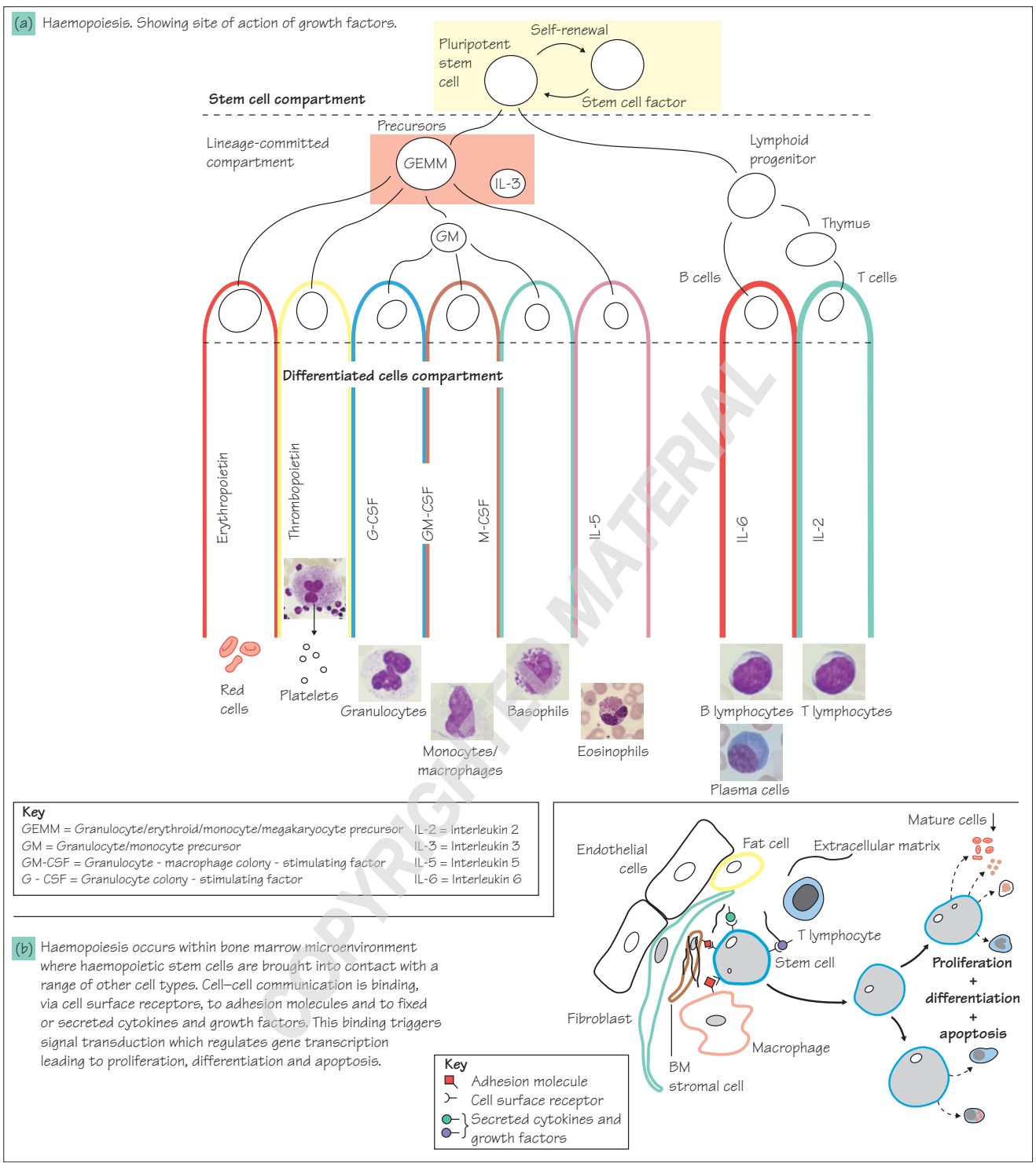
1 Haemopoiesis: physiology and pathology



Definition and sites

Haemopoiesis is the process whereby blood cells are made (Fig. 1a). The yolk sac, and later the liver and spleen, is important in foetal life, but after birth normal haemopoiesis is restricted to the bone marrow. Infants have haemopoietic marrow in all bones, but in adults it is in the central skeleton and proximal ends of long bones (normal fat to haemopoietic tissue ratio of about 50:50) (Fig. 8b). Expansion of haemopoiesis down the long bones may occur in malignancy, e.g. in leukaemias, or when there is increased demand, e.g. chronic haemolytic anaemias.

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The liver and spleen can resume extramedullary haemopoiesis when there is marrow replacement, e.g. in myelofibrosis, or excessive demand, e.g. in severe haemolytic anaemias such as thalassaemia major.

Stem cell and progenitor cells

Haemopoiesis involves the complex physiological processes of proliferation, differentiation and apoptosis (programmed cell death). The bone marrow produces more than a million red cells per second in addition to similar numbers of white cells and platelets. This capacity can be increased in response to increased demand and in malignancy. A common primitive stem cell in the marrow has the capacity to self-replicate and to give rise to increasingly specialized progenitor cells which, after many (13–16) cell divisions within the marrow, form the mature cells (red cells, granulocytes, monocytes, platelets and lymphocytes) of the peripheral blood (Fig. 1a). The earliest recognizable red cell precursor is a pronormoblast, and for granulocytes or monocytes, a myeloblast. An early lineage division is between lymphoid and myeloid cells. Stem and progenitor cells cannot be recognized morphologically; they resemble lymphocytes. Progenitor cells can be detected by in vitro assays in which they form colonies (e.g. colony-forming units for granulocytes and monocytes, CFU-GM, or for red cells, BFU-E and CFU-E). Stem and progenitor cells also circulate in the peripheral blood and can be harvested for use in stem cell transplantation.

The stromal cells of the marrow (fibroblasts, endothelial cells, macrophages, fat cells) have adhesion molecules which react with corresponding ligands on the stem cells to maintain their viability and to correctly localize them. The haemopoietic stem cells may be 'plastic', i.e. capable of forming cells of other tissues, e.g. liver, heart, nervous system, but this is controversial. The marrow also contains mesenchymal stem cells that can form cartilage, fibrous tissue, bone and endothelial cells.

Growth factors

Haemopoiesis is regulated by growth factors (GFs) (Table 1.1) which usually act in synergy. These are glycoproteins produced by stromal cells, T lymphocytes, the liver and, for erythropoietin, the kidney. While some GFs act mainly on receptors on primitive cells, others act on later cells already committed to a particular lineage. GFs also affect the function of mature cells. GFs inhibit apoptosis (programmed cell death) of their target cells. GFs in clinical use include erythropoietin, granulocyte colony-stimulating factor (G-CSF), and recently analogues of thrombopoietin.

Table 1.1 Haemopoietic growth factors

Act on stromal cells	
	IL-1 (stimulate production of GM-CSF, G-CSF, M-CSF, IL-6)
	TNF
Act on pluripotential cells	
	Stem cell factor
Act on early multipotential cells	
	IL-3
	IL-4
	IL-6
	GM-CSF
Act on committed progenitor cells*	
	G-CSF
	M-CSF
	IL-5 (eosinophil CSF)
	Erythropoietin
	Thrombopoietin

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, monocyte colony stimulating factor
*These growth factors (especially G-CSF and thrombopoietin) also act on earlier cells

Signal transduction

The binding of a GF with its surface receptor on the haemopoietic cell activates by phosphorylation, a complex series of biochemical reactions by which a message is transmitted to the nucleus (Fig. 1b). The signal activates transcription factors, which in turn activate or inhibit gene transcription. The signal may activate pathways, which cause the cell to enter cell cycle (replicate), differentiate, maintain viability (inhibition of apoptosis) or increase functional activity (e.g. enhancement of bacterial cell killing by neutrophils).

Assessment of haemopoiesis

Haemopoiesis can be assessed clinically by performing a full blood count (see Appendix II). Bone marrow aspiration also allows assessment of the later stages of maturation of haemopoietic cells (Fig. 8c; see Chapter 7 for indications). Trephine biopsy (Fig. 8b) provides a core of bone and bone marrow to show architecture. Reticulocytes are young red cells and reticulated platelets are young platelets. Assessment of their numbers can be performed by automated cell counters and will give an approximation of the age of the blood cell population. As a general rule, the action of GFs increases the number of young cells, in response to demand.