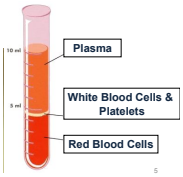
L14: BLOOD, BLEEDING, CLOTTING

Blood

- specialised body fluid, adults (70ml/kg, 5L, male>female), children (80ml/kg)
- pumped by heart (circulate once every min, ↑ when exe)
- deliver O2/nutrients, excrete waste via kidney (uric acid), immune response, haemostasis (bleeding⇌clotting), pH, body temp
- plasma: 55% blood, 90% water
  - proteins from many cells, nutrients, salt, waste
  - intracell/membrane protein secreted in plasma ∴ cell lysis & cellular turn over
  - 1 of the best reporter system: com with most body parts, take up protein → cells
- plasma protein: synthesised in liver, disease state reflected by Δ plasma protein
  - troponin in plasma: indicate acute ischemic heart disease/myocardial damage
  - cancer antigen (CA)-125 / prostate specific antigen (PSA): markers of cancers
- cellular element: platelets, RBC, WBC
- arteries: carry O2 blood from heart
- veins: carry blood with CO2 towards lungs



Haemostasis

- balance interaction of blood cells, vasculature (endo), plasma protein, low mol weight subs (Ca2+, ion, ATP)
- balance of bleeding & clotting (injury/disease tip the balance)
- by thrombus formation & breakdown at injury site
- maintain blood in fluid state when circulating throughout vascular system, impede blood loss & blood flow disturbance, repair injured vasculature & tissue
- blood vessels (endo, sub-endo), platelets, plasma coagulation factor & inhibitor, fibrinolytic system (breakdown clot)
- coagulation: activation of plasma protein, coagulation factors, fibrin (clot not stable unless got fibrin)
- arrest of haemorrhage: vasoconstriction, endo activation, platelet aggregation

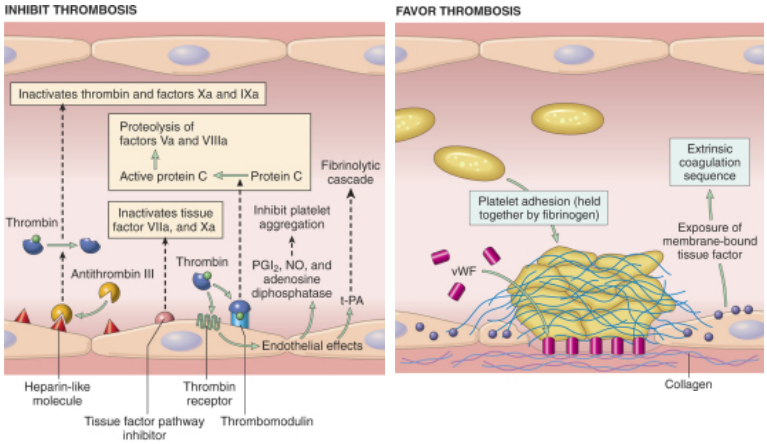
3 steps of haemostasis

Injury	Characteristic	Timing
1° haemostasis	vasoconstriction (prevent blood loss), platelet adhesion & aggregation (platelet plug)	immediate (sec, min)
2° haemostasis	activation of coagulation factors, fibrin formation & polymerisation, fibrin mesh (prevent blood loss)	min
counterregulation or fibrinolysis	confine haemostasis to injury site, fibrinolysis (break down clot), lysis of clot	min, hrs

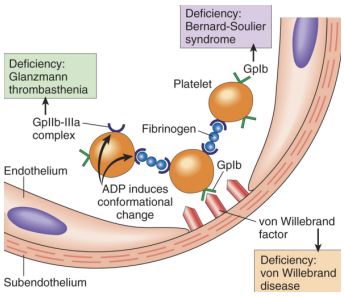
Vascular Endothelium

- baseline: antithrombotic
- injury: prothrombotic, vasoconstriction (∴ endothelin release)
- designed to limit clotting at vascular damage site

Antithrombotic	Prothrombotic
antiplatelet endo prostacyclin (PGI_2), NO, adenosine diphosphatase	platelet adhesion Von Willebrand factor (vWF)
anticoagulant heparin-like mol, thrombomodulin	procoagulant cytokines (TNF, IL1) → produce tissue factor (TF)
fibrinolytic tissue plasminogen activator (tPA)	anti-fibrinolytic plasminogen activator inhibitor (PAIs)



Platelets / Thrombocytes



- blood clotting [platelets no: bleeding⇌clotting]
- platelet membrane: interaction site with damage vessel wall (platelet plug), surface for interaction of coagulation factors
- anucleate cell fragments (✗ DNA), source of GF
- platelet aggregation → platelet plug → basis of clot
- platelet granules
  - dense granule: ADP, ATP, serotonin, his, Ca2+
  - α granule: vWF, fibrinogen, FV, FVII, FXI, FXIII, PAI-1, TFPI, thrombospondin, fibronectin
- vWF binds GpIb platelet receptor → fibrinogen binds GpIIb-IIIa platelet receptor → recruit more platelets (platelet aggregation)
- congenital deficiency in receptors/bridging mol → disease
- haemostasis
  - endo damage → platelet activation → platelet adhesion (to each other & the injured endo) → become spherical with projections → release granule (ADP, TxA_2) → recruit more → plasma coagulation response, aggregation, haemostatic plug

Tissue Factor

- membrane protein, intracell, transmembrane, extracell domain
- in sub-endo (exposed when endo is damaged)
- in almost all tissues (except joints: haemophiliacs got joint bleeding prob)
- TF+FVIIa = activate coagulation cascade

Coagulation Factors

- highly glycosylated plasma protein: factor I, II, V, VII, VIII, IX, X, XI, XII, XIII, PK, HMWK
- II, VII, IX, X: vitamine K dependent
  - newborns ↓ vitamin K → vitamin K injection at birth to prevent bleeding
- circulate as inactive precursor, except FVIIa (activated, but small quantity)
- activator (IXa) —proteolytic cleavage→ proenzyme (X) → activated peptide + enzyme (Xa)
  - proteolytic cleavage: conf change, expose active site of newly generated E (inside proE)
  - Ca2+: essential co-factor
- thrombin (FIIa)
  - prothrombin FII → thrombin FIIa
  - master regulator (control FB loop), convert fibrinogen → fibrin (negative FB when ↑[fibrin])
  - activate FXIII → form crosslink btw fibrin monomers → fibrin mesh
  - activate FV & FVIII in positive FB
  - activate platelets → platelet aggregation → TxA2
  - neutrophil adhesion, activate lymphocyte, monocyte (PDGF→SMC), endo (tPA, PGI2, NO)

Clot Formation

- stable (hr/day)
- mechanically (impact of flow, hang on to endo) & chemically (impact of E, ✗ digested) well protected
- limit blood loss during vessel injury, protect from infective agent, prevent emboli formation (occlude blood vessels in other areas)
- phys: normal, clot → clot lysed → ✗ consequences, but thrombosis is clotting for no reason

(1) initiation phase

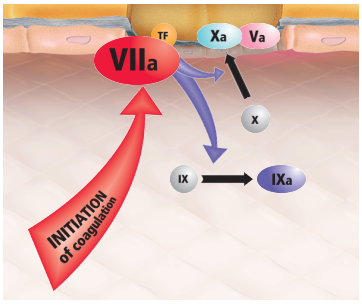
- vessel wall (endo) injury → blood in contact with subendothelial cell
- TF exposed → binds FVII/FVIIa → activate FIX & FX
- FXa binds FVa on cell surface

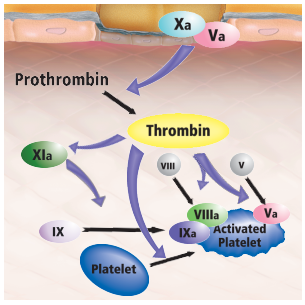
(2) amplification phase

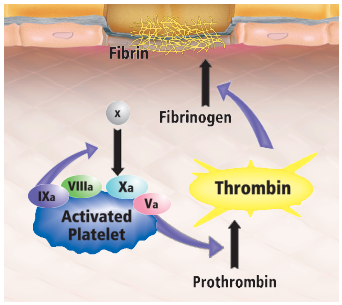
- FXa/FVa complex convert (↓amt) prothrombin → thrombin (✗ enough to form clot) → activates FV, FVIII, FXI, platelets locally
- FXIa converts FIX → FIXa
- platelets bind FVa, FVIIIa, FIXa

(3) propagation phase

- FVIIIa/FIXa complex activates FX on activated platelet surface
- FXa & FVa convert (↑amt) prothrombin → thrombin → thrombin burst → fibrinogen → fibrin (stable fibrin clot)



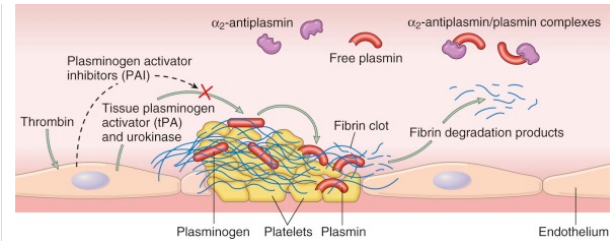




- control mechanism of haemostasis: ensure blood clot formed & maintained when/where necessary
  - endo (normally non-thrombogenic), blood flow, plasma inhibitor, fibrinolysis, FB mechanism
- plasma inhibitor
  - protease inhibitor: antithrombin/AT (Xa, thrombin), A2-macroglobulin, TFPI (TF/VIIa), heparin cofactor II
  - protein C pathway: thrombomodulin (thrombin), protein C (Va, VIIIa), protein S

Fibrinolysis

- lysis of fibrin via proteolytic reaction
- clot formed, wound sealed/healed → risk of ↓ blood flow in affected area → necrosis → so clot must be dissolved
- generate plasmin to dissolve clot
- fibrin degradation product inhibit fibrin polymerisation & platelet aggregation
- \+ FB for fibrinolysis, - FB for clot formation



Haemorrhage

- abnormality of blood vessels/platelets/plasma coagulation factors
- platelet number disorder (thrombocytopenia)
  - ↓ production: folic acid deficiency, leukaemia
  - ↑ destruction: idiopathic, antibody against platelets
  - drug: heparin
- platelet function disorder
  - Von Willebrand's disease (hereditary deficiency)
  - drug: aspirin
  - uremia: renal failure
- plasma coagulation factor
  - deficiency in ≥1 plasma protein (VIII, IX → haemophilia)
  - vitamin K deficiency: ↓ func of coagulation protein II, VII IX, X (haemorrhage of neonate)
  - drug: heparin, warfarin

Haemophilia

- 1/6000-10000 males
- haemophilia A (classical haemophilia): most common, deficiency in clotting factor VIII
- haemophilia B (christmas disease): deficiency in clotting factor IX
- bleeding: in joints/muscles, spontaneous
- treatment: venous injection with the deficient protein
- some require treatment only when bleeding, some require ongoing prophylactic treatment