

GATA factor mechanistic principle

- TFs
- Binds to a GATA sequence depending on how the DNA is packaged or co-binding partners.
- Can activate or repress genes
- GATA switch
 - GATA2 can drive expression of the GATA2 gene
 - When GATA1 expression is strong it can repress expression of GATA2
- GATA-2 mutations are a target for human haematological disorders

Shifts in site of haematopoiesis during development

1. Yolk sac
2. 1st hepatic colonisation
3. Arterial clusters
4. 2nd hepatic colonisation
5. Bone marrow colonisation

Haemoglobin

- 4 subunits
 - 2 alpha + 2 beta
 - Each contains a haem molecule = in total
- The x-ray determined structure of the haemoglobin molecule and representation of its very high concentration in the erythrocyte

Formation of haem

- Multi-stage process with several processes starting with delta levulinic acid
- Inherited defects in the cascade lead to various diseases known as porphyria
 - Skin disease/ photosensitivity

Haemoglobin and development

- Haemoglobin subunits are tightly regulated during embryonic and foetal development by transcription factors
 - GATA 1 & 2
 - EKLF & KLF1
- Early haemoglobin have increased oxygen affinity to allow uptake of oxygen from the placenta
- Specific haemoglobin in foetus and different ones in adult (needs are different needs to be able to pull O₂ from mother as it goes through circulation)
- Gamma Hb needed in-utero – production decreases after birth
- Alpha haemoglobin is produced after 6 weeks (from fertilisation) and throughout life
- Beta haemoglobin is not produced until birth
- The genomic structure of the clusters of α -like and β -like globin genes, on chromosomes 16 and 11 in humans

Oxygen dissociation curve

- At particular O₂ PP how much haemoglobin is saturated
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Haemoglobinopathies

- Thalassaemias
 - Inherited diseases causing abnormal production of haemoglobin
 - Frequently transfusion dependent
- Sickle cell disease
 - Group of diseases associated with inheritance of haemoglobin S
 - On β -globin chain – glu $\rightarrow$ val
 - Hb molecules crystallise when O₂ conc is low = can get stuck in small blood vessels (lungs)

Erythropoietin

- Most important cytokine involved in terminal differentiation of red cells – affects early erythroid differentiation