Hemostatic system

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- ***Major components of hemostatic system*** = 1. vessel wall 2. plasma proteins (coagulation or clotting, and fibrinolytic factors) 3. platelet

(I) Vascular endothelium

- ***As antithrombotic surface:***
  - **anticoagulants (eg. GAG, TFP, thrombomodulin, EPCR)**
  - **profibrinolytic (eg. tPA, uPA, binding sites for plasminogen, PA receptor)**
  - **platelet inhibition (eg. prostacyclin, nitric oxide, carbon monoxide, ADPase)**

- ***As prothrombotic surface:***
  - procoagulants (eg. tissue factors, binding sites for coagulation factors, fibrin)
  - antifibrinolytic (eg. PAI, TAFI)
  - platelet activation (eg. vWF, PAI)

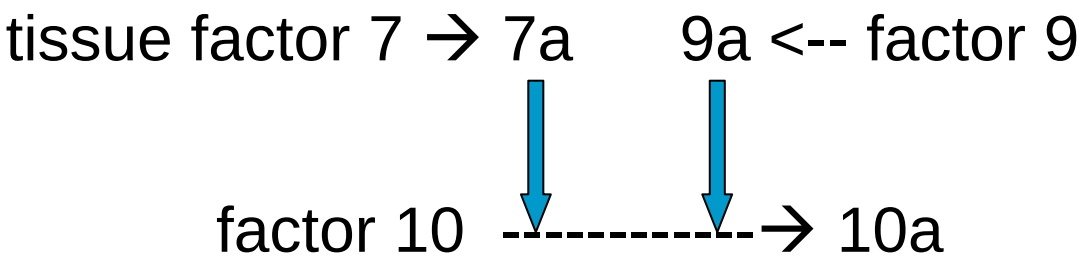
- ***Modulate vascular tone:***
  - vasodilation eg. nitric oxide, carbon monoxide, prostacyclin, ADPase
  - vasoconstriction eg. PAI, endothelin 1

(II) Coagulation

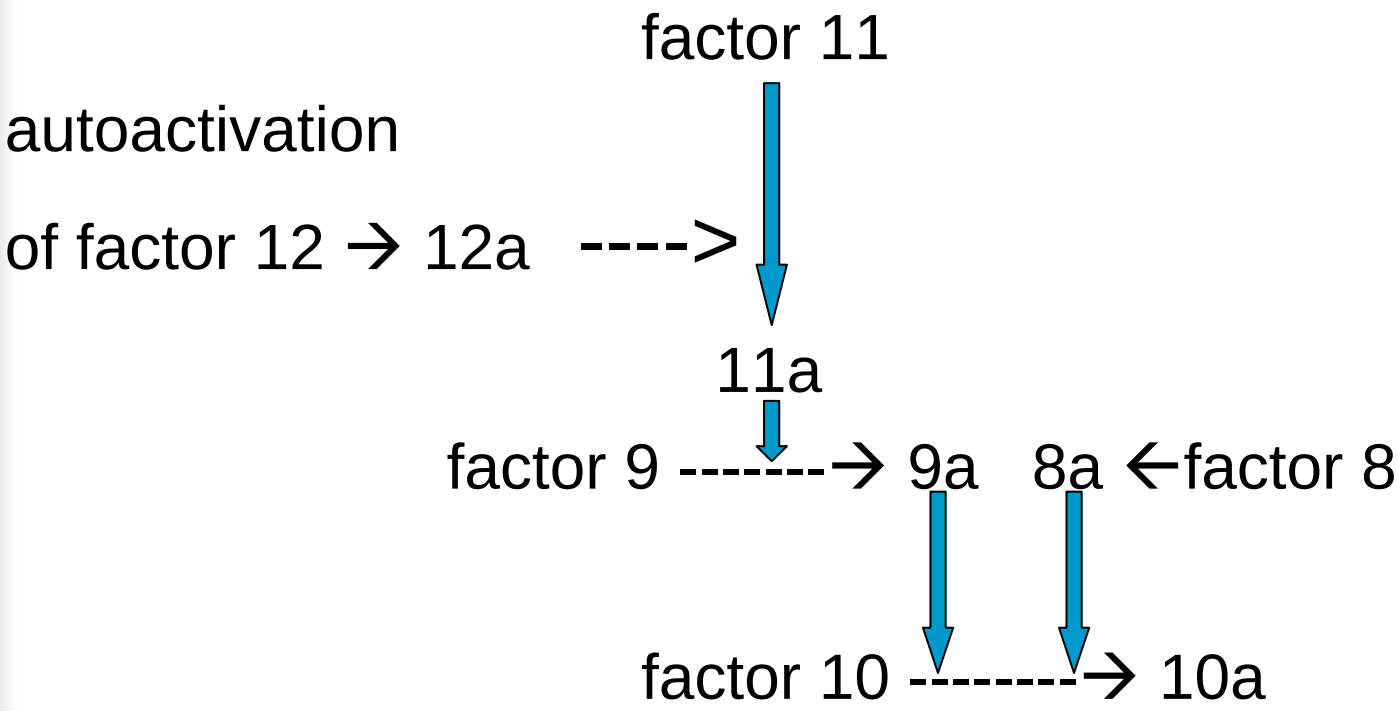
(1) Coagulation cascade:-

- **Extrinsic (tissue factor) pathway (initiate coagulation in vivo):**

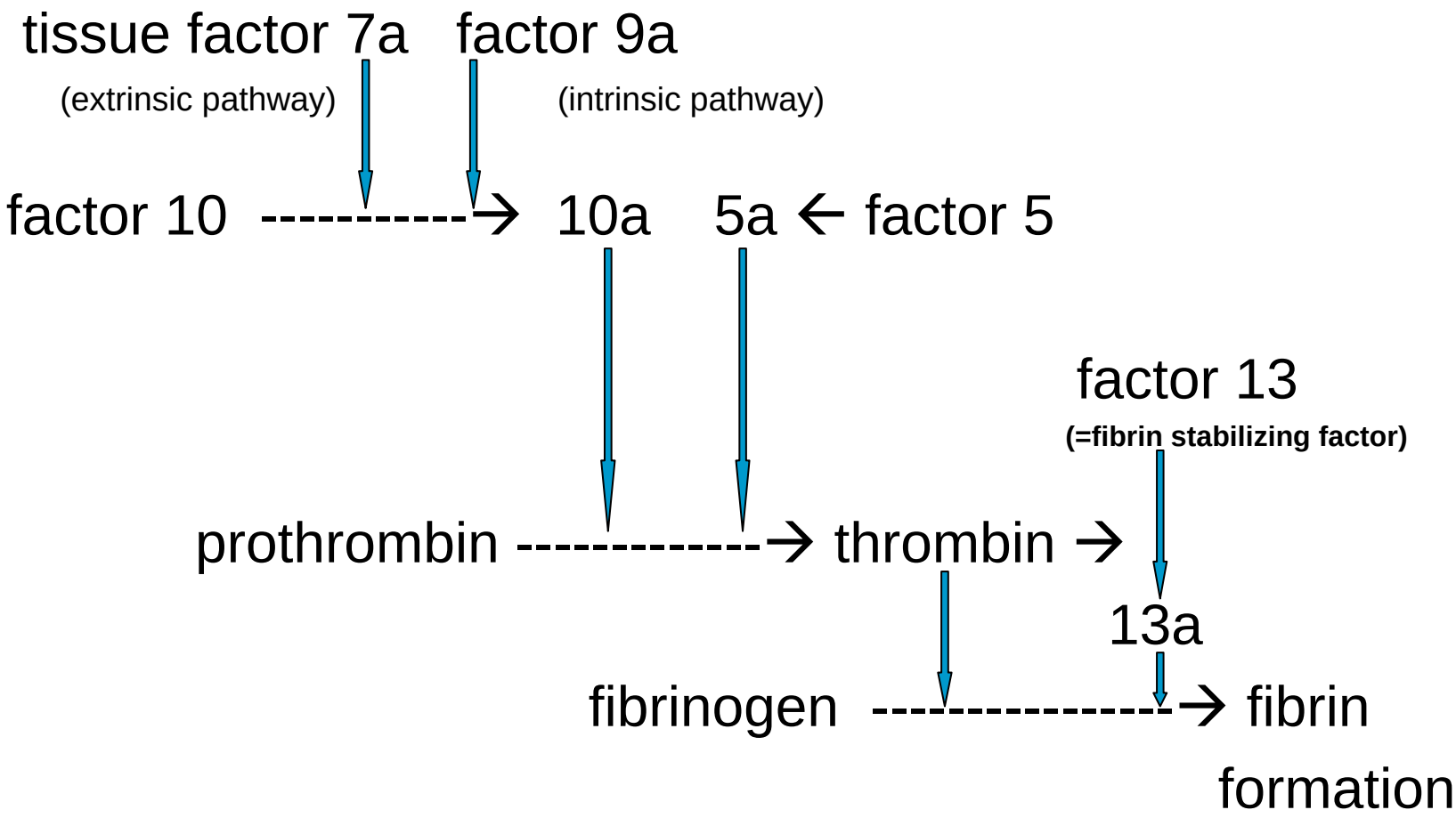
  - vascular injury → activate endothelial cells and blood cells (especially leukocytes) so that:



- ***Intrinsic (contact activation in vitro) pathway:***



Common pathway:



(2) Anticoagulation:-

- Endogenous inhibitors of platelets eg. endothelial PGI2, nitric oxide, carbon monoxide, ADPase

- Antithrombin = major plasma protease inhibitor of thrombin and other clotting factors
  - neutralize thrombin and other activated coagulation factors

- Protein C-protein S-thrombomodulin system:
  - bind and remove thrombin and other clotting factors

- Tissue factor pathway inhibitor (TFPI)

(3) Fibrinolytic system:-

Plasminogen activators eg. tPA, uPA

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Plasma plasminogen --→ plasmin

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fibrin ----------→ fibrin degradation products

(eg. D-dimer, potent anticoagulant and antiplatelet actions)

(4) Fibrinolytic inhibitor:-

- Plasminogen activator inhibitor (PAI)
- Antiplasmin (inhibit plasmin)
- Thrombin-activatable fibrinolysis inhibitor (TAFI)

(III) Platelets

(1) Adhesion:-

- **vessel intimal injury →impair antiplatelet properties of endothelin → platelet adhesion to site of injury (activated by von Willebrand factor vWF at platelet surface receptors = glycoprotein Ib; and collagen receptors GPIa/IIa = integrin)**

(2) Activation:-

- ***By:*** **humoral mediators in plasma eg. epinephrine, thrombin;**
- ***Releasing:*** **ADP, ATP, serotonin, adhesive proteins (eg. fibrinogen, vWF, fibronectin), growth factors (eg. platelet-derived growth factor, transforming growth factor), procoagulants (platelet factors 4 and 5), platelet activation and vasoconstriction TXA2 (= major cyclooxygenase, blocked by aspirin)**

(3) Aggregation:-

- Fibrinogen or vWF bind to GPIIb/IIIa platelet receptors → activated integrins on platelet surface → platelet spreading, irreversible aggregation, clot retraction → platelet plug (stabilized by fibrin mesh from coagulation cascade)

"Thrombin paradox"

- Thrombin can:
  1. ***promote clotting***, at site of vascular injury, by activating coagulation factors and platelet aggregation
  2. ***prevent clotting***, at intact noninflammed endothelium, by activating endogenous circulating anticoagulants, release of protein C, tPA, PGI2 and nitric oxide.

Antithrombotic drugs

(1) ***Heparin:-*** = anticoagulatnt of choice for rapid anticoagulation.
- thrombin inhibition by binding to antithrombin and thrombin.

(2) ***Warfarin (coumadin):-*** = antagonist of vitamin K (= coagulation cofactor for prothrombin and factors 7,9,10)

(3) ***Thrombin inhibitors:-*** eg. hirudin, argatroban

(4) ***Thrombolytic (fibrinolytic) drugs:-***
eg. streptokinase, urokinase, tPA

- activate plasminogen to plasmin (can degrade fibrin)

(5) ***Antiplatelet agents***:-

Aspirin – inactivate cyclooxygenase to block TXA2 (= potent mediator of platelet aggregation and vasoconstrition).

Clopidogrel (Plavix) – inhibit P2Y12 ADP receptor (for platelet activation and aggregation)

(6) ***Phosphodiesterase inhibitors***:-

Dipyridamole – inhibit phosphodiesterase → stimulate PGI2 synthesis (platelet inhibitory effects)

Cilostazol – inhibit phosphodesterase; and vasodilatory effect

(7) ***Glycoprotein IIb/IIIa antagonists***:-

eg. abciximab, eptifibatide, tirofiban (Aggrastat)

- inhibit platelet's GPIIb/IIa receptors (= binding sites for fibrinogen and vWF) hence inhibit platelet activation and aggregation.