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Reinhold Munker, Hillard M. Lazarus and Kerry Atkinson
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Section 1

Basic science

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Basic science

Reinhold Munker, Gary Brooke, and Kerry Atkinson

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The human hemopoietic system

Understanding of the human hemopoietic and immune systems has advanced markedly during the past 25 years. The key components of the human hemopoietic system are the hemopoietic growth factors, the hemopoietic stem cell, and the marrow microenvironment. Each of these is detailed further in the following sections.

Hemopoietic growth factors

- Colony-stimulating factors (CSFs)
  - Granulocyte colony-stimulating factor (G-CSF)
  - Granulocyte-macrophage colony-stimulating factor (GM-CSF)
  - Macrophage colony-stimulating factor (M-CSF)

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Interleukin (IL)-3
Erythropoietin
Thrombopoietin
IL-5

- Stem cell factors
  - Kit ligand (stem cell factor)
  - Flt ligand
- Synergistic factors
  - IL-1
  - IL-6
  - IL-7
  - IL-9
  - IL-10
  - IL-11
  - IL-12
  - Leukemia inhibitory factor (LIF)
- Inhibitors/bidirectional regulators
  - Tumor necrosis factor alpha (TNF-α)
  - Transforming growth factor beta (TGF-β)
  - Macrophage inflammatory protein-1β (MIP-1β)
  - Interferon gamma (IFN-γ)

Registered Hematopoietic Growth Factors

Native molecule	Form	Generic name	Brand name	Dosage	Manufacturer
G-CSF	Nonglycosyl	Filgrastim	Neupogen®	5 μg/kg/d	Amgen
Peg-G-CSF	Nonglycosyl	Pegfilgrastim	Neulasta®	6 mg/14 d	Amgen
G-CSF	Glycosylated	Lenograstim	Granocyte®	5 μg/kg/d	Chugai/ Rhone-Poulenc
GM-CSF	Nonglycosyl	Molgramostim	Leukomax®	250 $\mu g/m^2/d$	Berlex/ Immunex
GM-CSF	Glycosylated	Sargramostim	Leukine®	250 $\mu g/m^2/d$	Bayer
EPO		Epoetin α	Procrit®	50–150 U/kg 3 × weekly	Amgen/Ortho
EPO		Epoetin β	NeoRecormon®	60–150 U/kg (1-3 times weekly)	Roche
Darbepoietin-α		Darbepoietin	Aranesp®	25–500 μg/kg/week or 50 μg/kg/d	Amgen
Interleukin-11		Oprelvekin	Neumega®	5–30 μg/kg/d	Wyeth
Stem cell factor		Ancestim	Stemgen®	20 μg/kg/d*	Amgen

* Dosage for stem cell mobilization; not licensed in the United States.

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The hemopoietic stem cell

- 1 in 2000 bone marrow cells
- 2000-fold increase in ability to confer radioprotection
- The murine phenotype is Sca-1^+ Thy 1^{lo} Lin^-. Sca-1^+ Thy 1^{lo} Lin^-Mac 1^{-1} $CD4^-$ is the phenotype of stem cells with long-term repopulating ability. These have extensive self-renewal capacity and represent 80% of stem cells. Only 4%, however, are in the $S/G_2/M$ phases of the cell cycle at any one time (0.005% of bone marrow cells).
- Sca 1^+ Thy 1^{lo} Lin^-Mac 1^{lo} $CD4^-$and Sca-1^+ Thy l^{lo} Lin^-Mac 1^{lo} $CD4^+$ are the phenotypes of stem cells with short-term repopulating ability, representing 20% of stem cells in the marrow.
- The human phenotype is $CD34^+$ Thy 1^{lo} $Lin^-Rho^{123\ lo}$ (rhodamine^{123} is a mitochondrial dye, the uptake of which correlates with self-renewal capacity).
- Phenotype variations: $CD34^+$, HLA-$DR^{+/-}$, $CD38^{+/-}$, Thy $1^{+/-}$, Lin^-, *c-kit*$^+$, $Rho^{123\ dull}$; $CD34^+$/HLA-DR^+ do not produce long-term culture initiating cells (LTCIC); $CD34^+$/ HLA-DR – do produce LTCIC.
- Human multipotential stem cell characteristics:
  Multilineage differentiation
  Self-renewal capacity
  Ability to reconstitute myeloablated patient.
- Lineage negativity includes absence of the following:

Lineage	Cell surface antigens
T cell	CD7, 2, 3, 4, 8
B cell	CD19, 20
NK cell	CD56, 57
Myeloid	CD33, 15
Erythroid	Glycophorin

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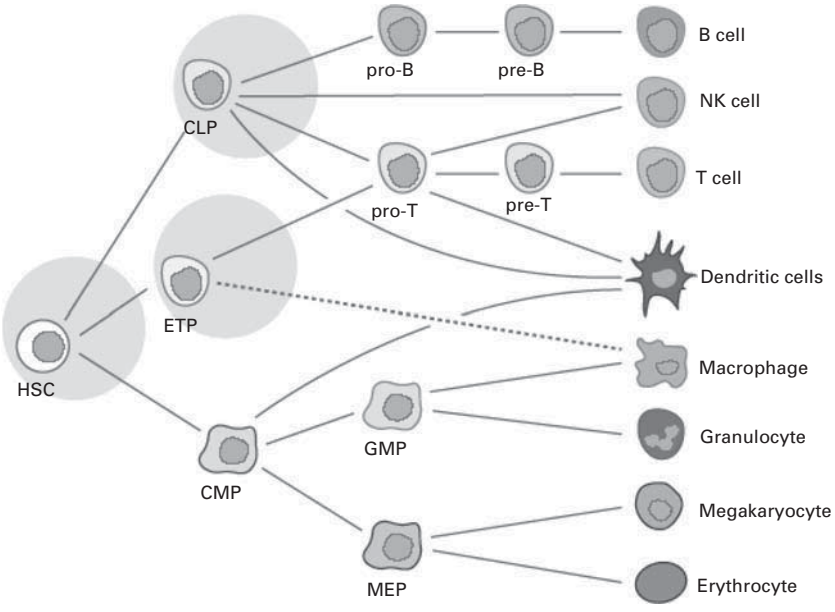
Hematopoietic stem cell differentiation



Scheme of human hematopoietic stem cell differentiation. Multiple transcription factors, cytokine receptors, secreted and surface-based cytokines determine the fate and lineage determination of stem cells.
Revised model of adult hematopoiesis based on work by Akashi, Kondo, and Weissman
Abbreviations: HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; ETP, early T-progenitor; GMP, granulocyte-macrophage progenitor; MEP, megakaryocyte-erythroid precursor. Reproduced with permission from Laiosa et al. (2006).

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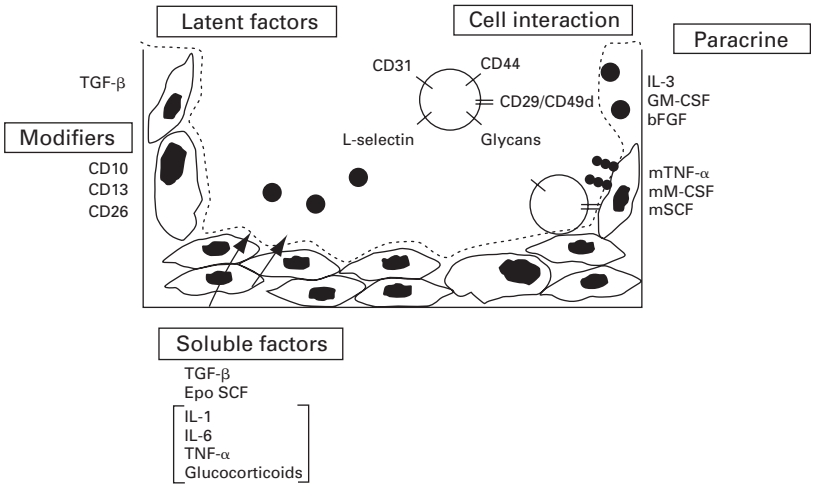
The human marrow microenvironment



A schematic diagram of features of the human marrow environment.
The major types of progenitor–stromal interactions thought to be important are boxed. Examples of each are listed beside the heading. The diagram illustrates stromal cells (arbitrarily drawn) and extracellular matrix (ECM). *Latent factors*: TGF-β, transforming growth factor β. Modifiers: CD10, CD13, CD26 represent the cluster of differentiation (CD) nomenclature for cell surface proteases and tuftsin endocarboxypeptidase. *Soluble factors*: Epo, erythropoietin; SCF, stem cell factor (c-kit ligand, mast cell growth factor); IL, interleukin; TNF-α, tumor necrosis factor α. The factors in brackets in serum at increased concentrations during infections and other systemic stresses. *Cell interaction:* CD, cluster of differentiation nomenclature for adhesion molecules; CD49d and CD29 are the α and β chains of α4β1-integrin, respectively; L-selectin, leukocyte-expressed member of the selectin family; glycans, saccharide structures that can act as ligands for molecules with lectin activity (e.g., selectins). *Paracrine:* bFGF, basic fibroblast growth factor; m-TNF-α, transmembrane form of TNF-α; mM-CSF, transmembrane isoform of M-CSF; m-SCF, transmembrane SCF; GM-CSF, granulocyte-macrophage colony-stimulating factor. Reproduced with permission from Atkinson et al. (2003).

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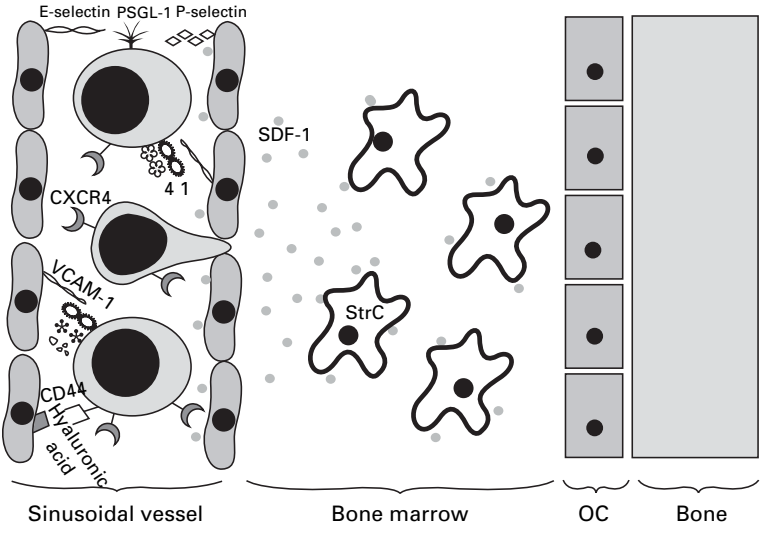
Stem cell homing



Human hematopoietic stem cells (HSCs) are administered intravenously and subsequently enter the bone marrow sinusoidal vessels. Cell adhesion molecules on the surface of HSCs bind to a variety of ligands on sinusoidal endothelial cells (ECs), allowing rolling and firm adhesion to occur. HSCs then transmigrate the sinusoidal endothelial cells, following a stromal derived factor (SDF)-1 gradient, into the bone marrow where they establish residence within the endosteal niche, adjacent to osteoblastic cells (OCs). PSGL-1: P-selectin glycoprotein ligand-1; VCAM-1: vascular cell adhesion molecule-1; StrC: stromal cell. Reproduced with permission from Chute (2006).

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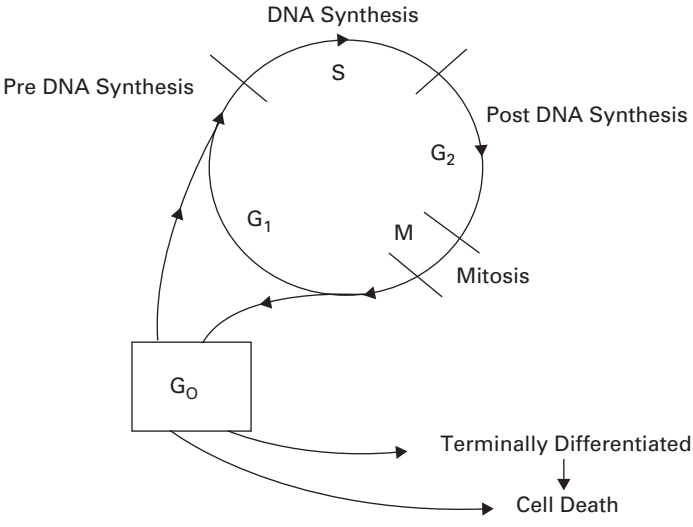
The cell cycle



The human immune system

In the last few years, it was increasingly realized that the immune system plays an important role in eradicating minimal residual malignant disease after marrow-ablative chemo-/radiotherapy and allogeneic or autologous stem cell transplantation. For that reason, an understanding of the integral components of the immune system is important for the clinical transplanter. A key event is the presentation of antigen to T cells by antigen-presenting cells using molecules of the major histocompatibility complex (MHC).

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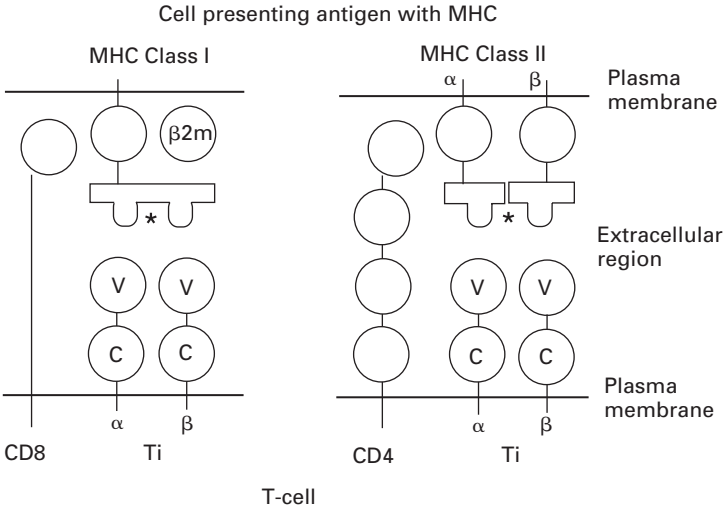
Antigen presentation by the MHC



Antigen presentation by the MHC; intercellular interaction between T cells and antigen presented by MHC.
The left part of the figure indicates antigen presentation by MHC Class I, and the right indicates antigen presentation by MHC Class II. The position of the peptide antigen is indicated by an asterisk. Each large circle represents an immunoglobulin-like domain of approximately 100 amino acids. The α and β chains of Class II are shown. β2m indicates β_2 microglobulin. The V (variable) and C (constant) regions of the Ti chains are shown.

T cell–B cell collaboration

T cells also collaborate with B cells to help them produce antigen-specific antibody.

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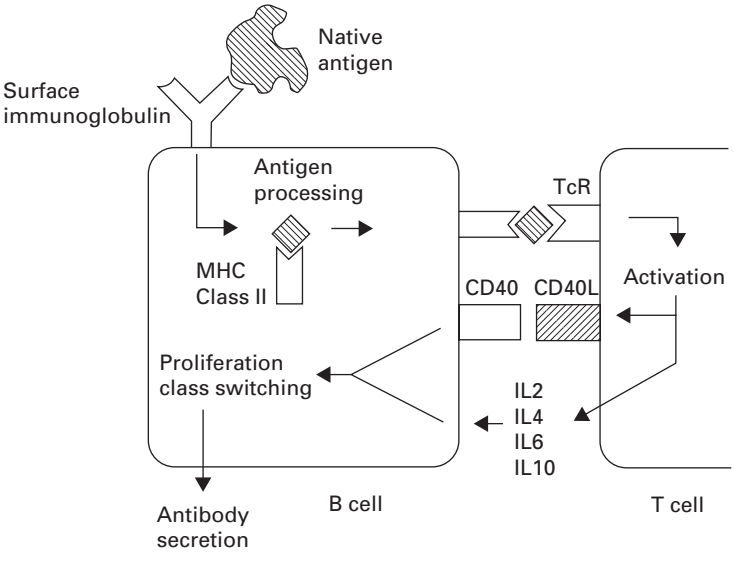
Collaboration between B cells and T cells



Native antigen binds surface immunoglobulin and is internalized and processed by B cells. Antigen binds to Class II MHC and is presented to T cells that become activated after the T-cell antigen receptor complex (TCR) recognizes the antigen. T cells help B cells by secreting several cytokines, including those shown, and by expressing the CD40 ligand (CD40L), which stimulates B cells by binding to the surface marker CD40. The B-cell responses of proliferation, class switching, and antibody secretion are shown.

CD markers and currently recognized leukocyte surface antigens

Another key component of the immune system is the array of molecules on the surface of leukocytes, known as CD (cluster of differentiation) antigens. The currently recognized human leukocyte differentiation antigens (recently updated, see Zola et al., 2007) can be accessed online at www.hcdm.org

Adhesion molecules

Group	Molecular characteristics	Example (Function)	Ligand	Function
Integrins	Transmembrane α and β chains	LFA-1 (intercellular adhesion) CR3, CR4 (opsonization) VLA-1–6 (binding lymphocytes to extracellular matrix)	ICAM-1,-2 C3b Various	Firm attachment

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