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ILLUSTRATED REVIEW

rpth research & practice in thrombosis & haemostasis

Fibrinogen and fibrin: An illustrated review

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Abstract

Since its discovery over 350 years ago, studies of fibrinogen have revealed remarkable characteristics. Its complex structure as a large (340 kDa) hexameric homodimer supports complex roles in hemostasis and homeostasis. Fibrinogen synthesis is regulated at the transcriptional and translational levels, undergoing both constitutive (basal) secretion from liver, and inducible upregulation in response to inflammatory events. In addition, alternative splicing yields fibrinogen variants with unique properties and contributions to coagulation biochemistry. During coagulation, fibrinogen conversion to fibrin occurs via thrombin-mediated proteolytic cleavage that produces intermediate protofibrils and then mature fibers that provide remarkable biochemical and mechanical stability to clots. Fibrin formation, structure, and stability are regulated by various genetic, biochemical, and environmental factors, allowing for dynamic kinetics of fibrin formation and structure. Interactions between fibrinogen and/or fibrin and plasma proteins and receptors on platelets, leukocytes, endothelial cells, and other cells enable complex functions in hemostasis, thrombosis, pregnancy, inflammation, infection, cancer, and other pathologies. Disorders in fibrinogen concentration and/or function increase risk of bleeding, thrombosis, and infection. This illustrated review covers fundamental aspects of fibrinogen and fibrin biology, biochemistry, biophysics, epidemiology, and clinical applications. Continued efforts to enhance our understanding of fibrinogen and fibrin in these processes are likely to advance treatment and prevention of many human diseases.

KEYWORDS

factor XIII, fibrin, fibrinogen, fibrinolysis, hemostasis, infection, thrombosis

Essentials

- Fibrinogen is a complex glycoprotein present in high concentrations in plasma.
- Fibrinogen is converted to fibrin, which stabilizes blood clots and promotes hemostasis.
- Fibrin structure and mechanical properties are modified by genetic and environmental factors.
- Fibrin(ogen) also contributes to thrombosis, host defense, inflammation, and wound healing.

Fibrinogen and Fibrin: an Illustrated Review

Once upon a time.....

If you enjoy a pretty sight, examine this blood [clot] with a microscope. You will see a fibrous texture, and a network of nerve-like threads, where small meshes and honeycomb-like interstices develop...From these and similar cases, we may surmise that Polyps appear when the mass of blood loses part of its proper fluid nature.[1]

Early microscope

1666: Marcello Malpighi discovers fibrin

1788: Antoine Fourcroy names "fibrin"

1838: Jacob Berzelius coins the term "protein"

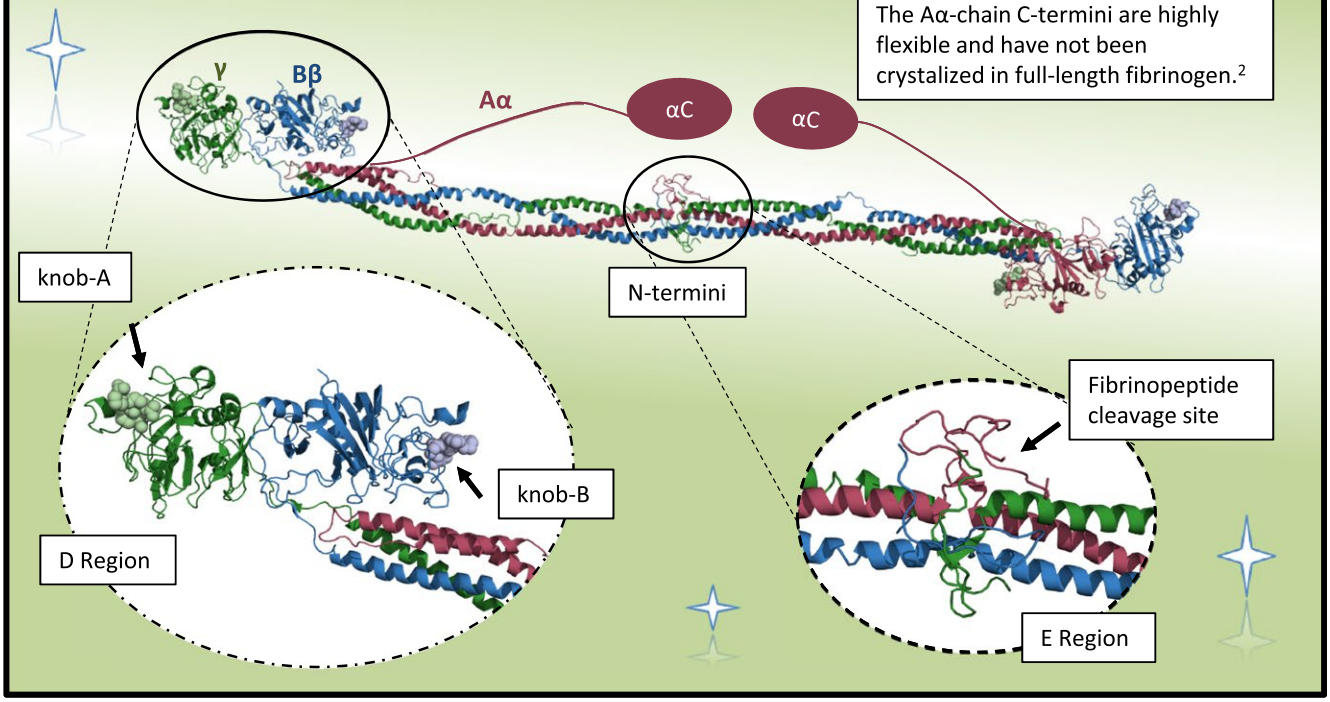
1847: Rudolf Virchow names "fibrinogen"

1872: Alexander Schmidt states fibrinogen-to-fibrin conversion is an enzymatic process

1879: Olof Hammarsten purifies fibrinogen

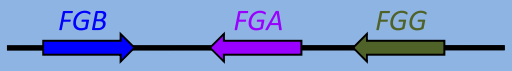
Fibrinogen is a hexamer with 2 each of 3 polypeptide chains: 2 Aα-, 2 Bβ-, and 2 γ-chains.

The Aα-chain C-termini are highly flexible and have not been crystalized in full-length fibrinogen.[2]

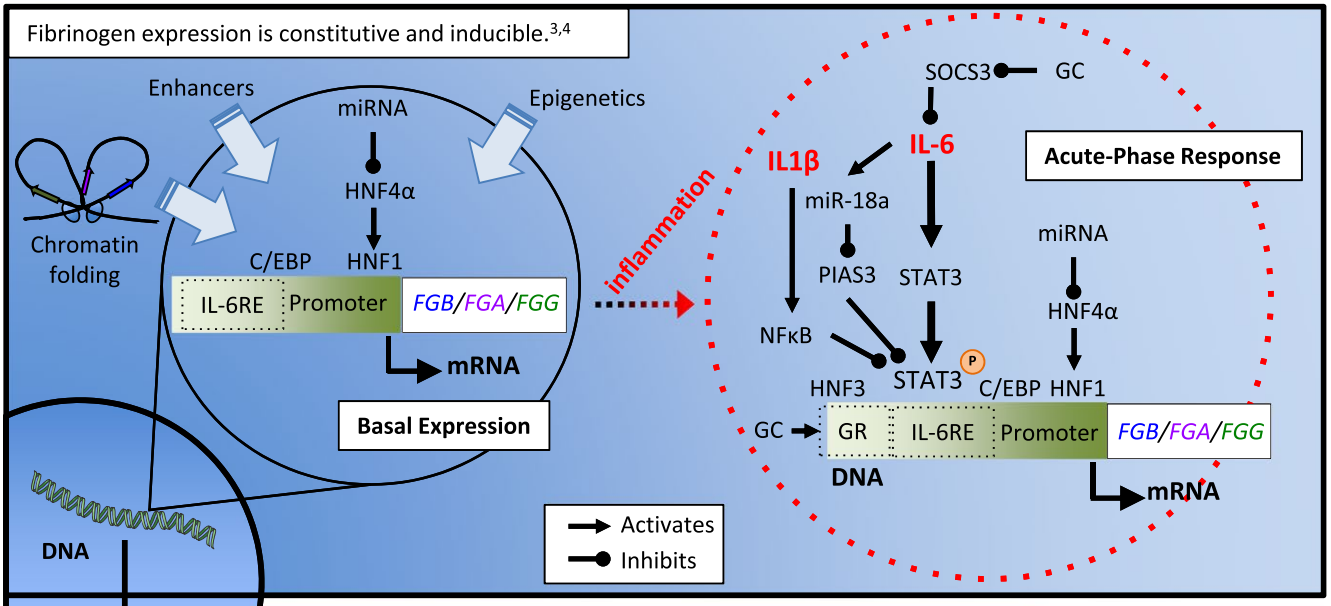


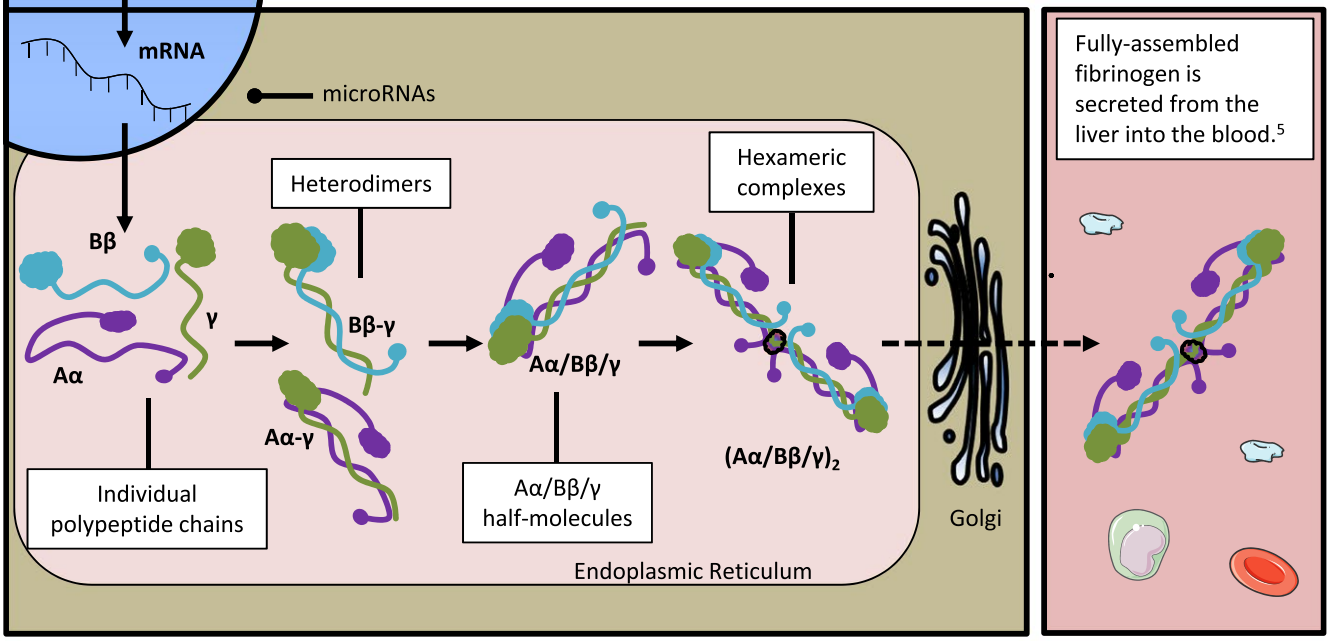
Fibrinogen is expressed primarily in hepatocytes and is regulated transcriptionally and post-transcriptionally.

The fibrinogen Aα, Bβ, and γ chains are encoded by a 3-gene cluster on the long arm of human chromosome 4.



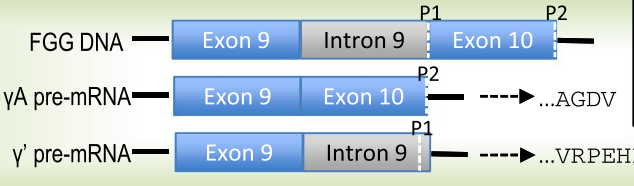
Fibrinogen expression is constitutive and inducible.[3,4]





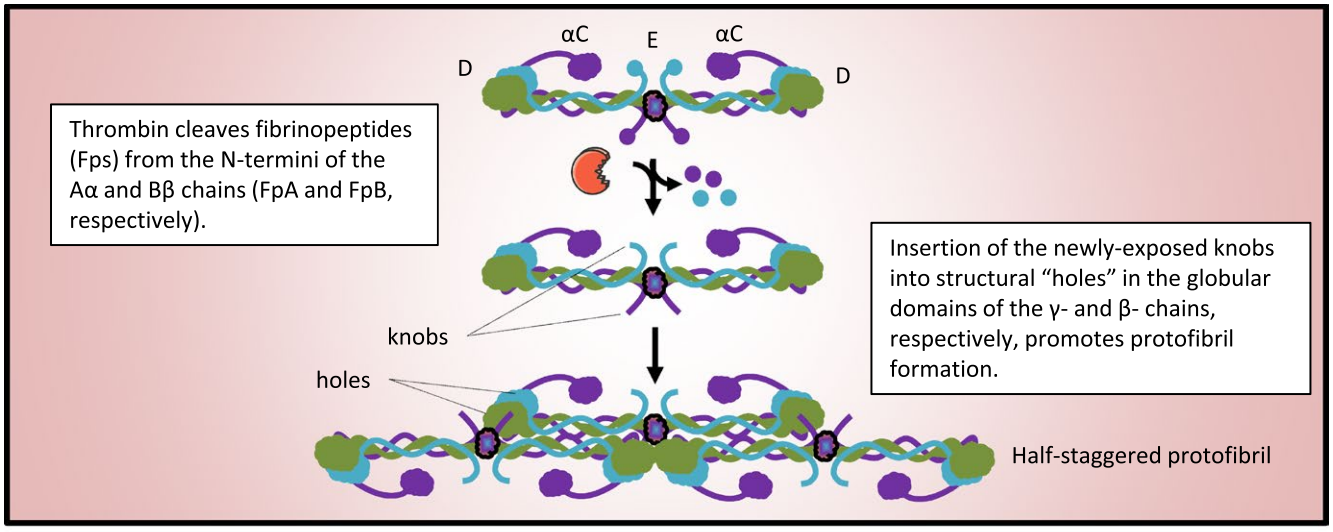
Fully-assembled fibrinogen is secreted from the liver into the blood.[5]

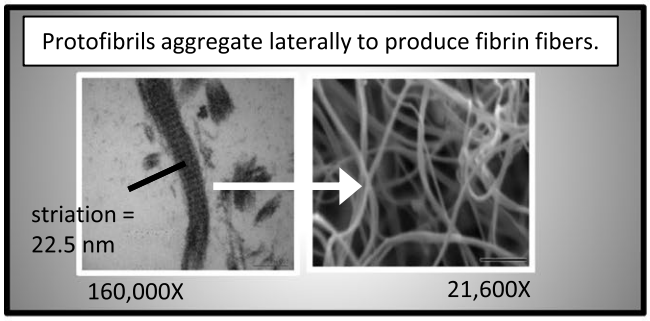
Common variant with biological relevance: Fibrinogen undergoes alternative splicing, producing an elongated γ-chain (γ').

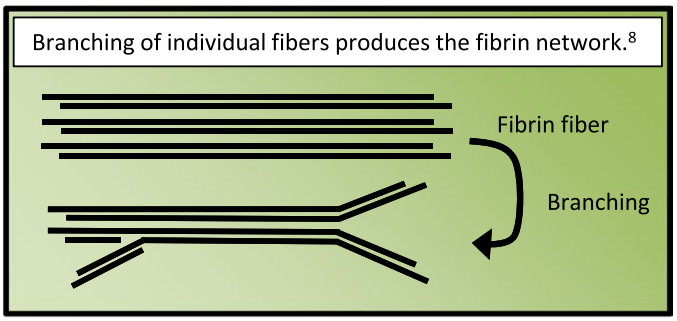


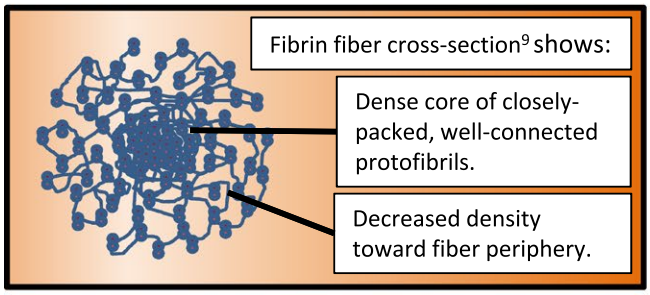
Molecules containing γ'-chains circulate mostly as γA/γ' and comprise 8-15% of total fibrinogen in healthy individuals.[6,7]

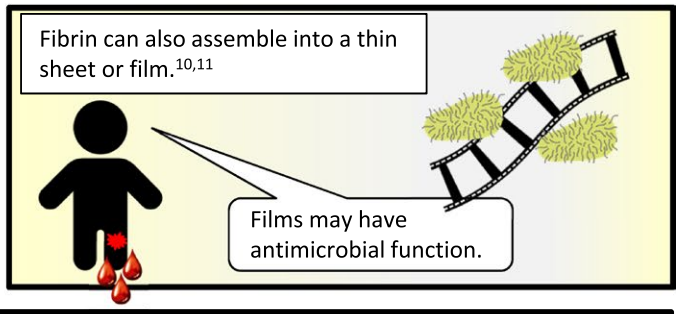
Fibrinogen is converted to fibrin by thrombin-mediated proteolysis.



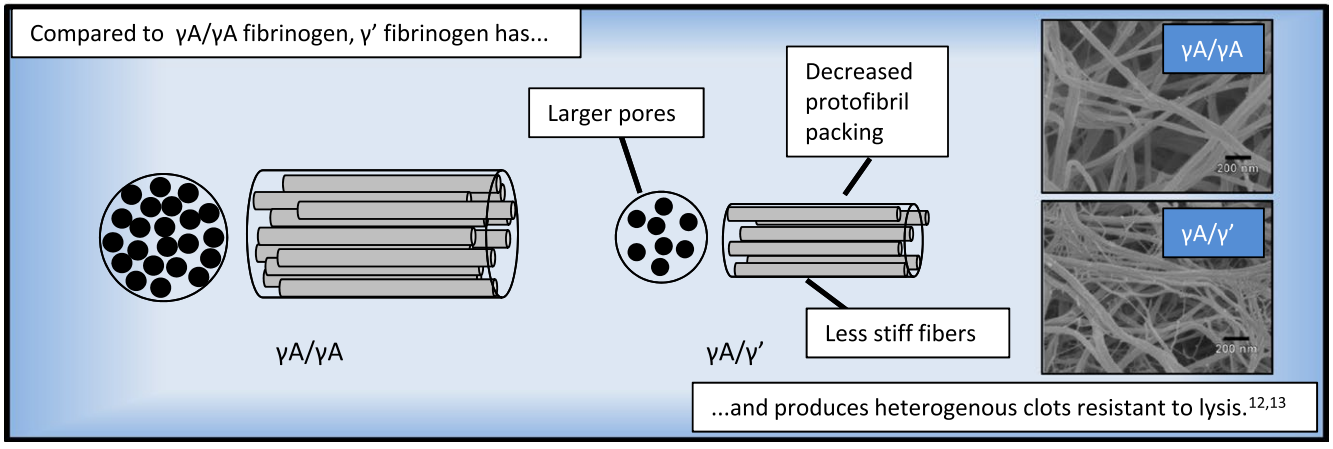




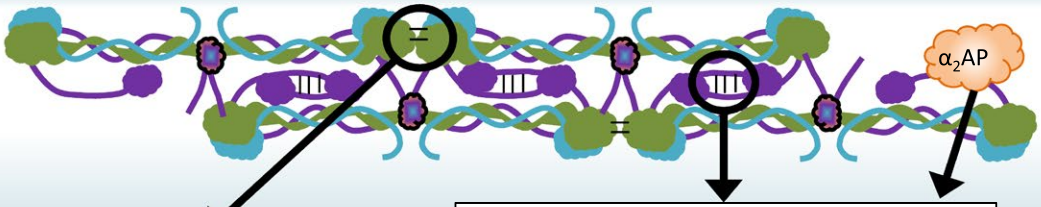




Alternatively-spliced γ' fibrinogen alters fibrin protofibril packing and clot structure.



Factor XIII (FXIII) generates ε-(-γ-glutamyl)-lysyl covalent bonds, protecting clots against lysis and mechanical disruption.

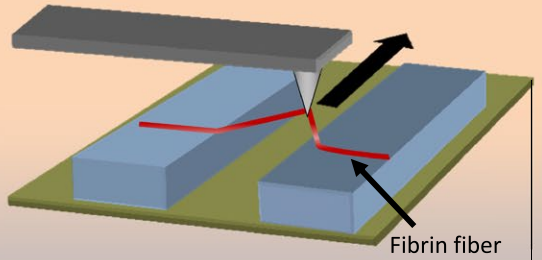


γ-chain crosslinks: longitudinal within a protofibril increase fiber density and stiffness.[14,15]

α-chain crosslinks: transverse between fibrin strands increase stiffness, decrease inelastic deformation, increase fiber thickness, promote red cell retention during clot contraction, and decrease clot lysis.[14,16-19]

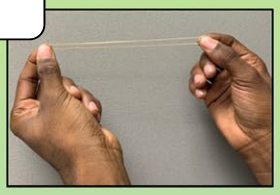
Crosslinking α_2-antiplasmin, TAFI, and fibronectin to fibrin ensures they are retained in the clot during contraction.[20-22]

Fibrin has remarkable biomechanical characteristics.



Material	Extensibility$_{max}$
Fibrin fiber	**>330%**
Fibrin network	100-200%
Spider silk	**270%**
Elastin	150%
Collagen	12-16%
Fibronectin	200-300%
Microtubules	≤20%

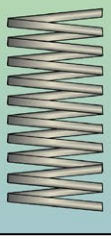
Fibrin is stretchy, like a rubber band…



…and has viscoelastic properties.[19,23]

Viscous

+



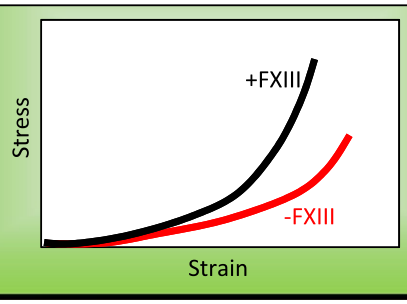
Elastic

Viscosity – likely the result of slippage of protofibrils under force. Fiber re-positioning brings new binding sites into alignment, enables new interactions that permit irreversible deformation without structural damage.

Elasticity – the result of reversible elongation of flexible, unstructured α-helical coiled-coils into β-sheets, and unfolding of γ-chain C-termini and αC regions.

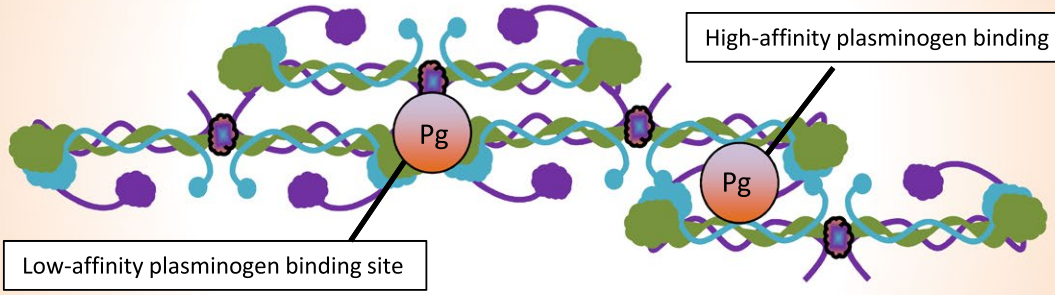
Clot mechanical properties originate from its multi-scale hierarchical structure, governed by single fiber properties (orientation, stretching, bending, buckling).[24]

Fibrin stiffens in response to shear, tension, or compression.[25]

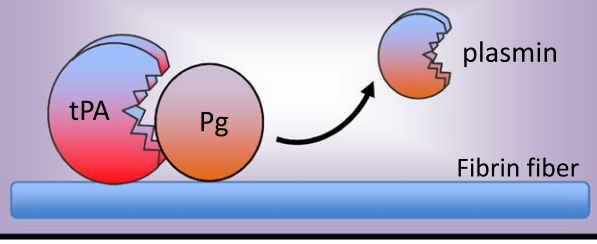


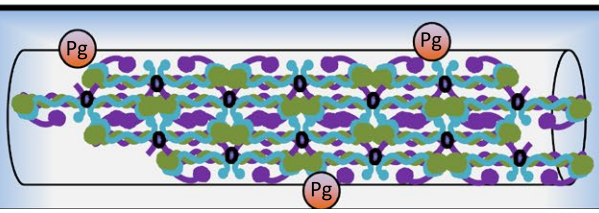
Fibrin is a cofactor for tissue plasminogen activator (tPA)-mediated plasmin generation.

Plasminogen (Pg) binding sites are cryptic in fibrinogen and become exposed during fibrin polymerization.[26]

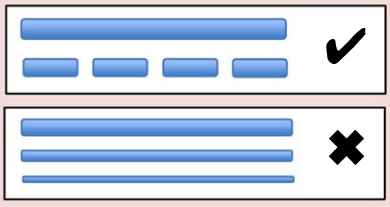


Fibrin also binds tPA, localizing it with plasminogen.





Due to tight protofibril packing, it is unlikely that lytic enzymes can diffuse through fibers.[27]



Fibers are lysed transversely, not longitudinally.[28,29]

Internal lysis: Fibrinolytic components circulating in blood become incorporated into clots and lyse clots from the inside, out.

External lysis: Plasminogen activators are presented to the clot edge during thrombolytic therapy.

Thinner fibers lyse faster than thick fibers, but clots with thick fibers are typically more susceptible to lysis.[28,30]

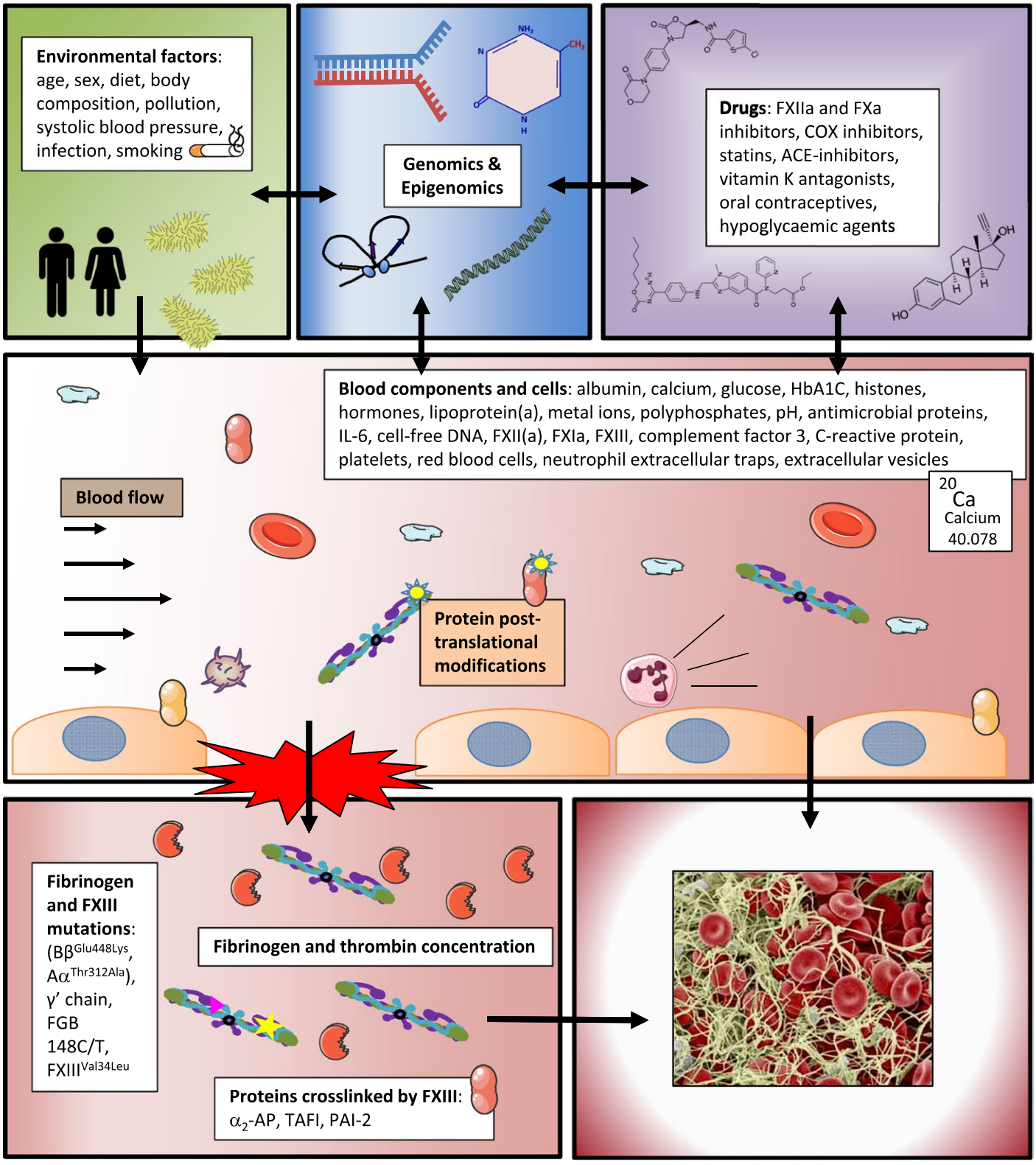
Individual Fibers

- Thin fibers have fewer protofibrils, so fewer molecules must be cleaved to transect a fiber.[31]
- In thin fibers, molecules are more densely-packed, so tPA and plasmin binding sites are closer together to facilitate plasmin crawling.[9]
- Thin fibers have increased tPA activation of plasminogen.[32]
- Thick fibers are under more tension than thin fibers. Tension is lost during lysis, leading to elongation which hinders lysis.[33]
- tPA binds thick fibers longer, decreasing lysis.[34]

Whole Clots

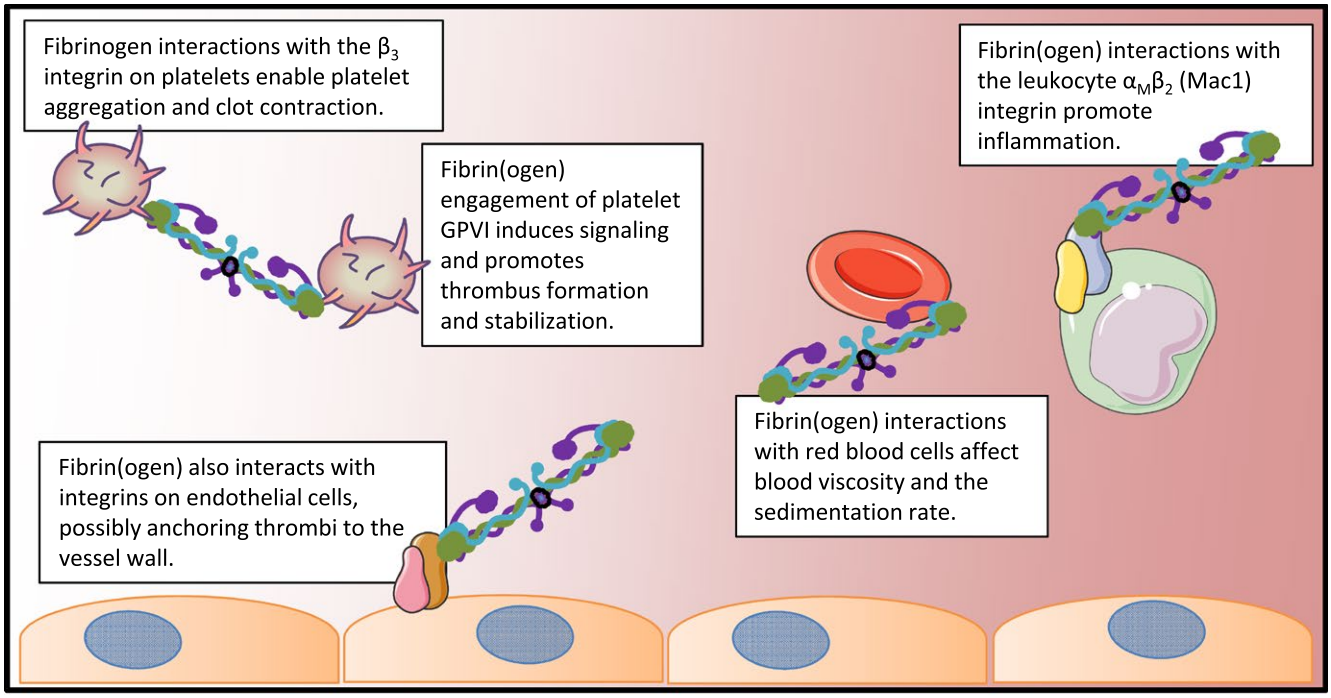
- Dense clots with small pores and thin fibers have decreased penetration of lytic enzymes.[28]
- Crosslinking increases α_2-antiplasmin in contracted clots and alters mechanical properties, decreasing lysis.[18]
- Tangential flow aligns fibers and decreases lysis.[35]
- Perpendicular flow improves penetration of enzymes into the clot and increases lysis.[36]
- Platelet-mediated clot contraction expels unbound lytic proteins (e.g., tPA, plasminogen), and decreases tPA-fibrin binding, decreasing lysis.[37]
- Fiber stretching decreases plasminogen activation and access to plasmin cleavage sites.[38]

Multiple factors influence fibrin clot formation, structure, and function. These may be direct, or indirect by altering fibrinogen or thrombin concentration or induction of post-translational modifications (reviewed in [39-44]).

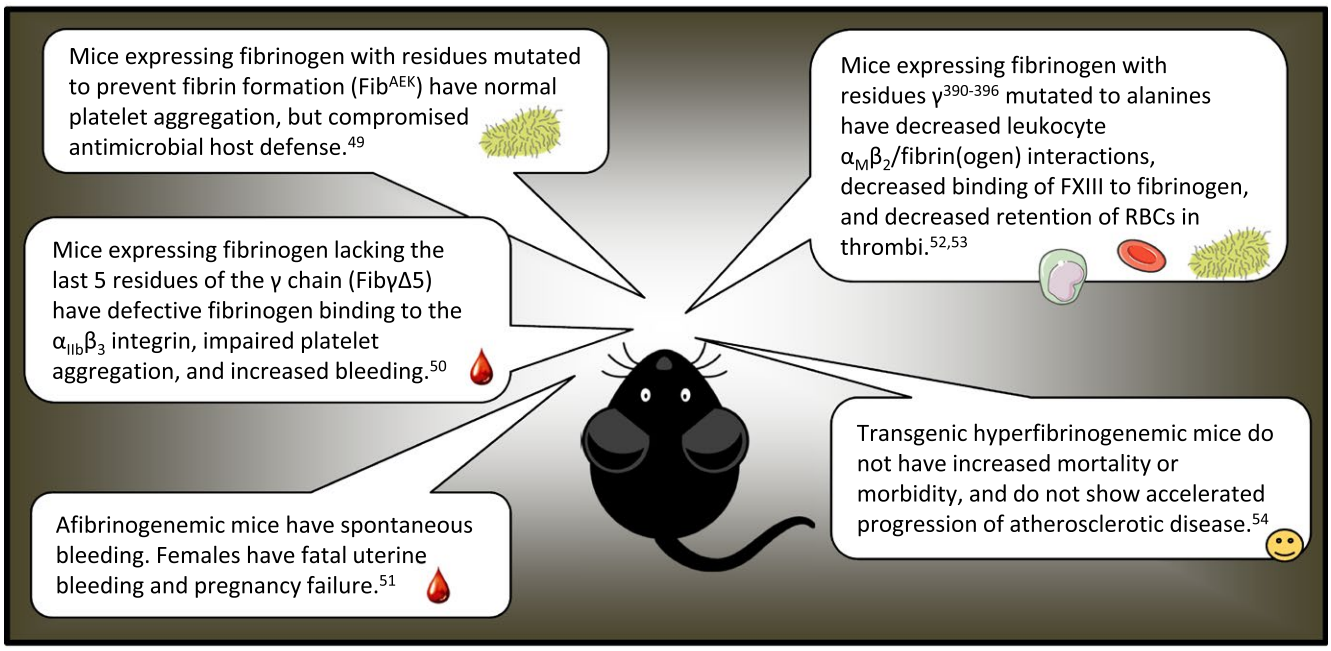


↔ Additional interactions between these factors also exist

Fibrin(ogen) interactions with cells mediate hemostasis, thrombosis, and inflammatory responses.[45-48]

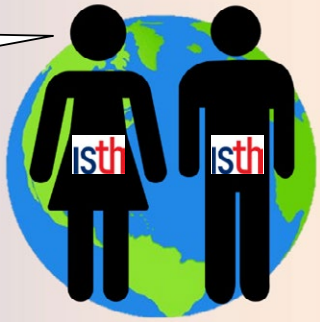


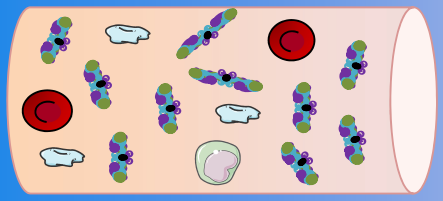
There are mouse and fish models of a-, dys-, and hyperfibrinogenemia.



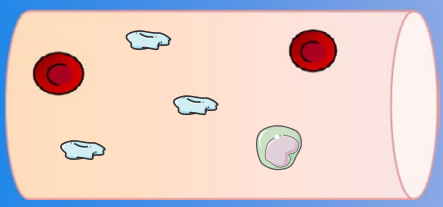
Fibrinogen abnormalities are associated with both bleeding and thrombosis.[57,58]

In 2018, the Scientific Subcommittee of the International Society on Thrombosis and Haemostasis reclassified the congenital fibrinogen disorders.[57]

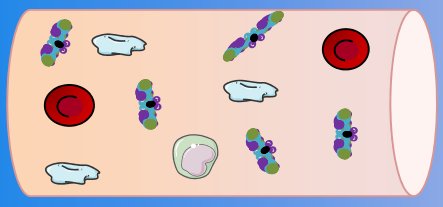




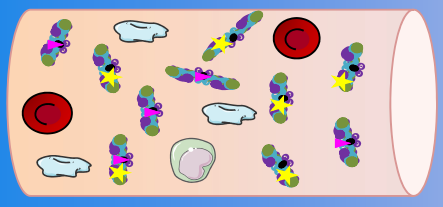
Normal: 2 – 4 g/L



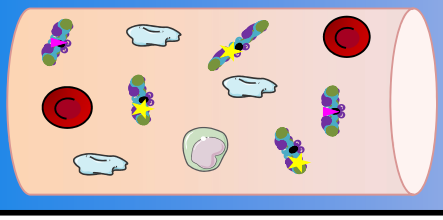
1. Afibrinogenemia
1A Patients with a bleeding phenotype or asymptomatic
1B Afibrinogenemia with thrombotic phenotype



2. Hypofibrinogenemia
2A Severe: Functional fibrinogen < 0.5 g/L
2B Moderate: Functional fibrinogen 0.5 – 0.9 g/L
2C Mild: Functional fibrinogen 1 g/L to lower limit of normal
2D Hypofibrinogenemia with fibrinogen storage disease: Familial, with histologically-proven accumulation of fibrin in hepatocytes



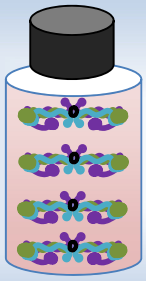
3. Dysfibrinogenemia
3A Patients with bleeding or thrombosis not fulfilling criteria 3B, or asymptomatic individuals
3B Carriers of a thrombotic fibrinogen mutation or suffering from thrombotic events with first-degree familial thrombotic history without other thrombophilia

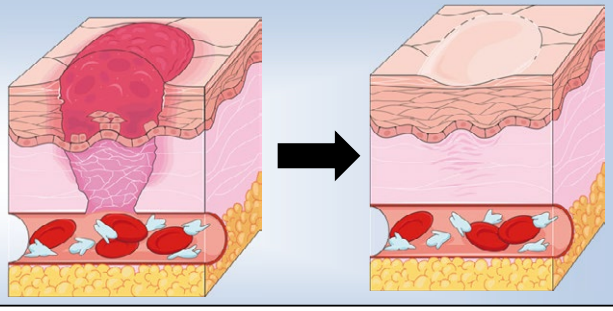


4. Hypodysfibrinogenemia
4A Severe: Fibrinogen antigen < 0.5 g/L
4B Moderate: Fibrinogen antigen 0.5 – 0.9 g/L
4C Mild: Fibrinogen antigen 1 g/L to lower limit of normal

Fibrinogen is used in the clinic to treat and prevent bleeding and promote wound healing.[59]

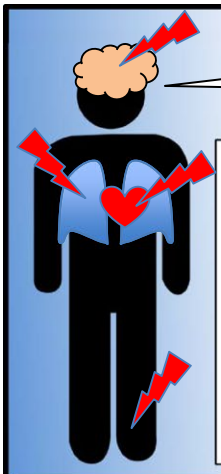
Fibrinogen concentrate is used clinically to manage congenital and acquired hypo- and afibrinogenemia, trauma-related bleeding, and bleeding from consumptive coagulopathy and hyperfibrinolysis.





Fibrin glue is used to seal cutaneous wounds and promote healing.

Fibrin clot properties are clinically-relevant (reviewed in [44,60-65]).



Clots with densely-packed fibers, increased stiffness, and resistance to fibrinolysis are found in cardiovascular and other diseases.

Arterial thrombosis:
Fibrin deposition in thrombi enhances thrombus resistance to thrombolysis.

Examples: ischemic stroke, coronary artery disease, peripheral arterial disease, acute coronary syndrome, no-reflow phenomena after acute myocardial infarction, in-stent thrombosis

Venous Thrombosis/ Thromboembolism:
Increased fibrin deposition in these fibrin-rich thrombi may also sequester thrombin within thrombi.

Examples: deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis

Atherosclerosis:
Fibrin in plaques contributes to plaque growth & (in)stability

Chronic inflammatory disease:
Fibrin may increase inflammation by recruiting inflammatory cells and enhancing leukocyte reactivity.

Examples: inflammatory bowel disease, antiphospholipid syndrome, rheumatoid arthritis, chronic obstructive pulmonary disease

Other:
Fibrin's role in other settings may contribute to disease pathogenesis or be a consequence of the inflammatory process.

Examples: chronic heart failure with sinus rhythm, atrial fibrillation, arterial hypertension, aortic aneurysm, disseminated intravascular coagulation, congenital dysfibrinogenemia with thrombosis, diabetes mellitus, end stage renal disease, malignancy, liver cirrhosis

Weaker clots are associated with bleeding.

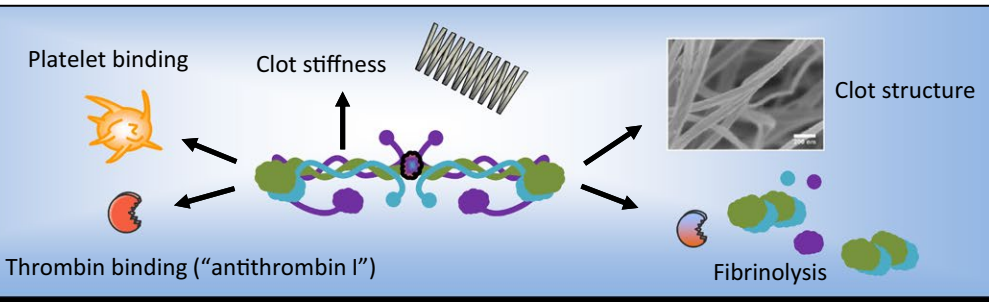
Bleeding: congenital dysfibrinogenaemia, haemophilia, liver disease and transplantation

Abnormal clot structures predict:
- recurrent deep vein thrombosis after anticoagulant withdrawal
- adverse clinical outcome following acute coronary syndrome
- recurrent thromboembolic events in antiphospholipid syndrome

But causality remains to be proven!

In general, ↑ γ' is associated with arterial thrombosis, ↓ γ' with venous thrombosis, although this remains inconclusive.[66]

Discord may reflect complex contributions of γA and γ' fibrinogen to clot properties.[67-69]



The remarkable biochemical and mechanical characteristics of fibrin(ogen) make it an intriguing target for new therapeutic approaches.

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RELATIONSHIP DISCLOSURE

The authors report no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

M. Pieters and A.S. Wolberg developed the concepts and images, wrote the manuscript, and approved the final content.

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