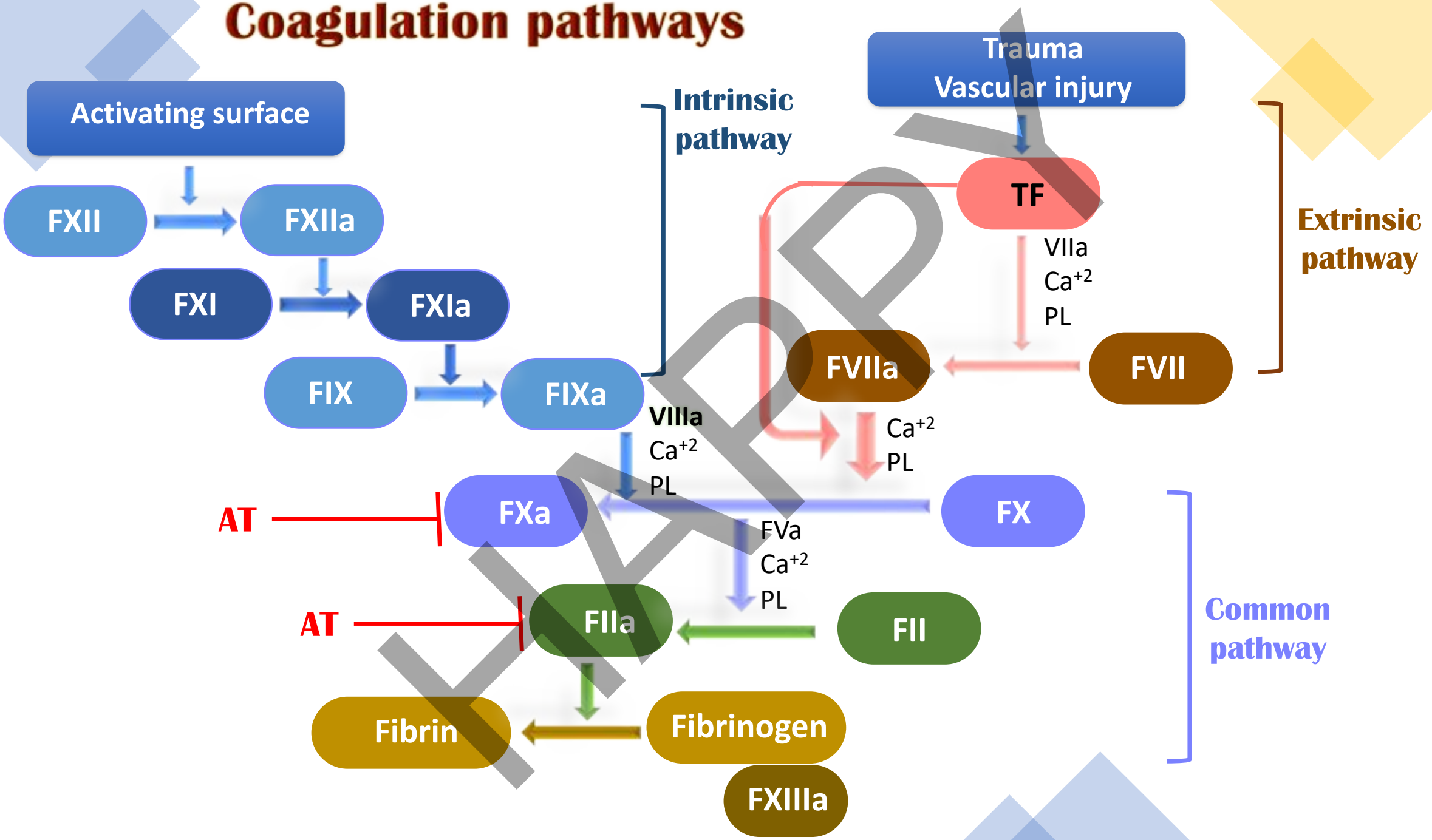
The Interplay Between Complement and Coagulation Systems

Prof.
Happy Sawires (MD, FESPN)
Professor of Pediatrics
Cairo University

Coagulation pathways



AGENDA

Sharing the same crime or well-balanced engagement

The reciprocal interaction (Dancing Together)

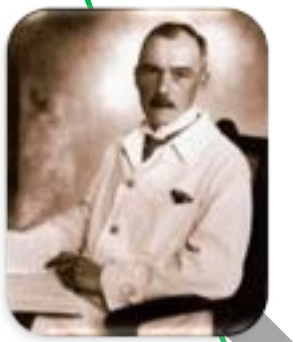
Factor H : the orchestrator of both systems

Clinical consequences of co-activation

Historical Perspectives

The term "complement" was proposed

Paul Ehrlich: German physician-scientist Nobel laureate



Classic theory of coagulation

Paul Morawitz: German Physician

Properdin & alternative pathway

Louis Pillemer: South African moved to USA

Seamless web of body protection

Louis Pillemer and Oscar Ratnoff

Front Immunol 2022;9(13): 918875

Did you observe any similarities between the TWO systems?

Coagulation system	Complement system
• Pathways of activation: intrinsic - extrinsic	• Pathways of activation: Classic – alternative - lectin
• Final common pathway	• Final common pathway
• Factors activated one after one	• Factors activated one after one
• Many regulators	• Many regulators

Sharing | Dancing | Factor H | Clinical

Activation of both the complement & coagulation cascades occurs simultaneously

Trauma with vascular injury

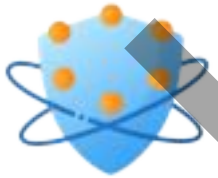
- Activates blood coagulation to secure bleeding & tissue damage
- Activates an inflammatory reaction and complement system

→ **Inflammation**

Aim

Synchronized activity of various biological effectors

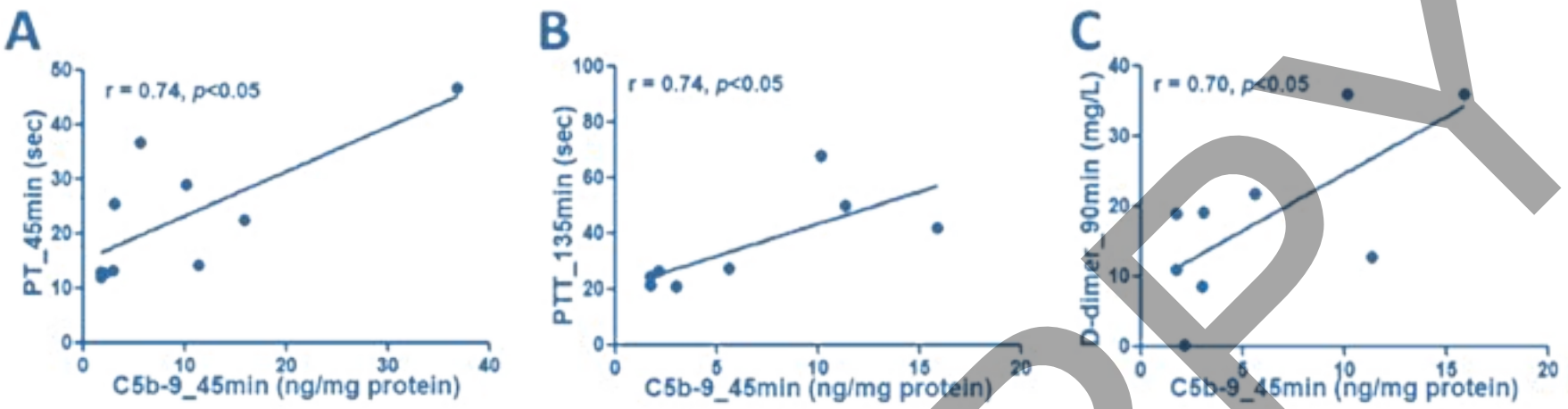
The local formation of thrombi provides a competent barrier to prevent spread of bacteria into circulation



Complement activation acts as a *BRIDGE* between innate & adaptive immunity

Trends Immunol 2007;28(4):184-192.

Correlation between complement activation and coagulation alteration



Trauma Surg Acute Care Open 2022;7:e000927

Activation of both the complement & coagulation cascades occurs simultaneously

01 **Pathogen defense:** by enhancement of immune response & localize inflammation

02 **Wound healing:** by fibrin formation & recruitment of ‘ inflammatory mediators

03 **Tissue repair :** clotting >>> framework for cell migration & CS >>> inflammatory response

PLoS One. 2007 18;2(7):e623

Activation of both the complement & coagulation cascades occurs simultaneously

Complement and coagulation cascades are intended to act locally

Complement at site of infection

Coagulation at site of bleeding

Systemic activation of these cascades

(as a result of failure of the relevant control mechanisms)

CRIME

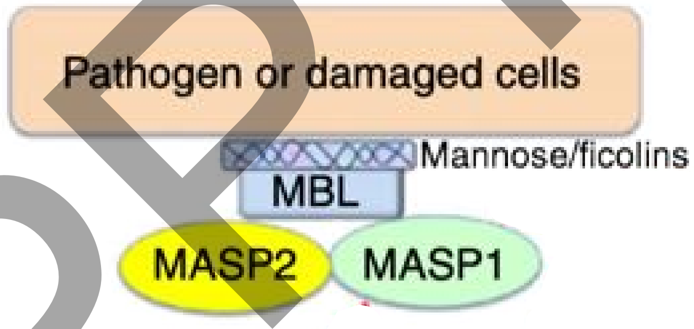
Trends Immunol 2007;28(4):184-192.

Start of the dance

Both cascades have many similarities:

They utilize (as catalysts) serine proteases with similar domain structure

Plos One 2007;2(7):e623.



MASP1 can activate PAR4 on endothelial cell, initiating a proinflammatory & procoagulant pathway

MASP1 cleaves prothrombin, convert fibrinogen into fibrin and activate factor XIII

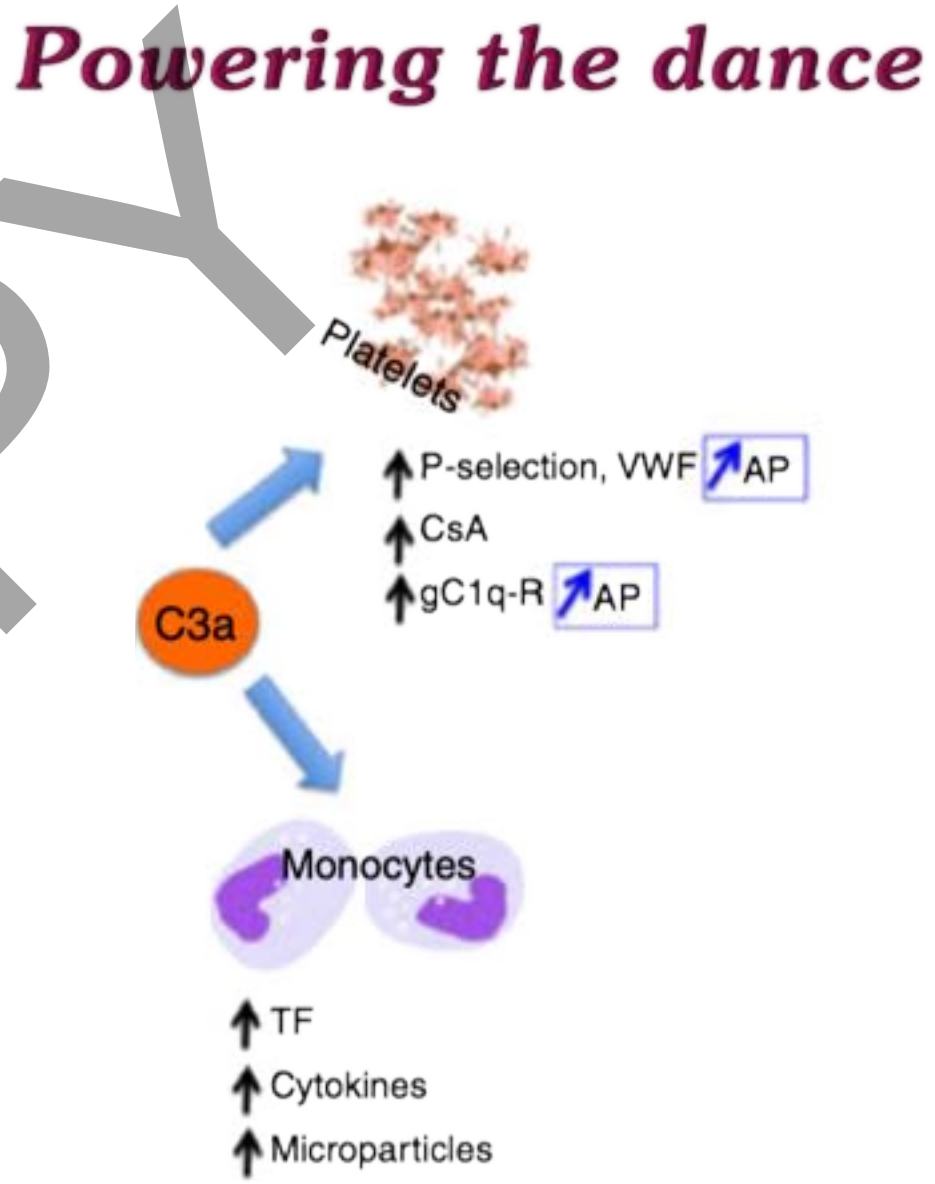
MASP2 cleaves C4 and C2 to generate C4b2a

J Thromb Haemost. 2015 Suppl 1:S121-32

Potent triggers of inflammation, anaphylatoxins

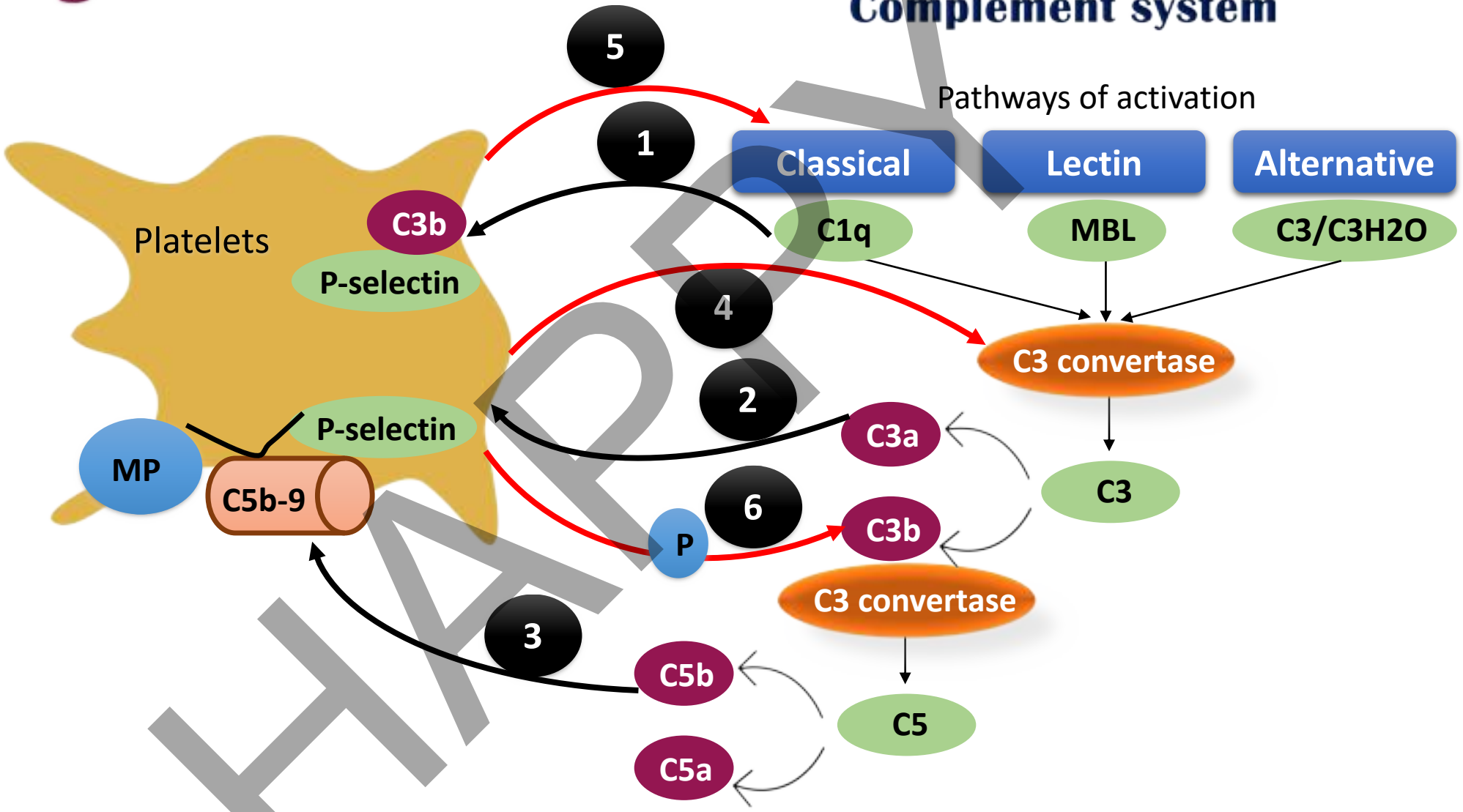
C3a and C5a

Mediated via interaction with their receptors C3aR and C5aR



J Thromb Haemost. 2015 Suppl 1:S121-32

Dancing together



Trends Immunol 2007;28(4):184-192.

Dancing together

Endothelial

Neutrophils

Monocytes

TF

TF

TF

Extrinsic pathway

FVIIa

FVII

FXa

FX

FIIa

FII

FXIIIa

Fibrinogen

Fibrin

Complement system

Pathways of activation

Classical

Lectin

Alternative

C1q

MBL

C3/C3H2O

C3 convertase

C3a

C3

C3b

C3 convertase

C5b

C5

C5a

Trends Immunol 2007;28(4):184-192.

Dancing together

Intrinsic pathway

FXII → FXIIa

FXI → FXIa

FIX → FIXa

FXIIa → FXI

FXIa → FIX

FIXa → FX

FX → FXa

FXa → FII

FII → FIIa

FIIa → FXIIIa

FXIIIa → Fibrin

Fibrinogen → Fibrin

Complement system

Pathways of activation

Classical — C1q

Lectin — MBL

Alternative — C3/C3H2O

C1q, MBL, C3/C3H2O → C3 convertase

C3 convertase → C3

C3 → C3a + C3b

C3b → C3 convertase

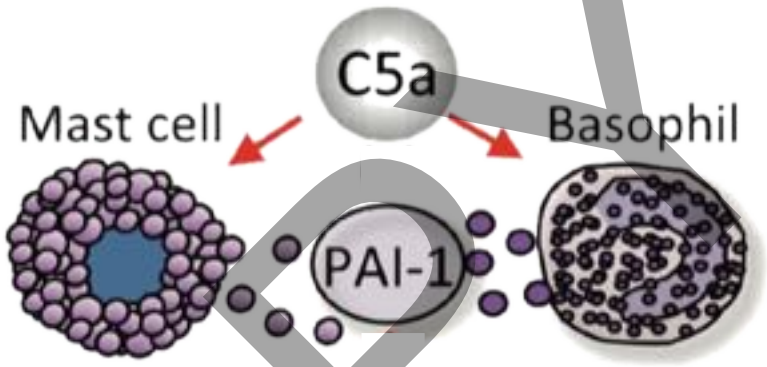
C3 convertase → C5

C5 → C5a + C5b

J Mol Med (Berl) 2013;91(11):1257-71.

The last dance

Fibrinolysis



C5a stimulates production of PAI-1 in mast cells and basophils

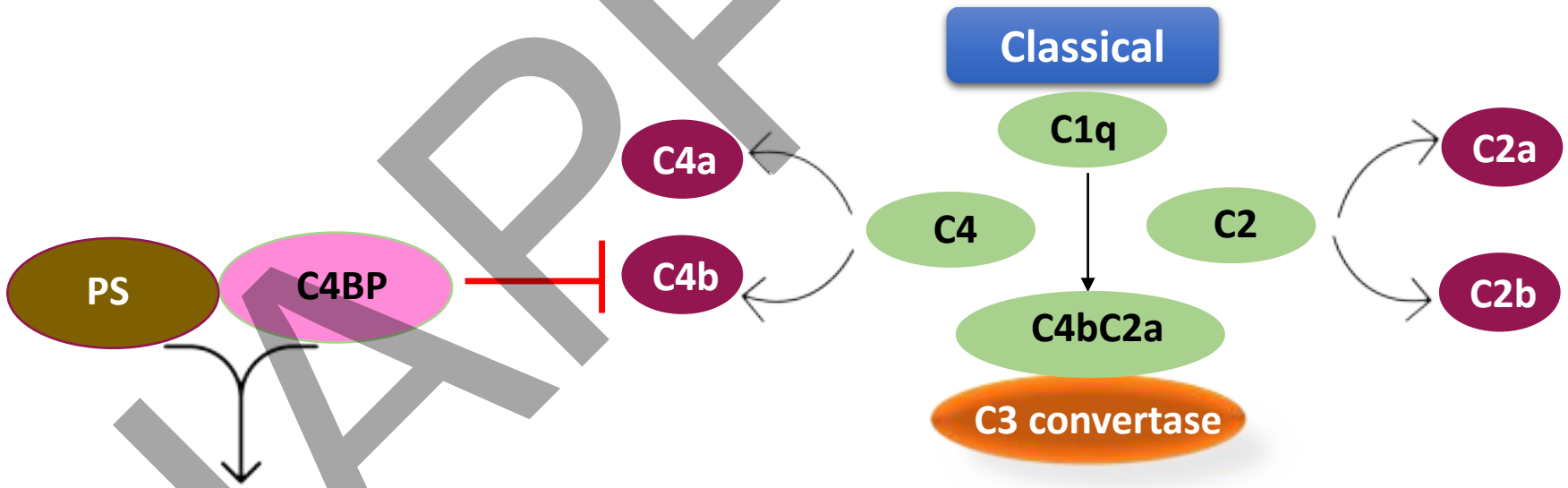
PAI-1 suppresses generation of plasmin and breakdown of fibrin

Iran J Kidney Dis. 2013;7(5):340-5

Inhibition of anticoagulation

Complement system

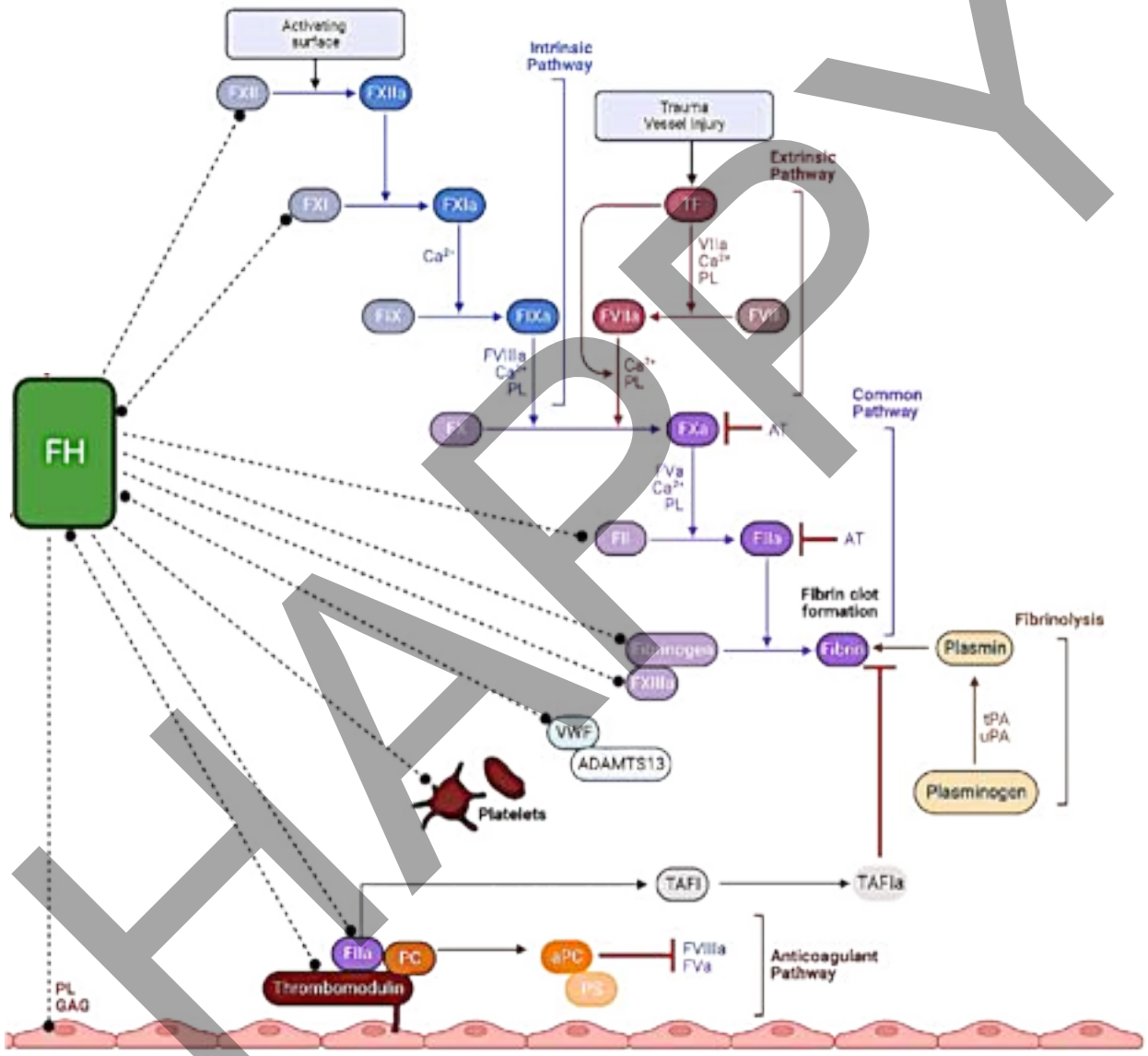
Pathway of activation



Loss of PS cofactor activity, thereby decreasing its anticoagulant effects

Blood. 2004;103:1192-1201

Factor H: the orchestrator of the dance



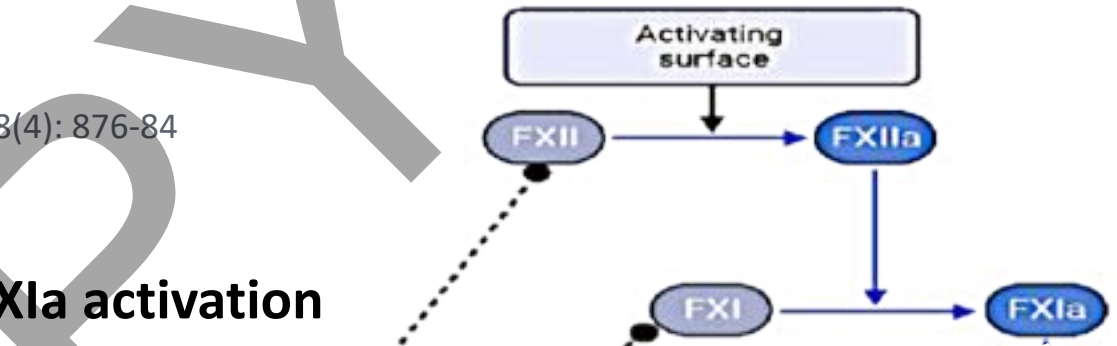
Factor H: the orchestrator of the dance

Factor H binding inhibits FXIIa activation

J Thromb Haemost. 2020; 18(4): 876-84

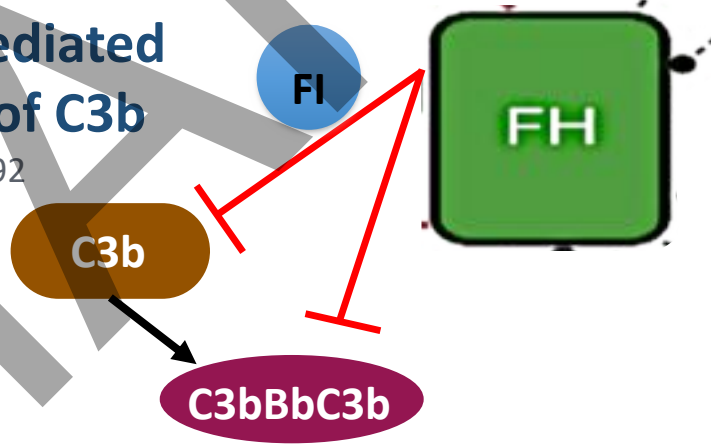
Factor H binding inhibits FXIa activation

J Immunol. 2021; 206(8): 1784-92



Factor XIa reduces Factor H-mediated decay of C3bBP and cleavage of C3b

J Immunol. 2021; 206(8): 1784-92



Factor H: the orchestrator of the dance

Physiological thrombin & fibrinogen do not affect Factor H dependent regulation of complement

bioRxiv 2021.07.22.452893

1. Factor H acts a cofactor for thrombin by enhancing fibrin generation.
2. In knockout $CFH^{-/-}$ mice, absence of Factor H prolongs bleeding time

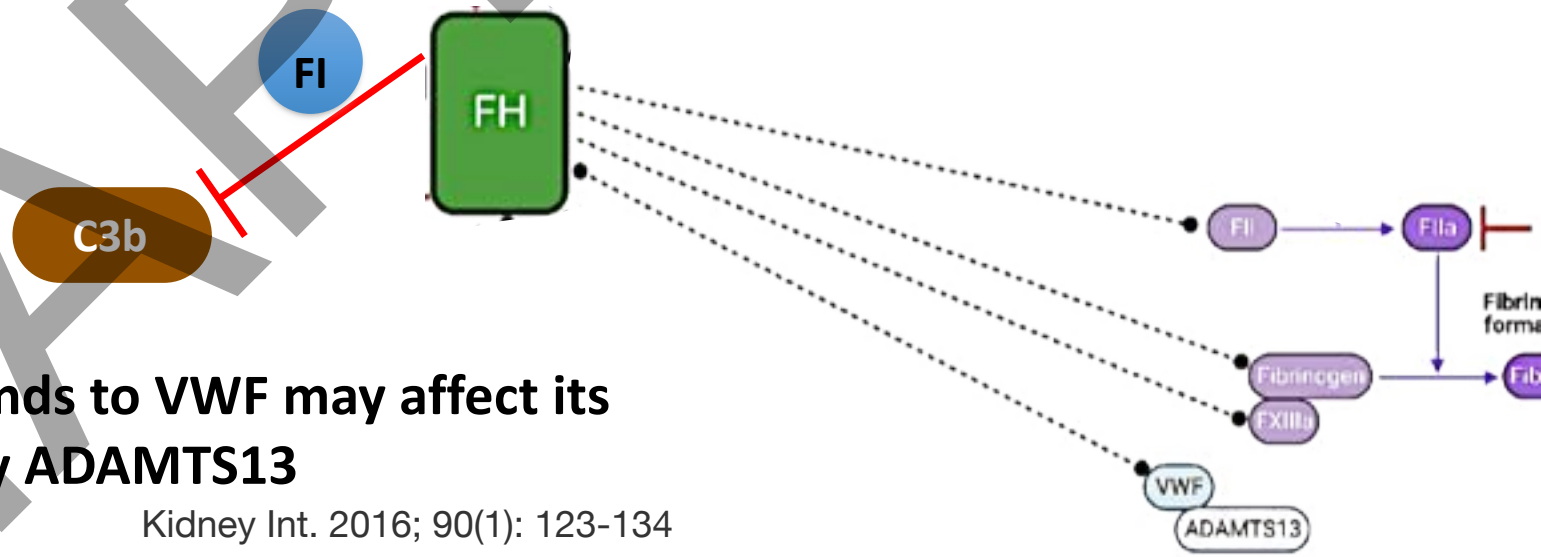
bioRxiv 2021.07.22.452893

In presence of Factor H, pure protein fibrin clots have larger fibers

bioRxiv 2021.07.22.452893

VWF enhances Factor H/Factor I mediated inactivation of C3b

Kidney Int. 2016; 90(1): 123-134



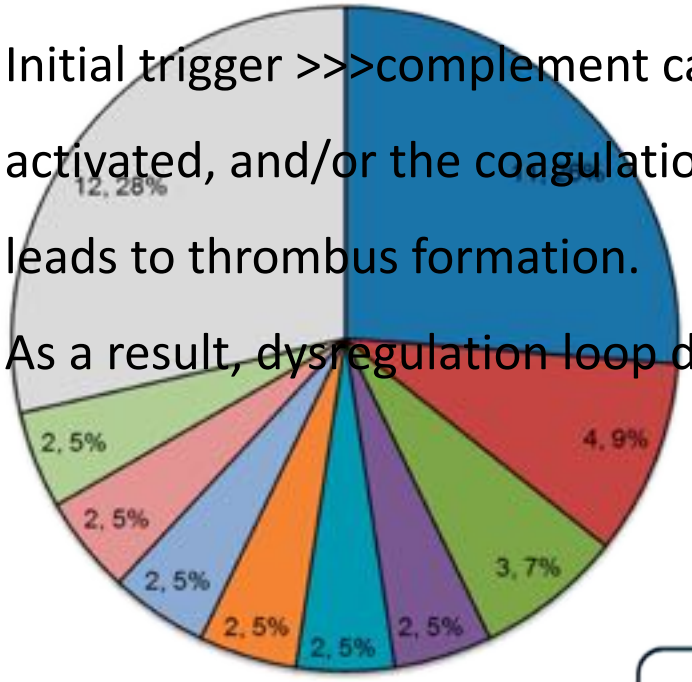
Factor H binds to VWF may affect its cleavage by ADAMTS13

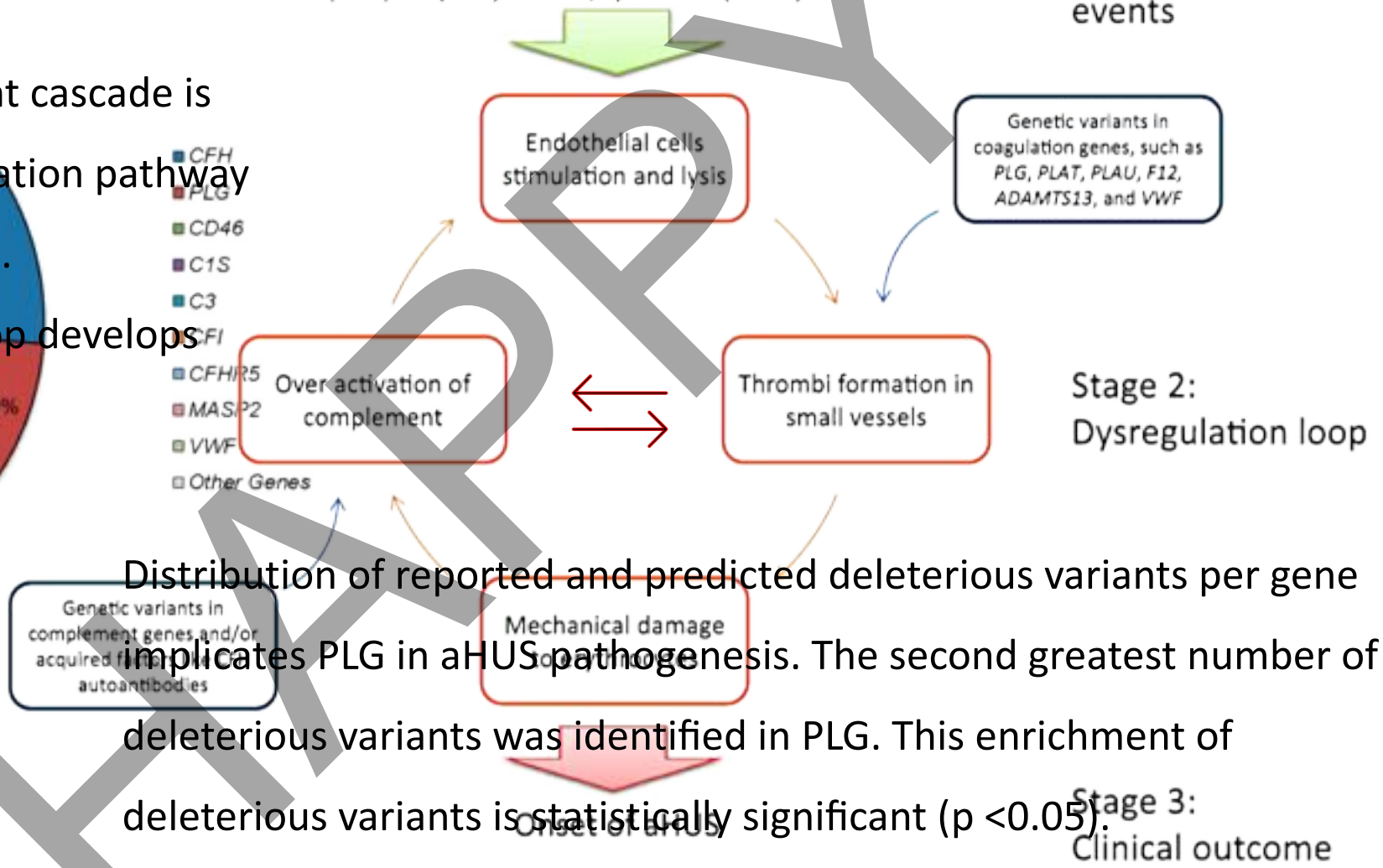
Kidney Int. 2016; 90(1): 123-134

1 Atypical HUS

Initial trigger >>>complement cascade is activated, and/or the coagulation pathway leads to thrombus formation.

As a result, dysregulation loop develops

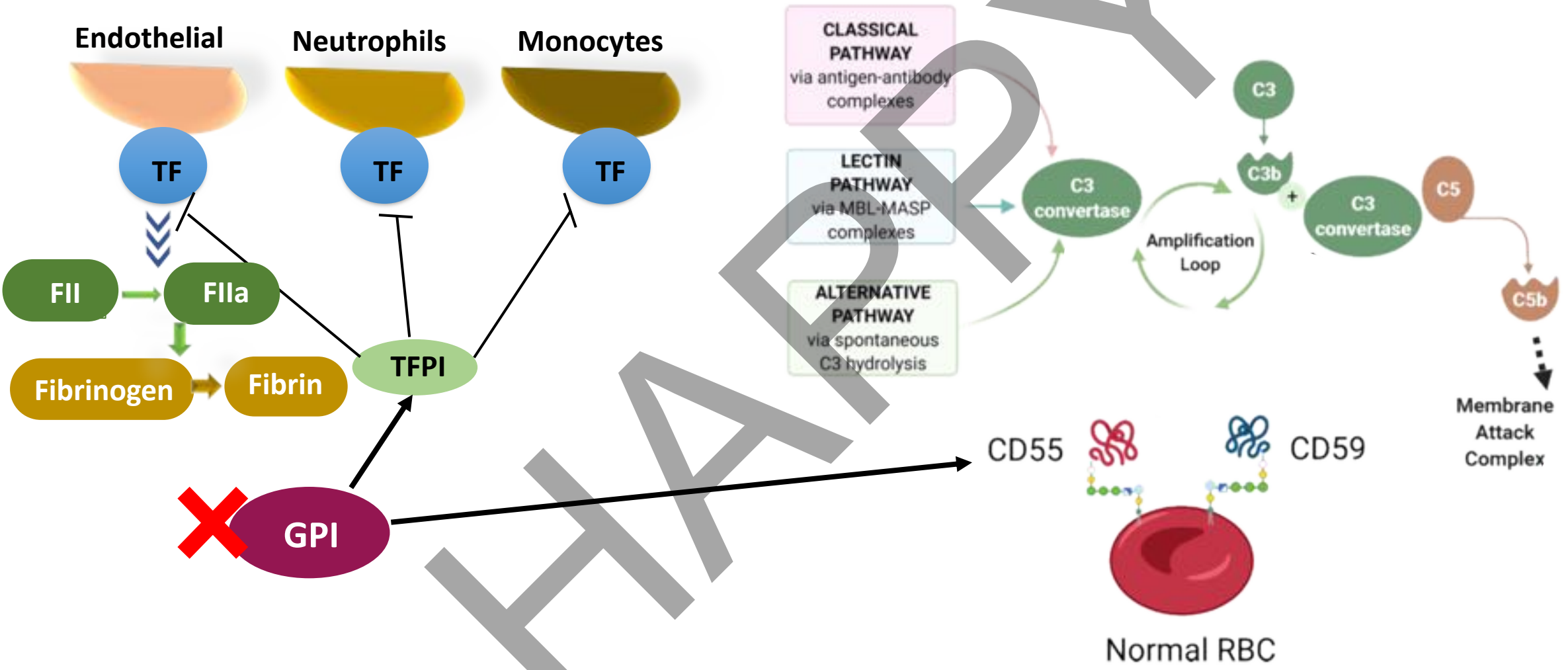




Distribution of reported and predicted deleterious variants per gene implicates PLG in aHUS pathogenesis. The second greatest number of deleterious variants was identified in PLG. This enrichment of deleterious variants is statistically significant ($p < 0.05$).

J Am Soc Nephrol 2014; 25(1): 55-64

2 Paroxysmal Nocturnal Hemoglobinuria (PNH)



Front Immunol 2022; 12: 830172

3 Anti-phospholipid Syndrome (APS)

Animals made deficient in complement were protected from thrombotic complications of infused APLA

Lupus 2012, 21:1497-1505

Inhibiting C5 activation with an anti-C5 monoclonal antibody prevents the thrombocytopenia that is induced by APLA

Ann. N. Y. Acad. Sci. 2005; 1051: 413–420

APLA activate complement on trophoblasts leading to C5a generation

C5a (via C5aR) on neutrophils resulting in upregulation of TF >>> Coagulation

Br J Haematol. 2018;180(6):782-798

Others

Sepsis , SIRS

Hered. angioedema

COVID

ANCA-vasculitis

SLE

AIHA

Br J Haematol. 2018;180(6):782-798

How to target this complex system without compromising other components?

- Complement & coagulation systems are 2 inter-related systems tend to act locally for protection against infection & bleeding.
- The two systems orchestrating together with many common regulators.
- Systemic activation of both systems result in many diseases (aHUS, PNH, APS, etc…)