Haemopoiesis — the formation of blood cells

Ted Gordon-Smith

Abstract

After birth and throughout life haemopoiesis takes place in the bone marrow. In the early embryo, blood cells, mainly erythrocytes, arise from blood islands in the yolk sac before more varied cells, including lymphoid and myeloid stem cells and precursors, are derived from the aorto-gonad-mesonephron of the para-aortic splanchnopleure. Fetal haemopoiesis occurs mainly in the liver. The haemopoietic stem cell (HSC) is the pluripotent progenitor cell from which the cells of the blood and lymphoid systems are ultimately derived. They are capable of self-renewal as well as proliferation and differentiation. Their proper function depends on the microenvironment of the haemopoietic organ in which they develop — the haemopoietic niche. They can migrate to and circulate in the blood, and home into and repopulate the bone marrow. HSCs give rise to lymphoid and myeloid precursors. The myeloid precursors differentiate further into the erythrocyte, granulocyte and thrombocyte lineages that deliver red cells, granulocytes, monocytes and platelets to the circulation. Cell production is tightly controlled through cytokine and humoral loops and can be increased rapidly in response to demand.

Keywords differentiation; erythropoiesis; granulopoiesis; haemopoiesis; pluripotent; stem cells; thrombopoiesis

In postnatal life the production of circulating blood cells occurs in the bone marrow (BM), in the honeycomb spaces of trabecular bone. In the infant and growing child, haemopoiesis takes place in all bones of the skeleton. In adults, blood cell production is confined mainly to the axial skeleton, the skull, vertebrae, sternum, ribs, scapulae and pelvis. Bone marrow for diagnostic purposes is usually taken from the posterior iliac crest, although the sternum is sometimes used for aspirates. In infants and young children the tibia is preferred. In the child, haemopoietic tissue occupies most of the BM space whereas in the adult only about 30% of the active marrow sites are haemopoietic, the remainder being fat cells (Figure 1). In the inactive (yellow) marrow all the space is apparently occupied by fat cells. Under conditions of increased demand, for example chronic haemolytic anaemias, the adult capacity may be increased up to sixfold both by increasing the cellularity of haemopoietic tissue and repopulating the yellow marrow. In myeloproliferative disorders haemopoiesis reappears in the liver and spleen — extra-medullary sites.

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What's new?

- Lifelong, controlled haemopoiesis depends on the interrelationships between the haemopoietic stem cell (HSC) and the stem cell niche within the bone marrow (BM).
- Haemopoiesis is initiated in the endosteal domains of the BM where the niche concentration is high. The niche is also found in the sinusoidal regions of the BM.
- A number of cells are important for control of haemopoiesis within the niche including osteoblasts, mesenchymal stem cells (MSC), macrophages, and possibly megakaryocytes.
- HSCs within the endosteal niche have mainly anaerobic respiration in hypoxic conditions. They actively traffic through the BM, acquire respiratory respiration, may leave the sinusoids to enter the systemic circulation and re-enter the BM through sinusoids to occupy an existing niche or previously quiescent niche.
- The factors which determine HSC /niche relationships and HSC trafficking are gradually becoming apparent and offer therapeutic opportunities for HSC mobilization and possibly control of malignant haemopoiesis.

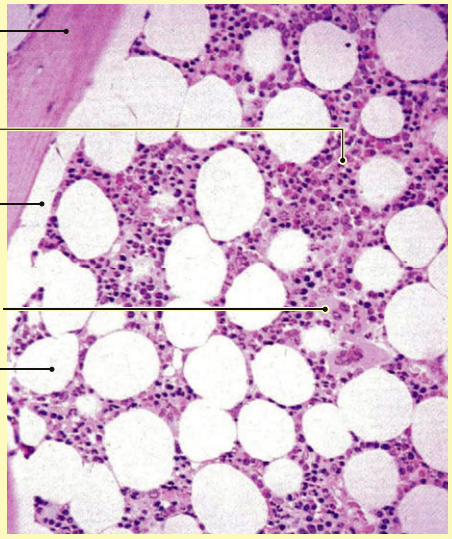
The BM microenvironment[1]

Haemopoiesis occurs within the microenvironment of the BM which is composed of cells including mesenchymal stem cells (MSCs), macrophages, fibroblasts and fat cells, a matrix of collagen and reticulin fibres, and a variety of extracellular matrix proteins.[2] This complex constitutes the stem cell niche. Bone turnover, particularly osteoblastic activity, is closely linked to HSC pathways. Within the active marrow, haemopoiesis is carefully structured, with the HSCs and early proliferating cells being located in the paratrabecular part of the marrow space. It is in this region that the osteoblastic niches essential for quiescent stem cell function are found.[3,4] The relationship between HSC proliferation and the heterogeneous population of MSCs seems to be crucial in the control of haemopoiesis.[5] Proliferation and differentiation of blood cell precursors occurs in an orderly distribution in the marrow so that mature cells can be released from the extravascular marrow into sinusoids and hence to the circulation. The control is exercised through a complex of cytokines and growth factors, both humoral and locally produced in the marrow. Receptors to specific ligands are expressed at different stages of haemopoiesis; delivery is to a considerable extent controlled by the microenvironment. A particular pathway for mobilization involves the CXCL12/CXCR4 ligand receptor axis. Inhibition of binding of CXCR4 to CXCL12 by drugs such as plerixafor may increase mobilization of HSCs from BM to peripheral blood in patients who do not mobilize adequately with granulocyte colony-stimulating factor (G-CSF) alone, an important observation for mobilizing stem cells for autologous stem cell transplantation.[6]

Haemopoietic stem cell

The HSC is the pluripotent progenitor of the cells of the haemopoietic and lymphopoietic systems. Stem cells depend on the

Normal adult marrow



Trephine biopsy from posterior superior iliac crest. Giemsa stain. Note haemopoietic tissue represents < 50% marrow space.

Figure 1

microenvironment niche for their function. In the niche the HSCs may be in a quiescent phase until cytokines and other signals switch them to an active phase, from which they may produce daughter cells capable of developing into lineage-specific precursors or of returning to the quiescent phase. The ability to traffic throughout the body is a characteristic of HSCs.[7] Small numbers may be found in the peripheral blood of normal adults. Numbers are greatly increased by certain cytokines, including G-CSF, and during regeneration of marrow following chemotherapy. This property has led to mobilized peripheral blood HSCs being preferred to BM HSCs in most transplant procedures because collection of adequate numbers of HSCs is simpler by this route. Proportionally greater numbers of HSCs are found in the umbilical cord blood, a discovery that has led to their use for stem cell transplantation[8] (see *MEDICINE* 2013; **41**(5)). HSCs are identified in mice by their ability to repopulate the BM from a single or very few cells. In humans the identification depends on the immunophenotype of colony-forming cells that most nearly equate to the mouse stem cell.[9] The immunophenotype has both positive (CD34+) and negative (lin−, CD33−, CD38−) characteristics, although there are probably more primitive HSCs even than this phenotype. As the progeny of the HSC enter the proliferation and differentiation pathways, so the immunophenotype matures (Figure 2).

Proliferation and differentiation

The initial step in differentiation is the multipotent progenitor cell (MPP), which does not express lineage-specific antigens (lin−) but gives rise to both common myeloid (CMP, CD33+, CD38+) and common lymphoid (CLP, CD38+, CD10+) precursors, which in turn give rise to specific lineages,[10] again depending on signals received. From the CMP comes the megakaryocyte–erythroid precursor (MEP), from which separate platelet and red cell differentiation occurs, and the granulocyte–monocyte precursor (GMP), from which monocyte–macrophage and granulocytic lineages descend. The lineage-committed cells include the morphologically recognizable precursors of haemopoiesis seen in BM preparations (Figure 2). The proliferative capacity of the haemopoietic system far outstrips normal requirements. Apoptosis (programmed cell death) plays an important part in the homeostatic mechanisms of haemopoiesis. Apoptosis is initiated by absence of specific cytokines, including erythropoietin (Epo) for red cells and G-CSF for granulocytes; upregulation of anti-apoptotic cytokines leads to rapid increase in mature cell production.

Granulocyte/monocyte production

Myeloid and lymphoid developments derive from the common MPP. Subsequent differentiation along the myeloid pathway is controlled by a series of transcription factors that are induced by a number of growth factors and cytokines.[10] The relationship between specific cell lineages and various cytokines has been elucidated by *in vitro* colony assays. Granulocyte–macrophage colony-stimulating factor (GM-CSF) increases colony formation of all monocyte and granulocyte preparations. G-CSF and its receptor GCSFR act mainly on the production of neutrophils rather than eosinophils and basophils, whilst monocyte CSF (M-CSF) upregulates monocyte production. An equally important action of these cytokines is to activate mature circulating cells when binding to their ligands. The GCSFR plays an important role in systems other than neutrophil production, including neutrophil activation and tissue repair.[11] The cytokines that increase granulocyte production are produced by cells at the site of infection and inflammation, including macrophages.

Monocytes

Monocytes make up a small part of the BM cellularity. Monocytes give rise to macrophages. These cells are long-lived, and tissue macrophages, including Kupffer cells in the liver and alveolar macrophages, are capable of some division in the tissues so the turnover is small. In response to cytokines released at sites of infection, circulating monocytes migrate to the site and mature into macrophages, which are potent phagocytes in the innate immune system.

Granulocytes

Granulocyte lineages arise from a granulocyte precursor. All have ligands for GM-CSF.

Eosinophil differentiation depends on the interleukins IL-3 and IL-5.

Neutrophil differentiation requires G-CSF amongst other ligands. The recognizable myeloid precursors in the BM progress from the myeloblast through the promyelocyte and myelocyte stages, where proliferation continues, to the metamyelocyte and neutrophil, in which final maturation occurs. Neutrophil precursors are the most numerous nucleated cells in the normal marrow. The total myeloid:erythroid ratio in the normal BM is 3.1 (range 2.0–8.3).