Immunology & Haematology – HMM104 – Deakin University

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Clotting

Vascular Wall Endothelium: lines entire circulatory system (10^{13} cells in a single layer)

Produces factors that:

- Inhibit Clotting (Prostacyclin, Thrombomodulin & Heparin)
- Activate Clotting (Von Willebrand Factor (vWF) & Tissue Factor (TF))
- Activate Clot Breakdown (Tissue Plasminogen Activator)

Platelets: *small cell fragments (between 140,000 - 400,000/uL of blood) with a 7–10-day life cycle*

- Lack a nucleus
- Contains mitochondria, glycogen (energy), granules (for clotting) & membrane glycoproteins (GPIb & IIb/IIIa for adhesion & aggregation)

At rest they act as smooth non-sticky discs. When stimulated, they become sticky spheres that aggregate & stick to injured surfaces & release chemical messengers.

After platelet aggregation granules are released:

- **α**-granules: fibrinogen (forms clot), platelet factor 4 (antagonises heparin, an anti-coagulant), platelet derived growth factor (growth factor) & **β**-thromboglobulin (chemokine)
- Dense (**β**) granules: ADP & calcium (used in aggregation & vasoconstriction)
- Lysosomes (**γ**) granules: hydrolytic enzymes
- Thromboxane A2 (aggregation & vasoconstriction)
- Phospholipids (enhances coagulation)

Platelet Production:

- Produced from Megakaryocytes (large cells with lobed nucleus & polyploid with up to 32 copies of normal DNA) which themselves are produced from MEP (megakaryocyte erythroid progenitors) via thrombopoiesis (TPO)
- Mature megakaryocytes form long processes which break into 1000's of platelets.
- Lungs are major source of platelet production (due to large vascular area)

Transcription Factors:

- FOG1 (Friend of GATA) → GATA1/FOG1 → FLI1/NF-E2

Cytokines

- IL3 (interleukin 3): converts HSC (haemopoietic stem cell) → MEP
- TPO (thrombopoietin) converts MEP → Megakaryocyte → Platelet Increases when platelet levels are low. TPO signals the conversion via:
  - Cell surface receptor (TPO-R)
  - Receptor associated JAK2
  - STAT3/5
  - PI3K/AKT
  - RAS/ERK

- Classifications: indolent, aggressive, or very aggressive
- Causes (variable): genetic, viral, or bacterial
- Clinical Signs: lymphadenopathy, cytopenia & immune dysfunction
- Treatment: remove clone (chemo, monoclonal antibodies) & remove cause (antibiotics)

Multiple Myeloma (MM): spectrum of disorders characterised by clonal proliferation of plasma cells (antibody producing b-cell)

- Manifestations
  - Immune dysfunction/infection
  - Bone marrow compromise
  - Renal dysfunction
  - Bone lysis, pain, fracture, hypercalcemia
- Causes: Unknown
- Treatments:
  - Clone suppression (chemotherapy), immune support (antibiotics) & promotion of calcium re-entry to the bones (vitamin D & calcium supplements)

Chronic Lymphocytic Leukaemia (CLL): B Cell proliferative disorder affecting older patients

- Cause: Unknown
- Clinical Signs: lymphadenopathy, cytopenia, immune dysfunction
- Treatments: remove clone (chemo, monoclonal antibodies)