Understanding blood and its components

A Guide for Nurses

Leukaemia Care
Nurse Academy

Introduction

Haematopoiesis is the process by which blood cells develop.

It begins with the emergence of haematopoietic stem cells (HSCs) from the major arteries of a developing embryo, which eventually seed the bone marrow. After birth, a steady 'pool' of HSCs from which all blood cells arise is maintained in the bone marrow by the carefully orchestrated regulation of HSC self-renewal and differentiation.

If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

In this booklet

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Webinars

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

Hierarchical relationship of blood cell development

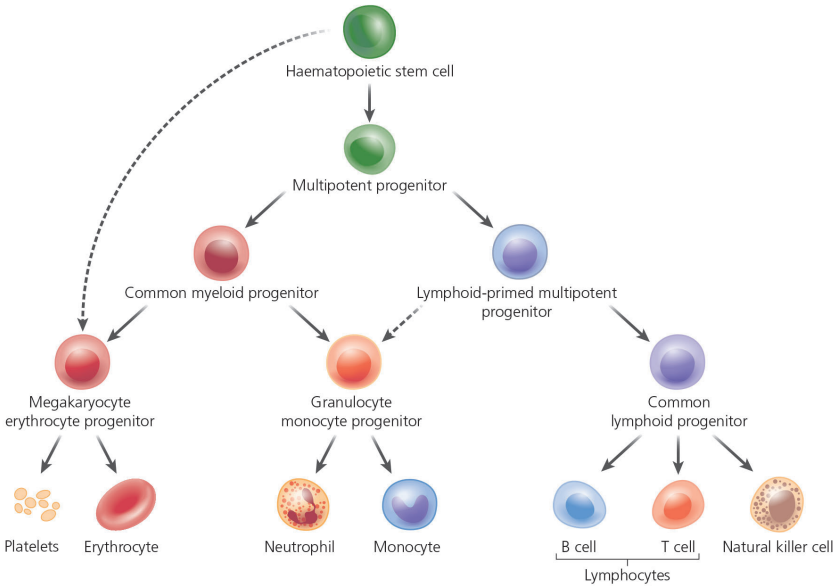

Figure 1.1 Hierarchy of haematopoiesis: the multiple stages of blood cell development from HSCs to terminally differentiated cells through intermediate progenitors. The dashed lines represent an alternative differentiation pathway proposed by Adolfsson et al. 2005, based on the presence of lymphoid-primed multipotent progenitors.

Differentiation. HSCs in the bone marrow subsequently develop into other terminally differentiated cells such as erythrocytes, granulocytes and monocytes (Figure 1.1). HSCs give rise to both myeloid and lymphoid lineages of blood cells. The commitment of differentiated cells is irreversible: for example, monocytes are unable to form erythrocytes.

Self-renewal. The second fundamental attribute of HSCs is the ability to self-renew to provide a continuous source of blood cells throughout the human lifespan. The ability to self-renew is maintained through several tightly regulated mechanisms that are gradually being elucidated. The incidence of uncontrolled proliferation (as in cancer) is rare compared

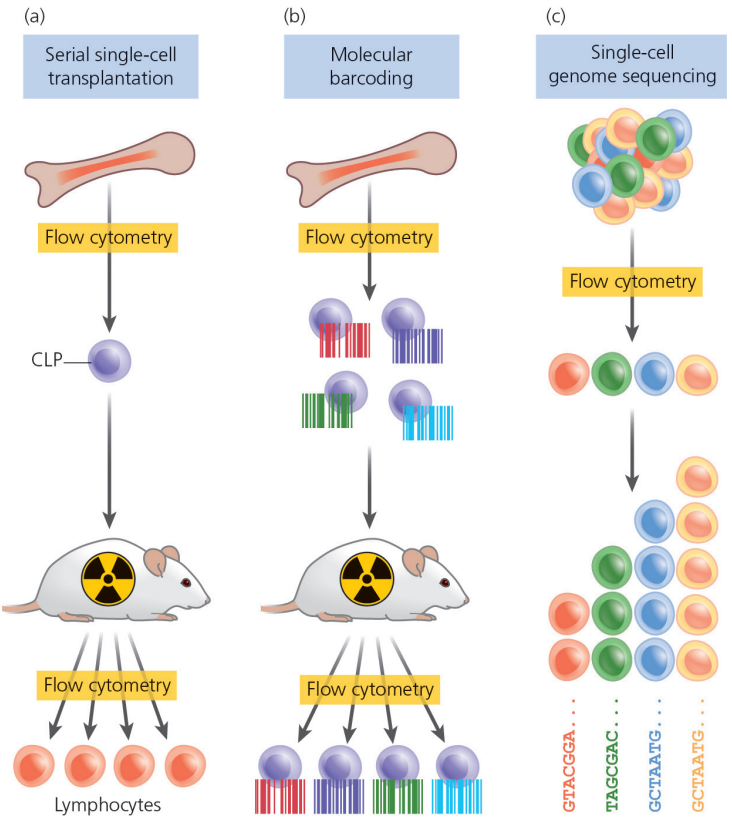

Figure 1.2 Experimental haematopoietic models used to query the fate of different cell populations. Flow cytometry is the most widely applied method for characterising and, in combination with cell sorting, isolating stem cells. (a) Flow cytometry can isolate populations of lymphoid or myeloid stem cells in vivo. First, a population of cells with the same surface cell markers (for example, CLPs) is isolated from a bone marrow sample by flow cytometry. This is transplanted into an irradiated mouse. The resulting cell line is then analysed by flow cytometry, in this case showing differentiation into lymphocytes only. (b) The in vivo differentiation of individual haematopoietic progenitor cells can be tracked by labelling each cell with a unique genetic barcode. Its progeny can then be tracked by high-throughput sequencing, permitting the contribution of clonal populations to the overall haematopoietic system to be identified. (c) Single-cell genome sequencing has helped to refine traditional views of cell differentiation. Single cells isolated from blood or bone marrow samples by flow cytometry can then be grouped according to their gene expression to establish the clonal relationship between individual cells.

Hierarchical relationship of blood cell development (cont.)

with the number of times the haematopoietic system responds by controlled proliferation to injury or infection. One way in which this is regulated is through the loss of self-renewal properties in differentiated cells such as neutrophils and monocytes. For example, vast numbers of neutrophils are drawn to sites of infection, but they have a limited lifespan and must be replaced by upstream progenitors. This requires the HSCs to exit dormancy and generate intermediate progenitors (see Figure 1.1) that can divide rapidly and replenish these peripheral cells.

Identification of upstream progenitor cells. The precursors of fully differentiated neutrophils and erythrocytes bear intermediate properties between the final cells and the HSCs. They have an increasingly restricted developmental potential as they complete their development. Traditionally, these precursor cells have been identified by labelling cell surface markers with antibodies conjugated to fluorescent proteins, which can then be identified by flow cytometry. Cells sorted by these cell surface markers have been transplanted into irradiated mice, and only specific populations of cells have been found to develop from them. For example, when common lymphoid progenitors (CLPs) are transplanted into irradiated mice, they only give rise to lymphocytes (Figure 1.2a). Similarly, upstream intermediate progenitors of myeloid and erythroid cells have been identified. However, the exact lineages and potentials of different intermediaries have been revised over the years.

More recent work based on single-cell analyses has revealed novel insights into the process of haematopoiesis (Figures 1.2b,c). Normal blood cells can be sorted into individual cells using flow cytometry and RNA extracted from them. From this, the expression levels of different genes can be identified using next-generation sequencing (NGS) and, in combination with traditional transplantation studies, the fate of these cells can be determined. These studies have further revised

the models of haematopoiesis, with some suggesting that haematopoietic development is a continuous process rather than one of sequential subpopulations with increasingly restricted lineage potential.

Regulation of normal blood cell development

Above, we have described the differentiation of HSCs through various oligopotent, and eventually unipotent, terminal effector cells. Research has shown that sufficient but not excessive numbers of fully differentiated cells are generated in response to infection and inflammation.

The role of cytokine signalling. Cytokines provide signals to cells to proliferate and differentiate. For example, dormant HSCs can be stimulated by the cytokine interferon-α (IFNα) to produce more proliferative oligopotent stem cells that can then differentiate into other cells such as neutrophils. Other cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) drive differentiation of progenitor cells into neutrophils and monocytes.

Permissive versus instructive signalling. An ongoing debate on the role of cytokine signalling is whether cytokines merely provide a permissive environment for HSCs to differentiate into a specific role (permissive model) or whether they have a more direct role, driving HSCs down a specific differentiation lineage (instructive model).

Permissive signalling. Mice in which the receptor for M-CSF had been removed produced only low numbers of monocytes. However, when the myeloid cells were rescued by the expression of the antiapoptotic gene BCL2, the monocyte numbers increased. This study suggests that cytokines allow the survival of HSCs, which enables them to fully differentiate.

Instructive signalling. In one study, the exogenous expression of specific cytokine receptors (interleukin-2 and GM-CSF) in progenitor cells that had already commenced lymphoid development enabled transdifferentation of the cells into myeloid development. This study suggests that cytokine signalling can regulate cell fate decisions.

Overlapping role of cytokines. Different cytokines can activate the same receptors, and different receptors can have overlapping downstream

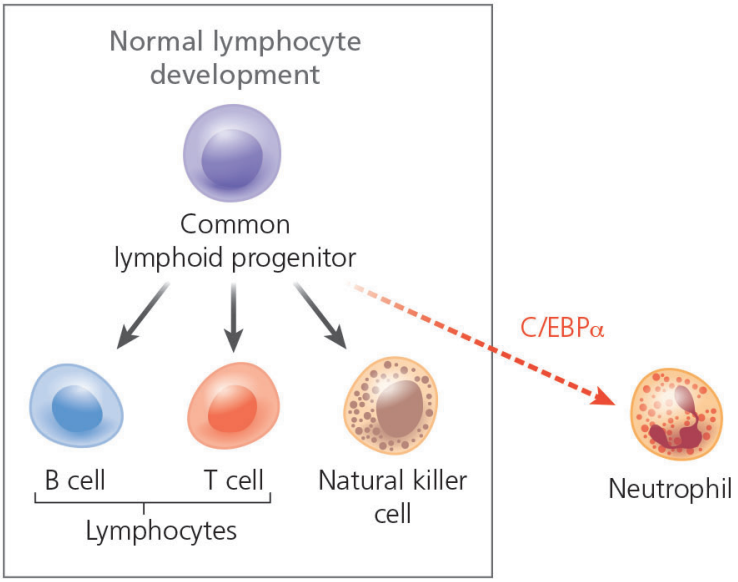

Figure 1.3 Transcription factors can transdifferentiate cells committed to other lineages. For example, overexpression of the CEBPA gene in CLP cells makes the transcription factor C/EBPα, which at high enough levels can reprogramme CLPs into mature myeloid cells such as neutrophils, rather than normal lymphocytes. C/EBPα, CCAAT-enhancer-binding protein α.

effects. For example, although knockout of the erythropoietin receptor results in the absence of mature erythrocytes, early erythroid progenitors can persist, in part because of the likely compensatory effect of thrombopoietin signalling, which normally regulates platelet production.

The role of specific transcription factors. Transcription factors are vital in the regulation of haematopoiesis. Evidence for this is seen through the disruption of haematopoiesis in both mouse models and in familial patterns of disease. Haematopoietic cells are exquisitely sensitive to subtle variations in expression levels of transcription factors. For example, a simple twofold increase in the levels of the transcription factor GATA binding protein 2 (GATA2) blocks differentiation of haematopoietic cells in mice. Powerful experimental data also show the ability of ectopically expressed transcription factors to transdifferentiate committed haematopoietic cells into different lineages (Figure 1.3).

One important master regulator of haematopoiesis is the RUNX1

Regulation of normal blood cell development (cont.)

(AML1) gene. This gene is essential for the emergence of HSCs in the developing embryo. A complete absence of RUNX1 results in the death of the developing embryo. A dysfunctional copy of RUNX1 is inherited in familial platelet disease. Affected family members, who inherit this condition in an autosomal dominant manner, are thrombocytopenic with a predisposition to the development of acute myeloid leukaemia (AML).

CCAAT-enhancer-binding protein α (C/EBPα) is another important transcription factor in haematopoiesis. Mice with a knockout of the CEBPA gene lack mature neutrophils, suggesting that this gene is vital for their development. Recent studies have shown that germline mutations in CEBPA are associated with an increased risk of developing AML, with a documented penetrance rate of 100%. The importance of transcription factors in haematopoiesis is underlined by the ability of C/EBPα to transdifferentiate cells into neutrophils (see Figure 1.3). Using retroviral vectors, overexpression of CEBPA can rapidly force lymphoid progenitors, lymphocytes and even AML cells to transdifferentiate into mature myeloid cells such as neutrophils.

Finally, there is an appreciation that transcription factors regulate each other's activities and form a network that defines the identity and function of each cell. Elucidating these networks will allow the de novo generation of different components of the haematopoietic system (for example, artificial blood) and help us to understand how they might be subverted in leukaemia.

Key points – understanding blood and its components

- HSCs develop into terminally differentiated myeloid and lymphoid cells through intermediate progenitor cells.
- The lineage of haematopoietic cells has been extensively studied using flow cytometry and traditional transplantation techniques.
- The precursors of fully differentiated blood cells have intermediate properties between the final cells and the HSCs. Developmental potential becomes increasingly restricted.
- The self-renewal of HSCs is a highly regulated process that provides a continuous source of blood cells in adult humans.
- Cytokines such as IFNα and GM-CSF provide signals to HSCs to proliferate and differentiate.
- Transcription factors are also vital in the regulation of haematopoiesis.

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemiacare.org.uk

support@leukaemiacare.org.uk

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