Normal haemopoiesis

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Haemopoiesis

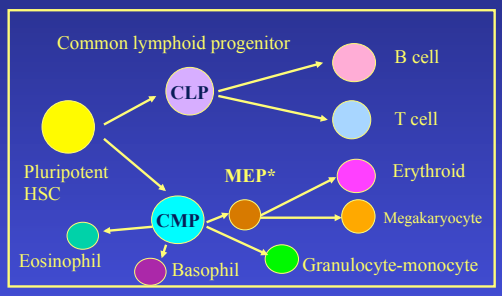
OBJECTIVES

- Definition of haemopoiesis
- Genes important in developmental haemopoiesis and in haemopoietic stem cells
- Haemopoietic stem cells: definition & properties
- Haemopoietic progenitor cells: different types and function
- Haemopoietic growth factors
- Role of marrow microenvironment

Haemopoiesis

Process which generates blood cells of all lineages from haemopoietic stem cells (HSC) throughout life

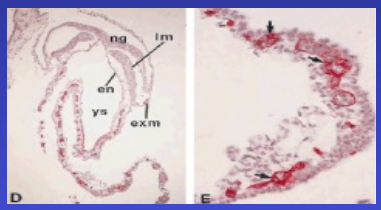
Haemopoiesis: differentiation from stem cells



* Megakaryocyte erythrocyte progenitor

Developmental haemopoiesis

- First signs are seen in the yolk sac at 3 weeks gestation (PRIMITIVE HAEMOPOIESIS)



Genes critical for primitive haemopoiesis

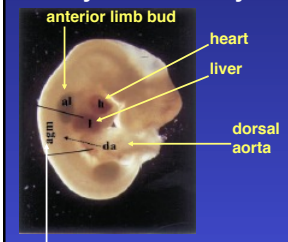
	Transgenic mouse	Yolk Sac haemopoiesis
LMO2	-/-	absent
SCL/Tal1	-/-	absent
GATA1	-/-	absent

Developmental haemopoiesis

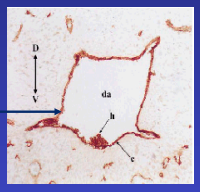
- First signs are seen in the yolk sac at 3 weeks gestation (PRIMITIVE HAEMOPOIESIS)
- DEFINITIVE HAEMOPOIESIS begins in the aorto-gonado-mesonephros (AGM) at 5 weeks gestation

Embryonic Haemopoiesis in the AGM

34-day human embryo



Aorto-Gonado-Mesonephros (AGM)



Cross section through the dorsal aorta to show haemopoietic cells (h) in the AGM

Genes critical for definitive haemopoiesis

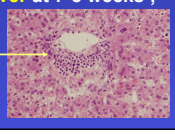
	Transgenic mouse	Primitive	Definitive
LMO2	-/-	absent	absent
SCL/Tal1	-/-	absent	absent
GATA1	-/-	absent	absent
AML1/ Runx1-/-	-/-	present	absent

Genes critical for definitive haemopoiesis: role in leukaemia

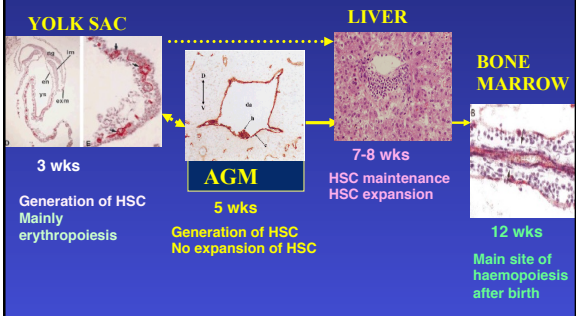
Genes critical for normal haem^{s}	Leukaemias due to mutations or aberrant expression
LMO-2	T-cell acute lymphoblastic leukaemia
SCL/Tal-1	T-cell acute lymphoblastic leukaemia
GATA-1	Myeloid leukaemia in Down syndrome
AML-1/Runx1	B-cell acute lymphoblastic leukaemia and also acute myeloid leukaemia

Developmental haemopoiesis

- First signs are seen in the yolk sac at 3 weeks gestation (PRIMITIVE HAEMOPOIESIS)
- DEFINITIVE HAEMOPOIESIS begins in the AGM at 5 weeks gestation
- Haemopoiesis begins in fetal liver at 7-8 weeks ; this is main site of haemopoiesis in fetal life



Embryonic and fetal haemopoiesis: sites of haemopoiesis during ontogeny



Haemopoiesis: differentiation from stem cells

Pluripotent HSC

Abnormalities of haemopoietic stem cell number and function as a cause of disease

- Bone marrow failure, eg aplastic anaemia
- Leukaemia
- Myelodysplasia
- Myeloproliferative disorders

Haemopoietic stem cells: potential clinical uses

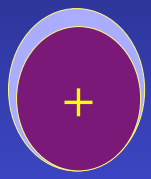
- Transplantation for haematological disorders (bone marrow failures, leukaemia)
  - highly purified HSC populations
  - in vitro expansion (eg by cytokines)
- For repair of tissue damage eg heart, liver
- Gene therapy, eg SCID-X1 (immune deficiency)

Haemopoietic stem cells

PROPERTIES OF HSC

- Can undergo self-renewal
- Can undergo multilineage differentiation
- When transplanted can sustain life-long haemopoiesis

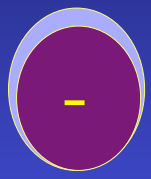
Regulation of HSC self-renewal



Positive regulators

HoxB4
SCL
Notch pathway
Wnt/β-catenin pathway
Myc
Bmi
Gfi
VEGF
Telomerase

Regulation of HSC self-renewal



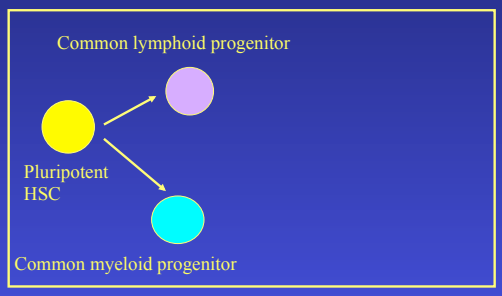
Maintenance of quiescence (negative regulators)

Max network, eg MAD-1

CIP / KIP family, eg CDKip27^{Kip1}

Angiopoietin / Tie-2

Haemopoiesis: differentiation from stem cells



Haemopoietic progenitor cells

Progenitors have less self-renewal capacity than stem cells

Multipotent progenitors: multiple lineages

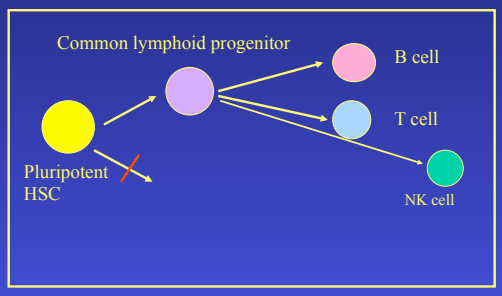
Committed progenitors: 1 or 2 lineages

Haemopoietic progenitor cells

Multipotent progenitors

- **Common lymphoid progenitor (B, T & NK cells)**
- **Common myeloid progenitor (granulocytes, erythroid cells, megakaryocytes and monocyte/ macrophages)**

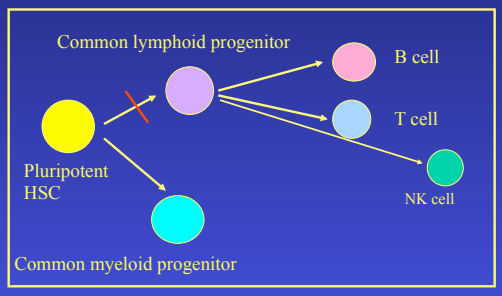
Haemopoiesis: differentiation from stem cells



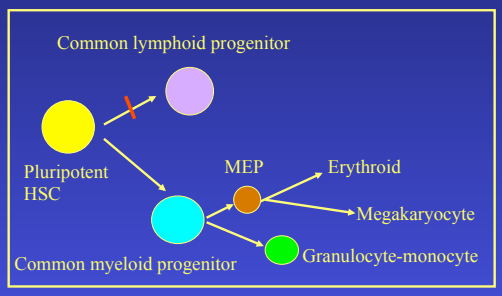
Haemopoiesis: lymphocyte development

- All lymphocytes (B, T and NK cells) are derived from HSC
- B cell maturation is initiated in the bone marrow at the end of the first trimester
- T cell development originates from HSC which colonize the fetal thymus in the first trimester

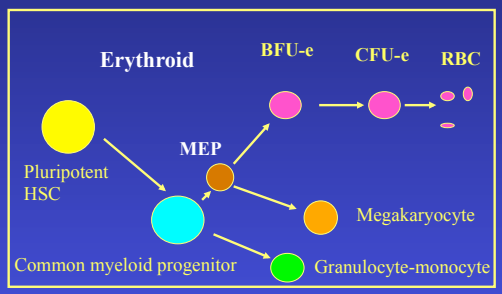
Haemopoiesis: differentiation from stem cells



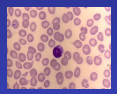
Haemopoiesis: differentiation from stem cells



Haemopoiesis: erythroid progenitors



Erythropoiesis: red blood cell production



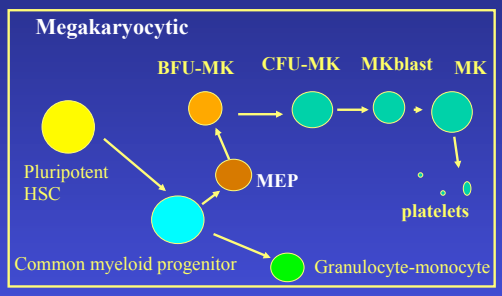
Sites:

- begins in yolk sac (3 weeks)
- liver is main site in fetal life
- bone marrow main site after birth

Control:

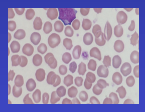
- erythropoietin (produced in the kidney in response to hypoxia)

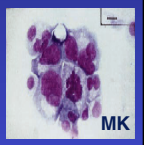
Haemopoiesis: megakaryocyte progenitors



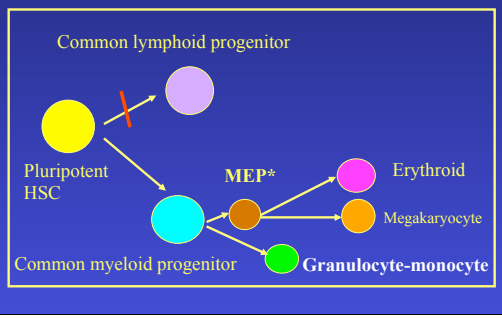
Megakaryocytopoiesis (platelet production)

- Megakaryocytes (MK) first in the yolk sac at 5 wks
- Platelets in fetal blood at 8 wks
- Normal platelet count (>150 x 10^9/l) by 16 wks gestation
- Control: thrombopoietin

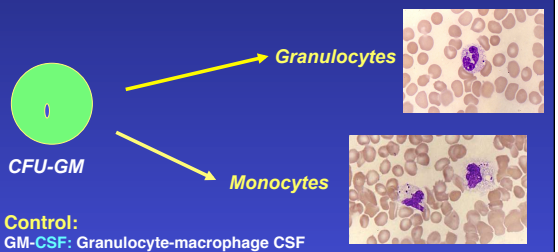




Haemopoiesis: differentiation from stem cells



Granulocyte and monocyte (macrophage) progenitor cells



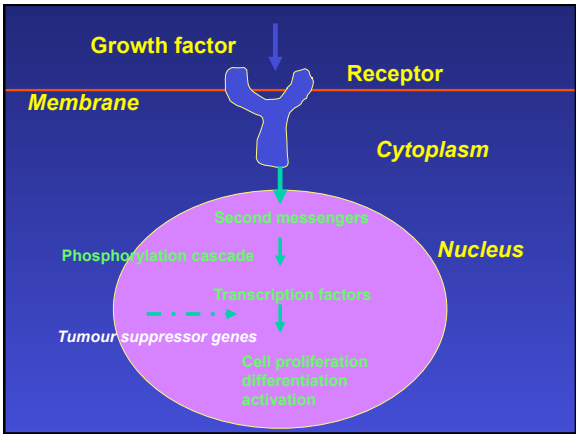
Control:
GM-CSF: Granulocyte-macrophage CSF
G-CSF: Granulocyte CSF
M-CSF: Macrophage Colony Stimulating Factors

Haemopoietic growth factors

- Glycoprotein hormones
- Regulate proliferation and differentiation of haemopoietic stem and progenitor cells
- Regulate function of mature blood cells
- Act locally at site of production or circulate in plasma
- Main source: lymphocytes, monocytes, stromal cells

Haemopoietic growth factors

- **Biological effects are mediated through specific receptors on target cells**



Lineage specific HGFs

- Megakaryocytopiesis and platelet production → THROMBOPOIETIN
- Erythropoiesis (red cell production) → ERYTHROPOIETIN
- Granulocyte and monocyte production → GM-CSF, G-CSF and M-CSF

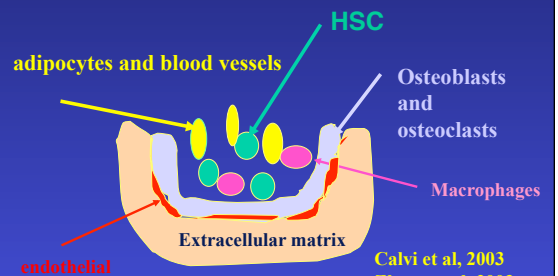
Haemopoietic growth factors that act on stem cells

- Stem cell factor
- Flt3 ligand
- BMP4
- Interleukin 11

Inhibitory haemopoietic cytokines

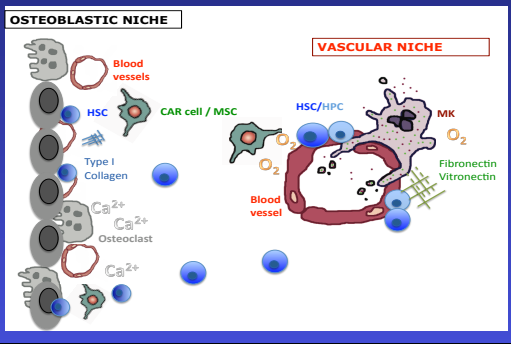
- Interferons
- Interleukins
- Tumour necrosis factors

The role of the microenvironment : the haemopoietic stem cell niche



Calvi et al, 2003
Zhang et al, 2003
Arai et al, 2004

The role of the microenvironment in haemopoiesis: - structure of bone marrow haemopoietic niches



The role of the microenvironment in haemopoiesis

- Production of growth factors:
  - to achieve a balance of self-renewal and differentiation of stem cells
  - to increase mature cells in response to increased demand (eg anaemia, infection)
- Physical support
- Homing of stem and progenitor cells

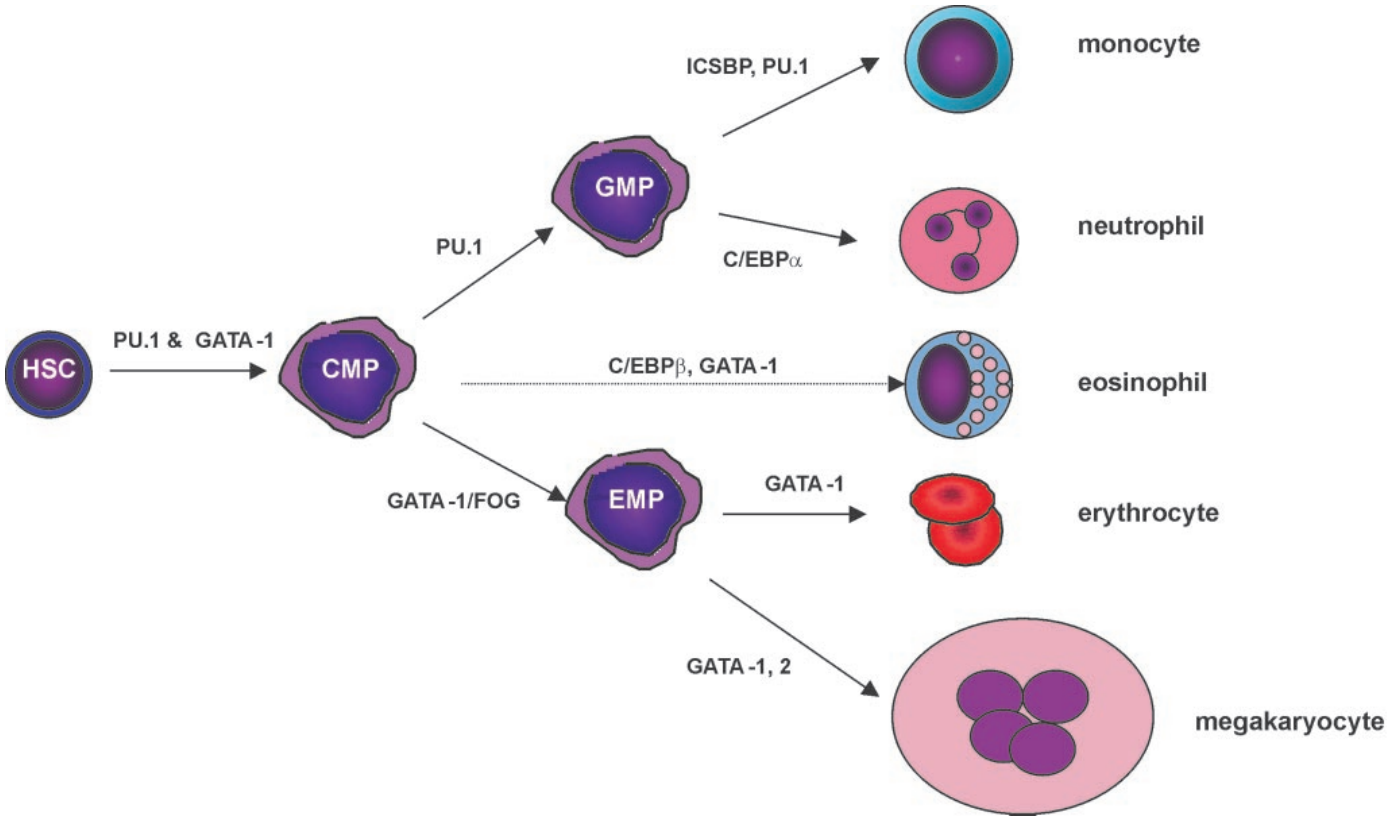


Figure 3 Transcriptional regulation of common myeloid precursor (CMP) commitment. CMPs differentiate into either common precursors for granulocytic and monocytic lineages (GMPs) or common precursors for both erythroid and megakaryocytic lineages (EMPs). A separate, possible, pathway leading to eosinophils is depicted by dotted line. Dual expression of PU.1 and GATA-1 leads HSCs to CMPs, but then dominant expression of PU.1 is restricted to GMPs, while unopposed GATA-1 expression directs differentiation to EMPs

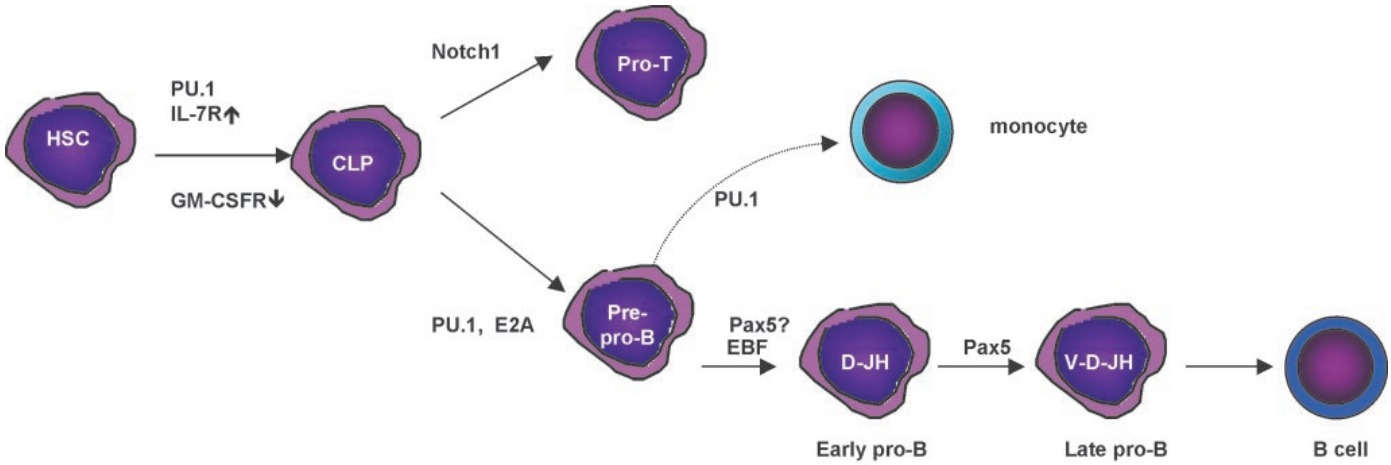
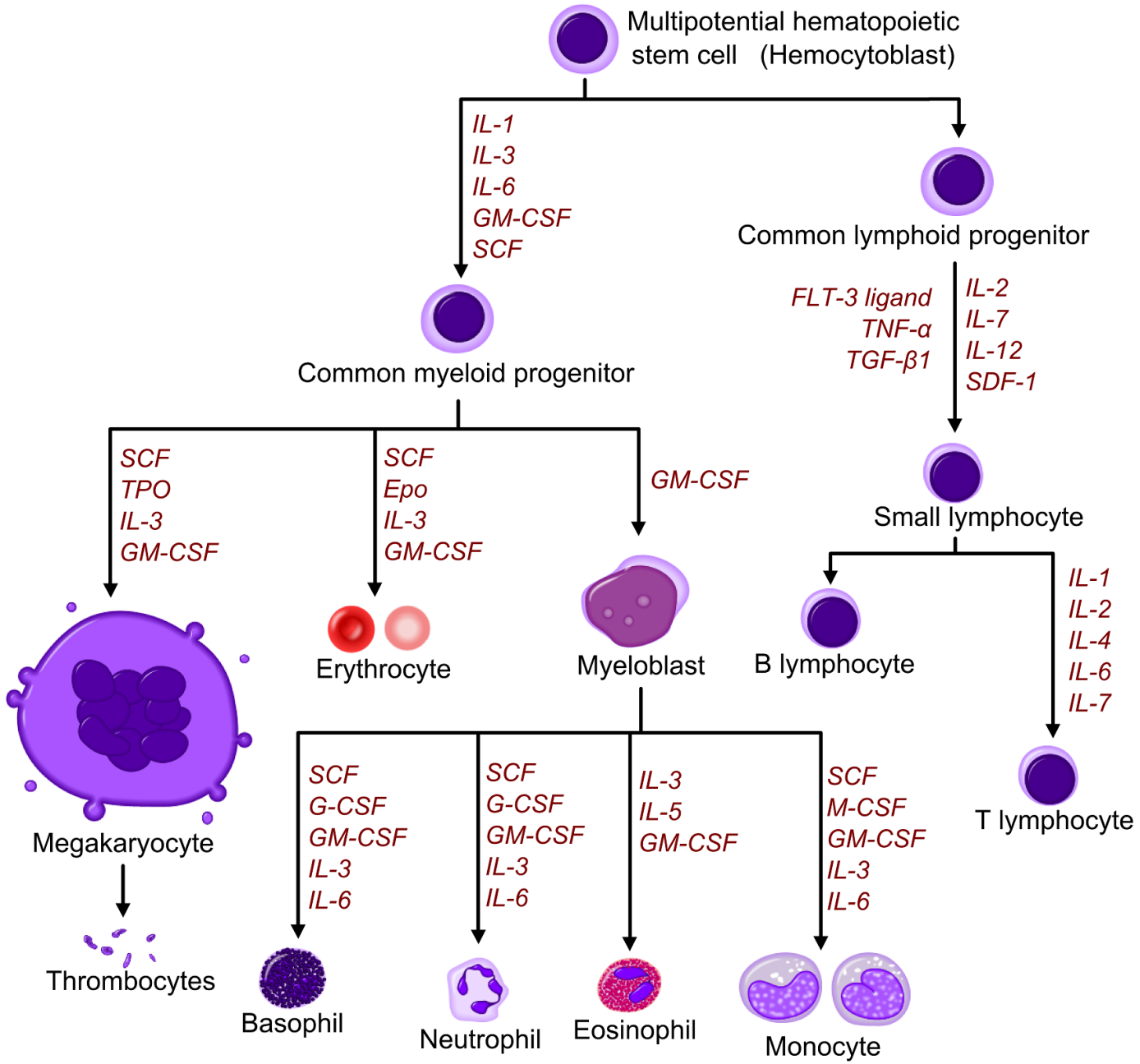


Figure 4 Transcription regulation of common lymphoid precursor (CLP) commitment. B lymphocytes and T lymphocytes are derived from a common lymphoid precursor (CLP). The early development of B cell is distinguished into distinct stages by the sequential expression of different transcription factors that direct Ig gene recombination and the expression of B cell specific cell surface phenotypes. A proposed (alternative) differentiation pathway of macrophages from pro-B is also indicated by a dotted line

of those fates have been found. However, most of these transcription factors have not been tested in clearly interpretable *in vivo* models. Moreover, the primary events and mechanism leading to the induction of differentially expressed genetic programs are obscure. Of the transcription factors studied to date, the largest body of published evidence relates to the transcription factor PU.1. Predominance of PU.1 could be among one of earliest events biasing HSCs to lineage commitment, for the co-upregulation of PU.1 and GATA-1 heralds the commitment to CMPs, and PU.1 expression is maintained in CLPs and also absolutely



Taken from http://commons.wikimedia.org/wiki/File:Hematopoietic_growth_factors.png, modified after "Molecular cell biology" Lodish, Harvey. (2003) and "Rang & Dale's pharmacology" Flower, Rang et al. (2007)