L1 Introduction and Haematopoiesis

Body maintains output of blood cells through haematopoietic stem cells – HSCs in bone marrow
HSCs are multipotent – can form several cell types
HSCs can give rise to all blood cell types

Control of HSCs numbers

- HSCs are self-renewing and proliferative – asymmetric division
- Long term HSCs (LT-HSC) can self-renew – symmetric division
- ST-HSC have limited self-renewal is more committed down a lineage. Can form blood cells
- Therefore, the pool of HSCs are heterogeneous
- Mixture of self-renewing LT-HSCs and multipotent ST-HSCs
- Intrinsic and extrinsic factor regulate balance of symmetric to asymmetric cell division to maintain HSC number and blood cell production

Defining a HSC

- HSCs are defined by the expression of different cell surface marker proteins
- Can use Fluorescence-activated cell sorting (FACS) look for surface proteins
- Quiescent cells are: **Lin^-, $Sca\text{-}1^+$, $c\text{-}Kit^+$**
- LT-HSC are: **Lin^-, $Sca\text{-}1^+$, $c\text{-}Kit^+$, $Flk2^-$, $CD34^-$**
- ST-HSC are: **Lin^-, $Sca\text{-}1^+$, $c\text{-}Kit^+$, $Flk2^-$, $CD34^+$**
- Multipotent Progenitors (MPP): **Lin^-, $Sca\text{-}1^+$, $c\text{-}Kit^+$, $Flk2^+$, $CD34^+$**

Site of Haematopoiesis - Embryonic Development

- During early development – the yolk sac is responsible for any haematopoiesis – process call primitive haematopoiesis
- The first blood cells are produced from the mesoderm layers of the yolk sac
- Following onset of circulation – primitive HSCs re-distribute from the yolk sac to the AGM (aorta-gonad-mesonephros) region where they form HSCs. These then populate the foetal liver, thymus, spleen which take oer haematopoiesis
- This process is called definitive haematopoiesis
- HSCs capable of reconstituting adult bone marrow (LT-HSCs) are first found in the foetal liver
- Towards the end of gestation, LT-HSCs populate the bone marrow which becomes the primary source of haematopoiesis in adults

The haematopoietic stem cell niche

- At all stages of primitive and definitive haematopoiesis, the environment in which the HSC finds itself is important for proper function
- E.g. in the transition from primitive to definite haematopoiesis, the environment of the AGM is important for formation of LT-HSCs
- The bone marrow niche, which supports self-renewal and commitment to differentiation has several components
    - Cellular components
    - Molecular components
        - Secreted ligands and their receptors
        - The extracellular matrix
        - Adhesion molecules
        - Chemical gradients
- Bone marrow niche is vital for the proper regulation and function of HSCs
- Cytokines, signalling molecules and transcription factors drive lineage specific differentiation