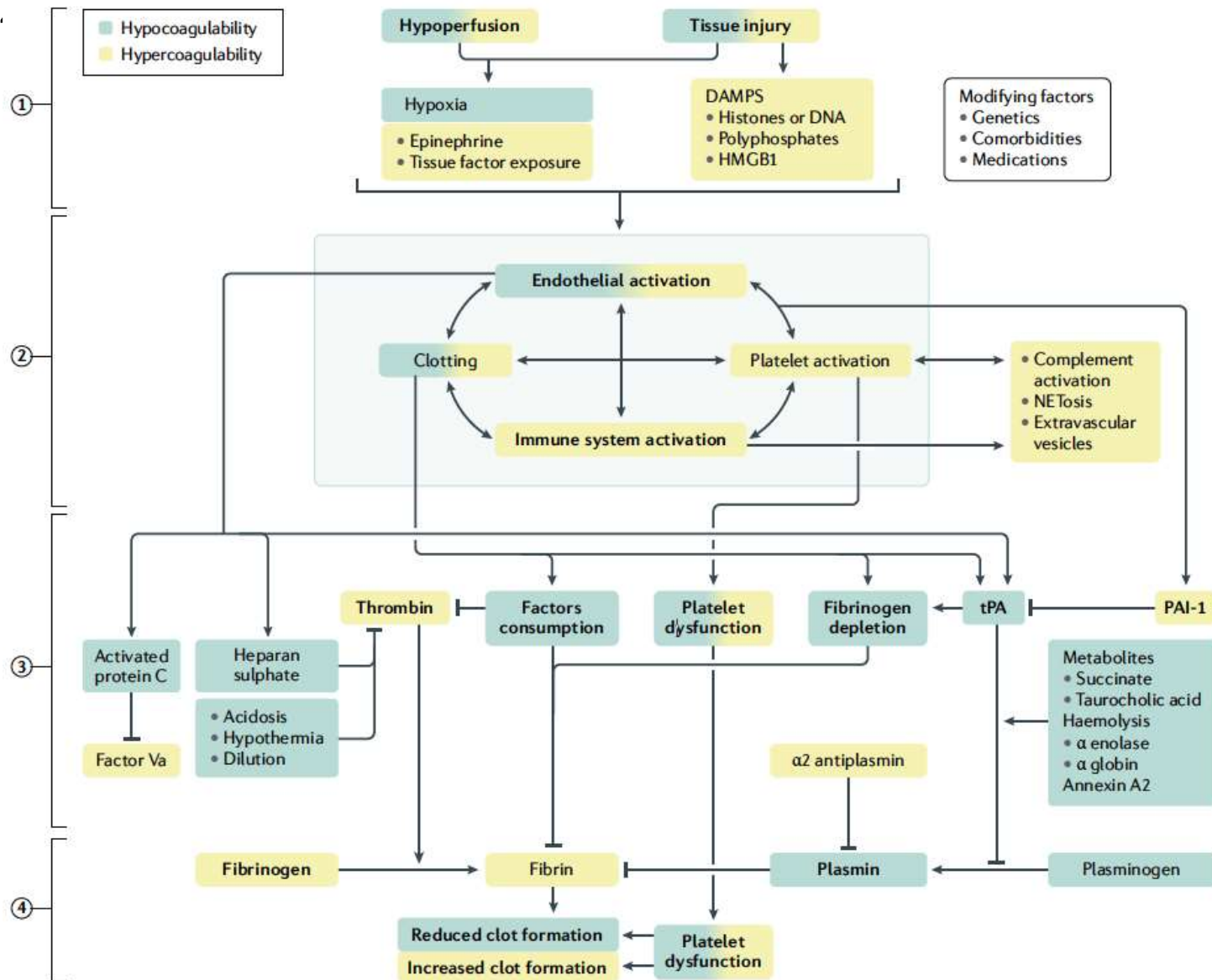
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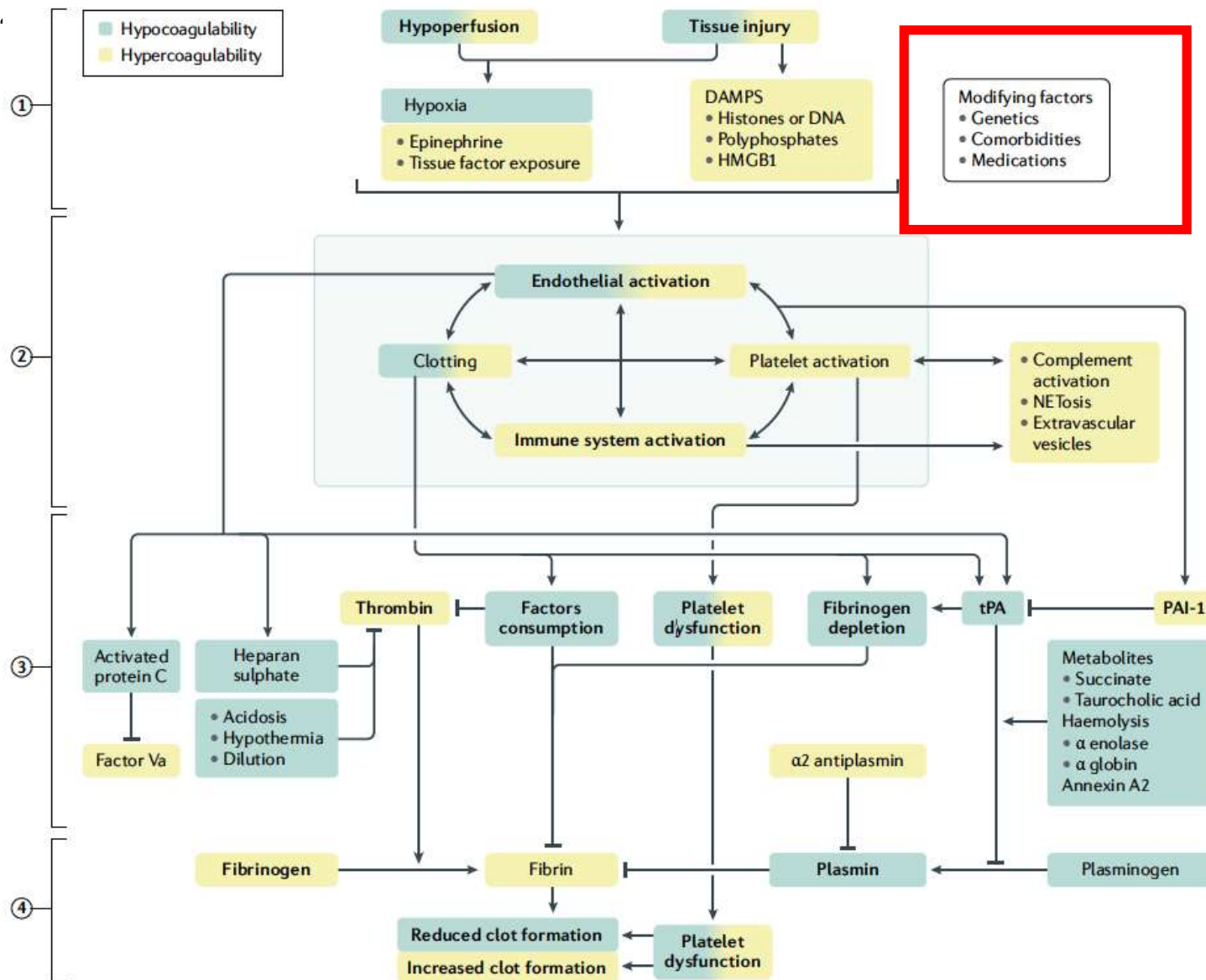
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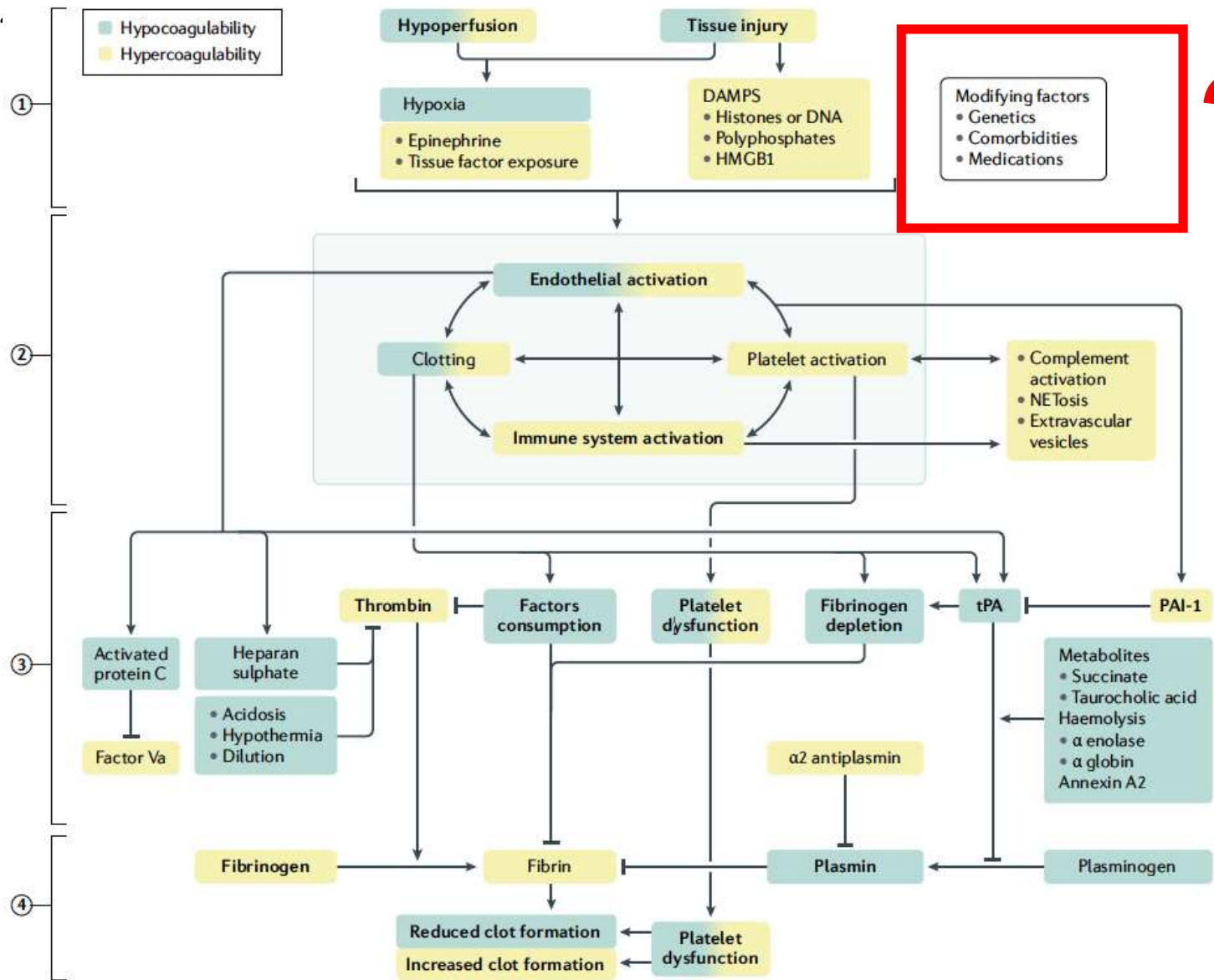
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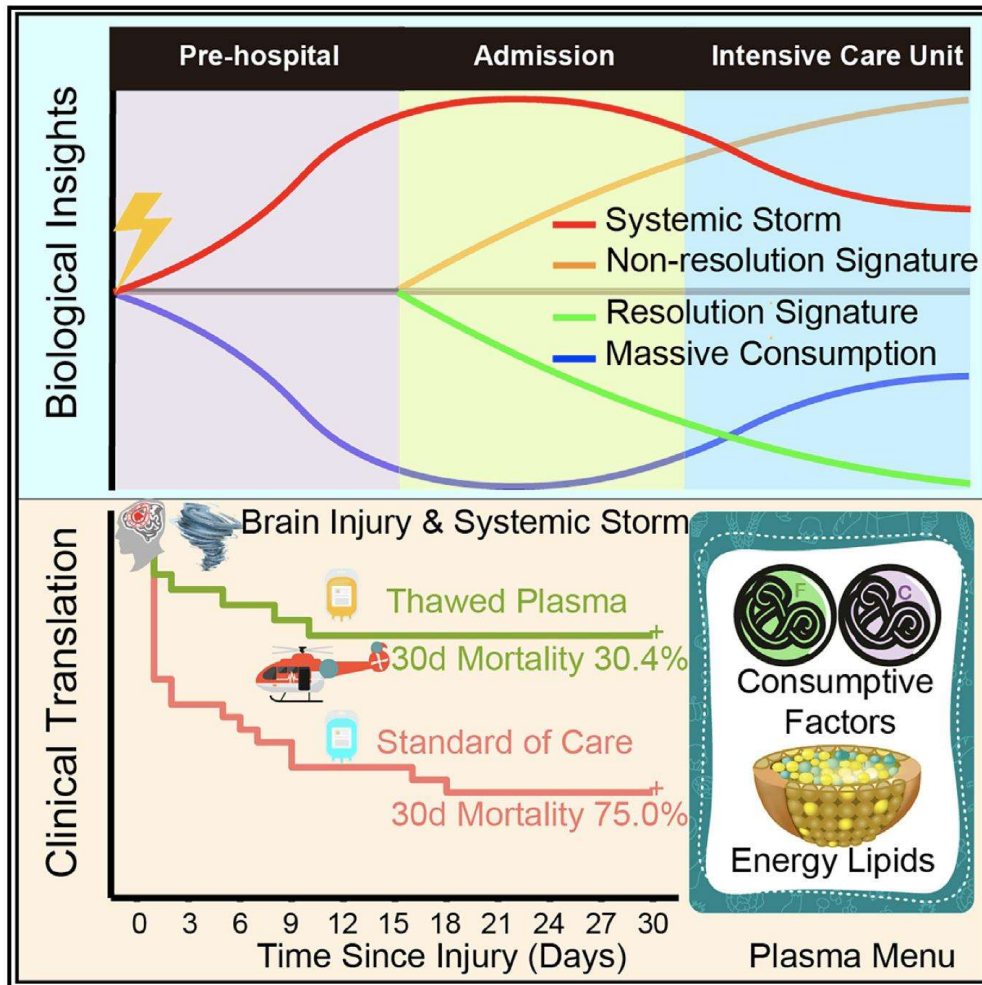
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# Treatment of TIC

- Mechanically stopping the hemorrhage
- Reversing shock
- Restoring vascular homeostasis
  - Whole blood
  - Plasma
  - Platelets
  - Fibrinogen
  - Coagulation factors
  - Anti-fibrinolytics (TXA)
- Viscoelastic goal-directed resuscitation

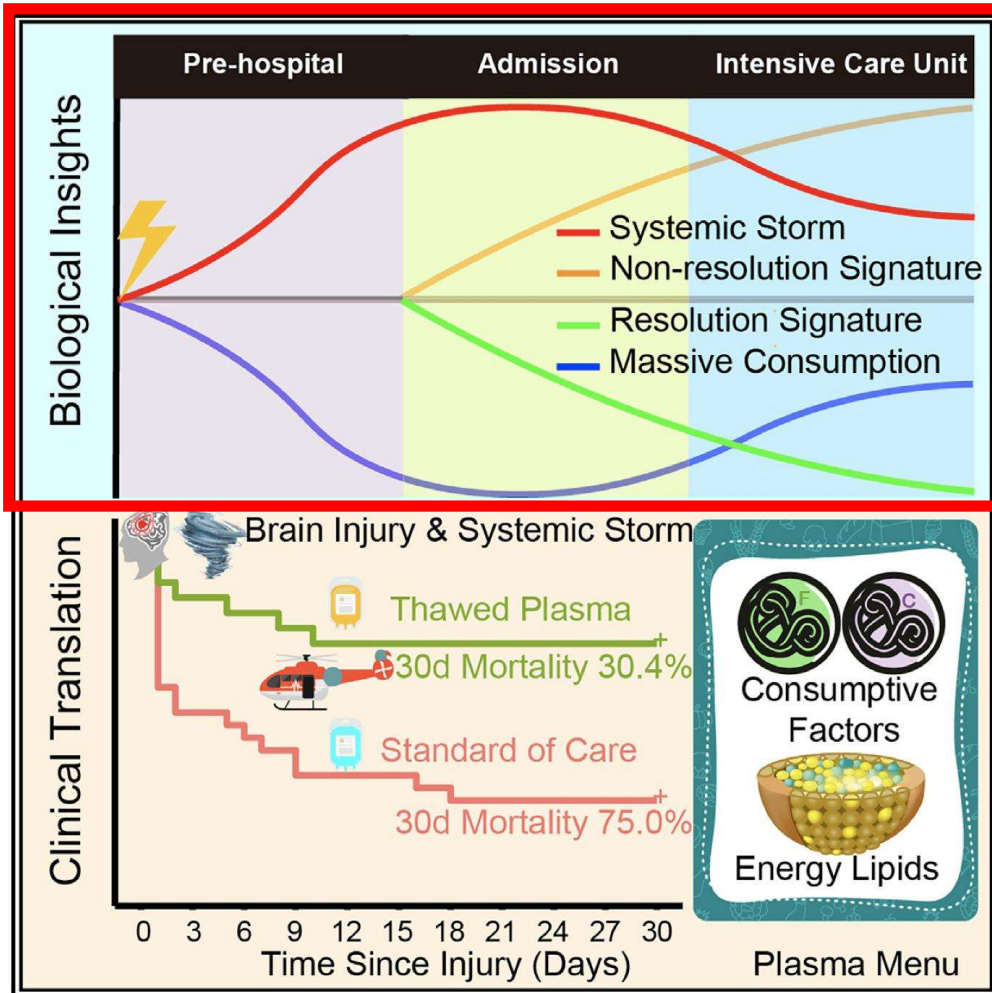
# Endotypes



Wu J, Vodovotz Y, Abdelhamid S, Guyette FX, Yaffe MB, Gruen DS, Cyr A, Okonkwo DO, Kar UK, Krishnamoorthi N, Voinchet RG, Billiar IM, Yazer MH, Namas RA, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Zuckerbraun BS, Johansson PI, Stensballe J, Morrissey JH, Tracy RP, Wisniewski SR, Neal MD, Sperry JL, Billiar TR; PAMPer study group. Multi-omic analysis in injured humans: Patterns align with outcomes and treatment responses. Cell Rep Med. 2021 Dec 21;2(12):100478

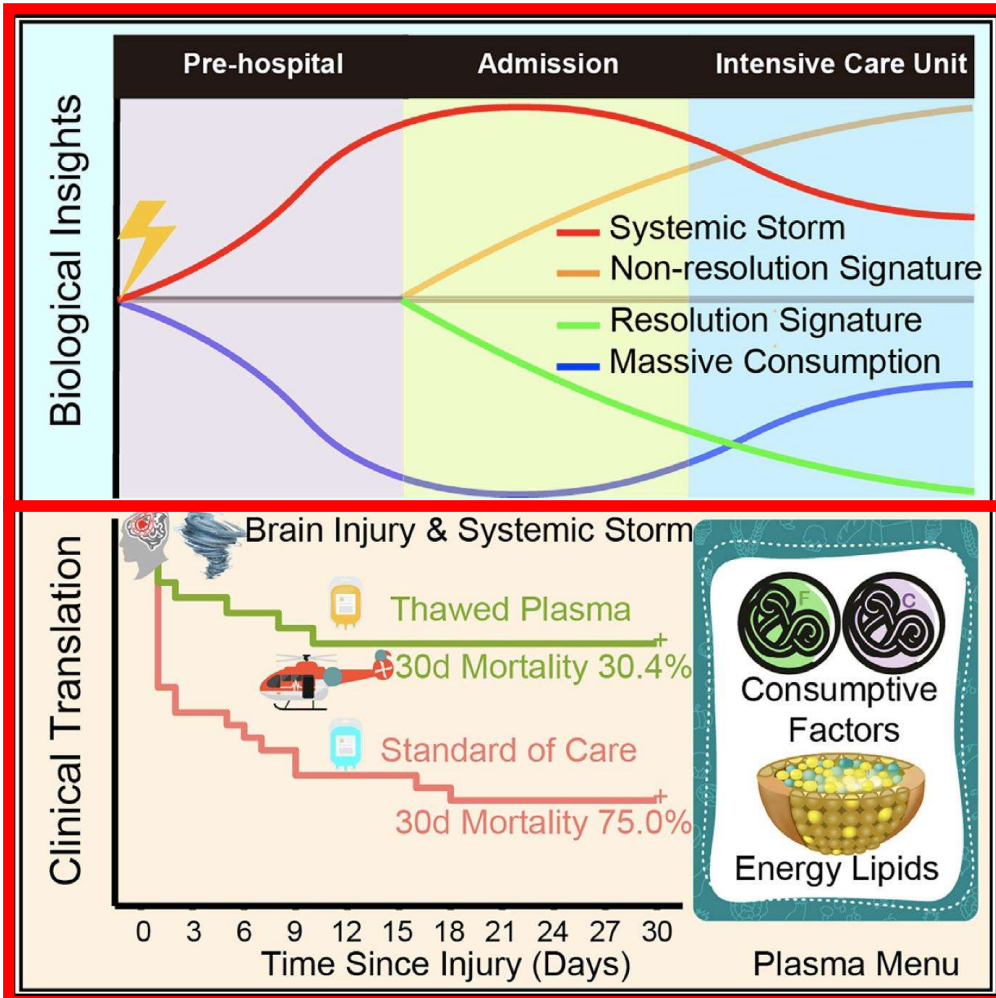


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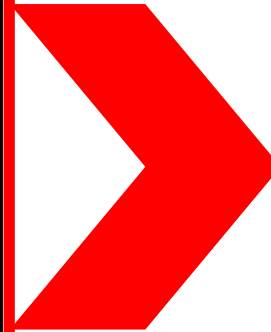
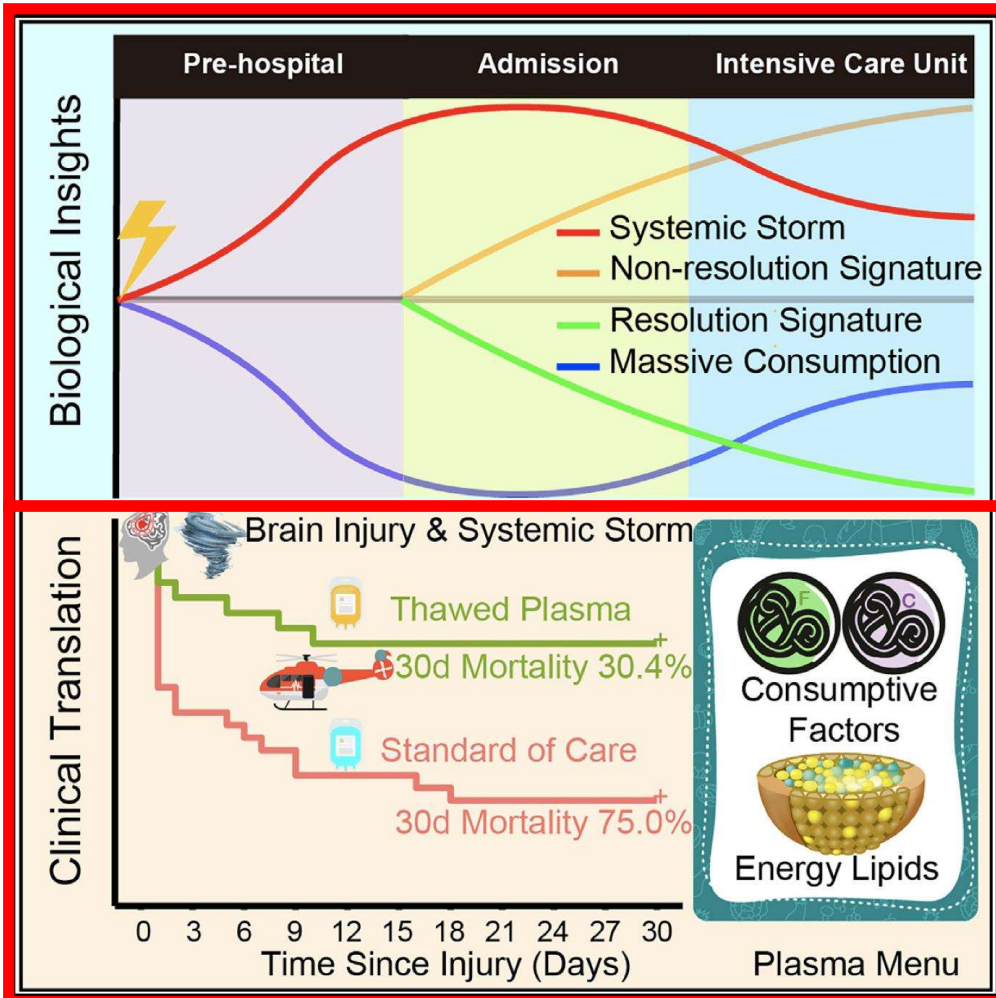
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# Endotypes



## DISCOVERY

Biologic targets

Point-of-care endotyping

Novel therapy development

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# More questions than answers...

- How do we distinguish dynamically the transition between hypocoagulable and hypercoagulable endotypes? Can a patient have both at the same time? Does this start immediately?
- What are the mediators of tissue injury and shock that induce early TIC?
- What is the crosstalk between inflammation and coagulation in TIC?
- What are the relative contributions of each identified mediator and are these biomarkers or mechanistic drivers?
  - *Yes, ENDOTHELIUM, BUT: Does endothelial injury cause TIC or does TIC cause endothelial injury? Or both? Is heparan sulfate involved?*
  - *Yes, PLATELETS, BUT: Are platelets truly dysfunctional? What does ex-vivo platelet impairment really mean?*
  - *Yes, PROTEIN C, BUT: Is this part of bleeding and clotting, or inflammation, or both? What is the right balance?*
  - *Yes, THROMBIN, BUT: What is the appropriate thrombin concentration in TIC and when?*
  - *Yes, FIBRINOGEN, BUT: What is the critical level of fibrinogen that warrants replacement?*
  - *Yes, FACTORS, BUT: What level of factor activity is really needed in TIC and when?*
  - *Yes, FIBRINOLYSIS, BUT: How does time play a role in the fibrinolytic system in TIC and what is the right amount of activity across the phases of TIC?*
- How do we maintain adaptive desired biologic responses and prevent maladaptive undesired responses?
- What ARE the desired adaptive responses?
- What about sex effects? Specific organ injury effects? Other modifiers?
- And, many more...



## QUESTIONS?

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## THE KORNBLITH LAB

### Pictured (left to right):

Alex Fields-Staff scientist

Kim Herrera Rodriguez-SRA

Christopher Lee-CRC

***Lucy Kornblith-Lab Director***

Jake Corvera-Undergraduate student

Aubrey Fife-Undergraduate student

Marcela Matheus-CRC

Carolyn Hendrickson-collaborator

Brenda Nunez-Garcia-Program Manager

Rocco-Resident canine

### Not pictured:

Yale Santos-Data Scientist

Nasima Mayer-PhD candidate

Deanna Lee-CRC

Celine Chou-CRC

Suzanna Chak-CRC

Saigeetha Bhaskar-Graduate student

Nikoo Marageh-Undergraduate student

Jordyn Pinochi-Volunteer

