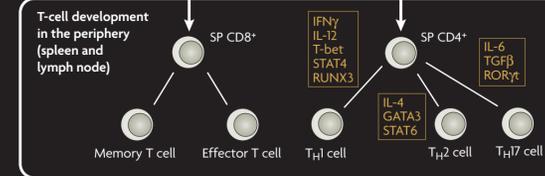
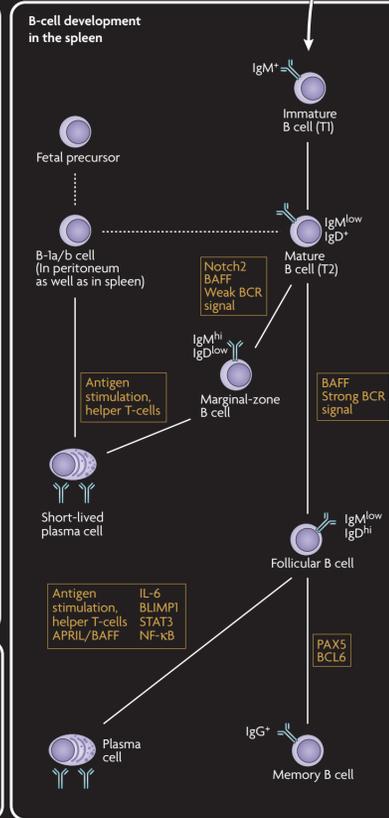
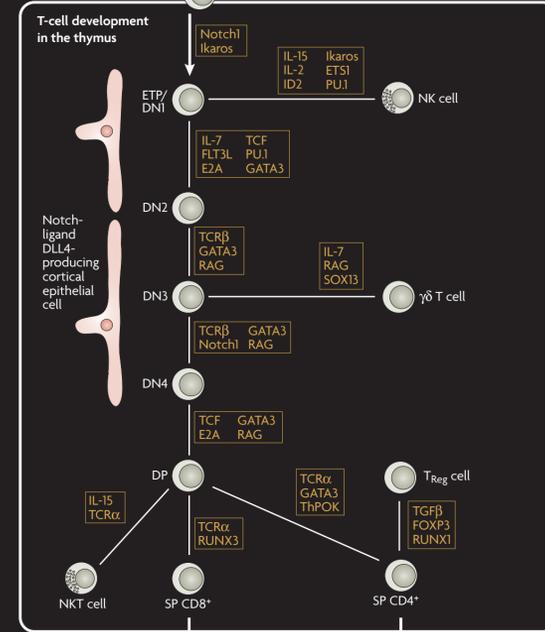
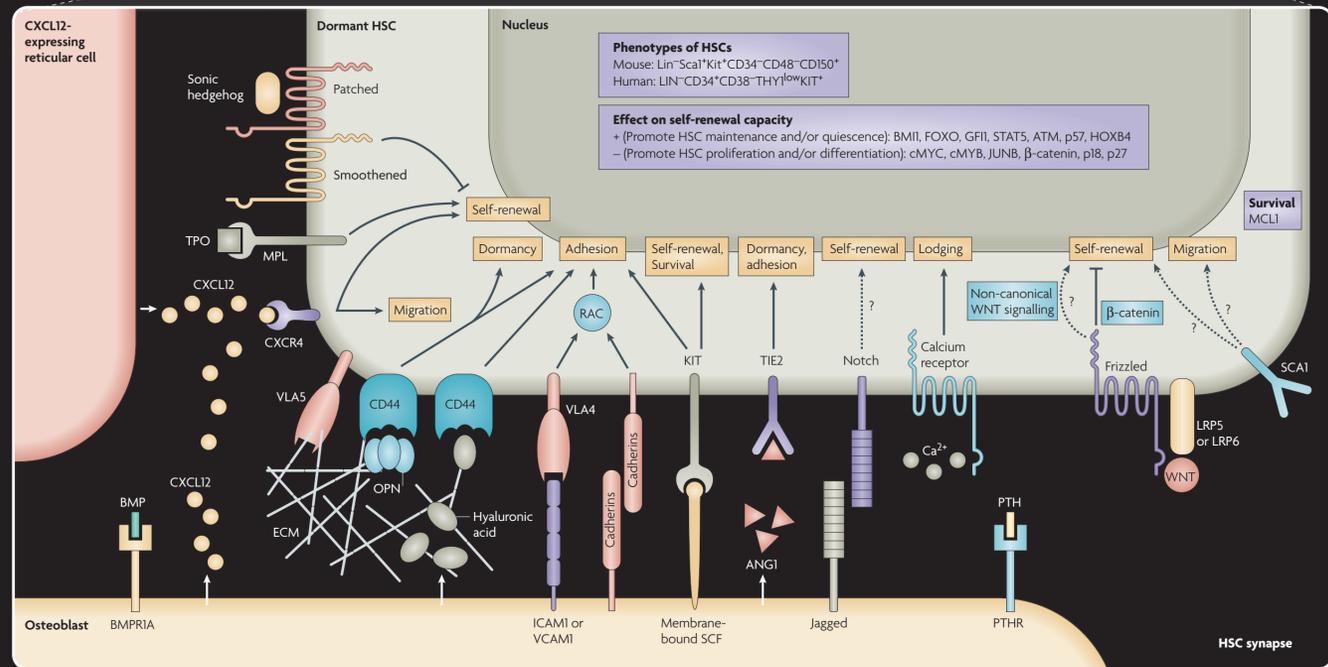
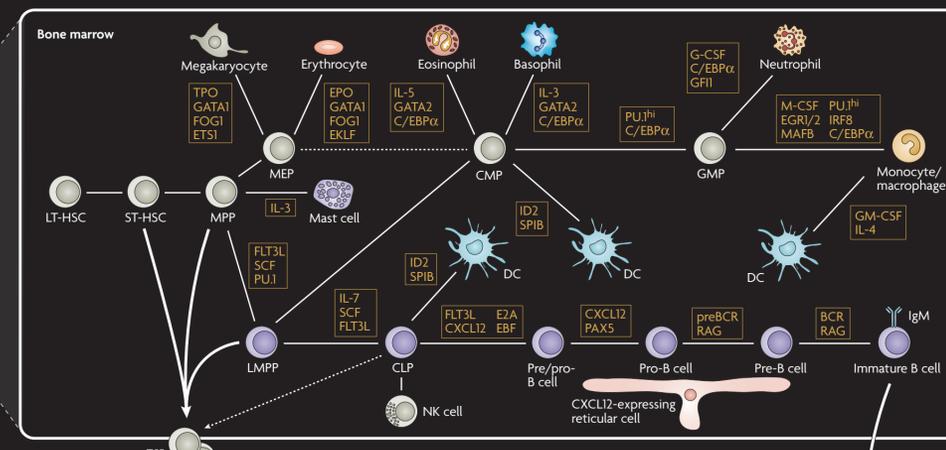
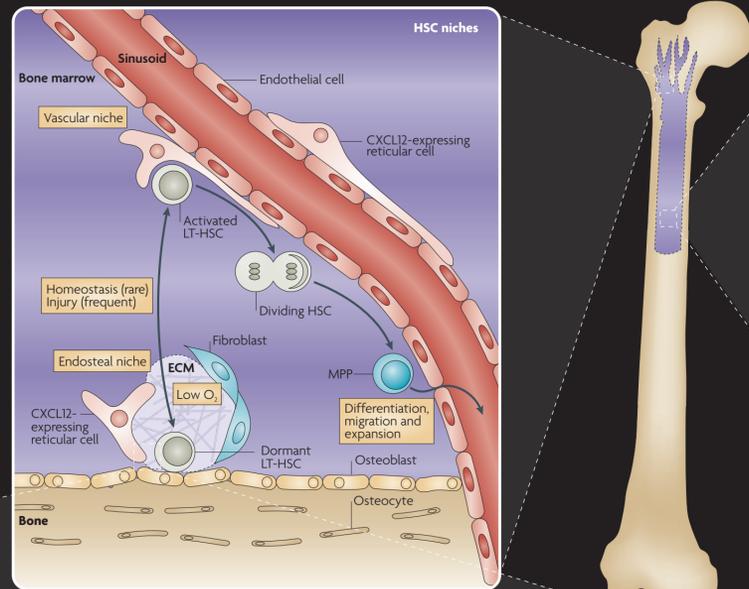
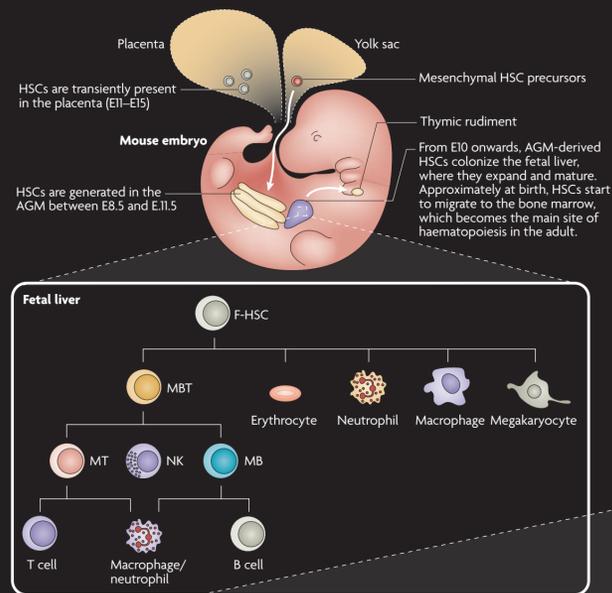


Haematopoietic stem cells, niches and differentiation pathways

Thomas Graf and Andreas Trumpp

Haematopoietic stem cells (HSCs) continuously replenish blood cells that are lost by attrition or tissue damage. They are capable of self-renewal and are currently the only adult stem-cell type routinely used in clinical settings to replace lost cells. HSCs are mostly quiescent but can be mobilized from their niche to proliferate and differentiate into lineages of the innate and adaptive immune system, as well as into red blood cells and platelets. Cell-fate decisions are initiated and maintained by specific combinations of

transcription factors, the activity of which is orchestrated by extrinsic and intrinsic signals. The study of changes in regulatory networks during haematopoietic differentiation has long served as a paradigm for basic processes of cell-fate specification and its aberrations, such as those that occur in leukaemia. The easy accessibility and transplantability of normal and leukaemic haematopoietic cells has led to the discovery of cytokines, oncogenes and cancer stem cells and to some of the most celebrated successes of targeted drug design.



Guide through the poster

The upper left region of the poster shows a mouse embryo with its haematopoietic anlagen. Although the extent of yolk-sac contribution to the formation of adult HSCs is controversial, most HSCs are probably formed in the aorta-gonad-mesonephros (AGM) region. From here, stem cells seed the fetal liver, where they expand and differentiate into myeloid and lymphoid lineages. Subsequently, HSCs exit the liver and populate specialized bone-marrow microenvironments (niches) in which they gradually become quiescent. As shown in the lower left panel, dormant HSCs are mostly located close to the lining of the trabecular bone, the endosteal niche. This niche contains osteoblasts and CXC-chemokine ligand 12 (CXCL12)-expressing reticular (CAR) cells. Several cell adhesion molecules, together with short-range signalling molecules, control HSC lodging and maintenance (lower left panel). In response to specific signals, it is thought that HSCs are recruited to vascular niches — that are comprised of CAR cells and fenestrated sinusoidal endothelial cells — where they begin to divide, differentiate and enter the circulation. Bone-marrow-derived thymus-seeding progenitors (TSPs) seed the thymus and become committed to the T-cell lineage (lower right panel). In the thymus, the cells travel from the cortex through the subcapsular zone to the medulla, encountering different epithelial niches that guide them through several developmental stages. Finally, CD4+ and CD8+ T cells enter the circulation and differentiate into mature effector and helper T cells in the spleen and lymph nodes. B-lineage cells become committed in the bone marrow and, after immature B cells enter the circulation and home to the spleen, they mature into antibody-secreting memory B cells and plasma cells (lower right panel).

The differentiation pathways are shown beginning with HSCs and ending with mature cells. Dotted lines represent transitions in which the origin of the more mature cell is not clear. Arrows indicate points of migration of circulating cells (with the exception of the HSC synapse panel). It is likely that the early stages of HSC development represent a continuum. There are still uncertainties about several parts of the pathways. The poster shows multipotent progenitors (MPPs) branching into megakaryocyte/erythroid progenitors (MEPs) and lymphoid-primed multipotent progenitors (LMPPs). LMPPs either become common lymphoid progenitors (CLPs) or common myeloid progenitors (CMPs) and granulocyte/macrophage progenitors (GMPs). However, GMPs can also generate eosinophils, basophils and mast cells and it is possible that more than one pathway to granulocytes and macrophages exists. Finally, there are controversies about the developmental origin of the different types of dendritic cells and B cells. The poster also shows lineage-instructive signals such as chemokines, cytokines and transcription factors at the points where they are required. The definition of a lineage-instructive factor is complex and is ideally based on gene ablation, cell-type-specific gene inactivation and gain-of-function experiments. Since this applies only to a fraction of the factors shown here, the information provided is somewhat speculative. Also, only transcription factors that act dominantly during lineage commitment are listed, but not those that need to be silenced.

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Abbreviations

AGM, aorta-gonad-mesonephros; ANG1, angiopoietin 1; APRIL, a proliferation-inducing ligand; ATM, ataxia-telangiectasia mutated; BAFF, B-cell-activating factor; BCL, B-cell lymphoma; BCR, B-cell receptor; BLIMP1, B-lymphocyte-induced maturation protein 1; BMP, bone morphogenetic protein; BMPRIA, bone morphogenetic protein receptor, type 1 A; C/EBPα, CCAAT/enhancer-binding protein α; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; CXCL12, CXC-chemokine ligand 12; CXCR4, CXC-chemokine receptor 4; DC, dendritic cell; DLL4, delta-like ligand 4; DN, double negative; DP, double positive; E2A, transcription factor E2A; EBF, early B-cell factor; ECM, extracellular matrix; EGR1, early growth response; EKL, erythroid Kruppel-like factor; EPO, erythropoietin; ETP, early T-cell-lineage progenitor;

ETS1, v-ets erythroblastosis virus E26 oncogene homologue 1; F-HSC, fetal HSC; FLT3L, FMS-related-tyrosine-kinase-3 ligand; FOG1, friend of GATA 1; FOX, forkhead box; GATA1, GATA-binding protein 1; G-CSF, granulocyte colony-stimulating factor; GFI1, growth-factor independent 1; GM-CSF, granulocyte/macrophage colony-stimulating factor; GMP, granulocyte/macrophage progenitor; HOXB4, homeobox B4; HSC, haematopoietic stem cell; ICAM1, intercellular adhesion molecule 1; ID2, inhibitor of DNA binding 2; IFNγ, interferon-γ; IL, interleukin; IRF8, interferon-regulatory factor 8; LIN, lineage; LMPP, lymphoid primed MPP; LRP5, low-density-lipoprotein-receptor-related protein 5; LT-HSC, long-term repopulating HSC; MB, myeloid/B-cell precursor; MBT, myeloid, T- and B-cell precursor; MCL1, myeloid-cell leukaemia sequence 1; M-CSF, macrophage colony-stimulating factor; MEP, megakaryocyte/erythroid progenitor; MPL, myeloproliferative leukaemia virus oncogene;

Thomas Graf is an ICREA investigator at the Centre for Genomic Regulation, Dr Aiguader 88, E08003 Barcelona, Spain. e-mail: thomas.graf@crpg.edu
Andreas Trumpp is at the Swiss Institute for Experimental Cancer Research (ISREC) and the Ecole Polytechnique Fédérale de Lausanne (EPFL), Chemin des Boveresses 155, 1066 Epalinges, Lausanne, Switzerland. e-mail: Andreas.Trumpp@isrec.ch
Supplementary information (glossary terms and background reading) is associated with the online version of this poster. www.nature.com/nri/posters/hsc
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Glossary

Haematopoietic stem cells

(HSCs). Cells that are capable of reconstituting all lineages of the haematopoietic system after transplantation into lethally irradiated mice. Long-term repopulating HSCs (LT-HSCs) do this life-long and after secondary transplantations into irradiated hosts, whereas short-term repopulating HSCs (ST-HSCs) only show multilineage repopulation for a few weeks. LT- and ST-HSCs can be identified and isolated by flow cytometry on the basis of their expression of specific cell-surface antigens.

Lineage commitment

Also known as cell-fate determination; a process whereby HSCs become specialized while losing their self-renewal capacity.

Progenitor cells

Also known as precursor cells; are intermediates between HSCs and differentiated cells with restricted differentiation potential, high proliferative capacity, but little or no self-renewal capacity. They are probably equivalent to the transit amplifying cells of other adult stem-cell systems.

Myeloid cells

A term variously used to define non-lymphoid cells or cells of the monocyte–macrophage compartment (known as myelomonocytic cells).

Granulocytes

A group of cells including neutrophils, eosinophils, and basophils, but the term is often used for neutrophils only.

Stem-cell niches

Specialized microenvironments that control stem-cell dormancy and the balance between stem-cell self-renewal and differentiation.

Plasticity

The capacity of defined cell types to acquire new identities. The extent of plasticity of HSCs and haematopoietic progenitors under physiological conditions is controversial and probably quite limited. However, re-specification of cell fate can be induced by enforced transcription factor expression, cell fusion or nuclear transfer.

Self-renewal

The ability of cells to repeatedly generate at least one identical daughter cell.

Background reading

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Bone-marrow and/or HSC transplantation

A procedure involving injection of HSCs or bone marrow into irradiated hosts to determine the cell's biological potential. In the clinic it is a life-saving procedure after chemotherapy or radiation therapy that destroys the haematopoietic system. Bone-marrow transplantation typically requires immunosuppression to prevent graft rejection due to tissue mismatch.

Cord-blood stem cells

These are fetal HSCs present in the umbilical cord of newborns. They are used clinically as an alternative to bone-marrow-derived HSCs. If stored frozen and thawed years later, they can be useful for regenerating the haematopoietic system of the donor, obviating the danger of tissue rejection of mismatched transplants.

Dormancy and mobilization

Although HSCs self-renew, they are mostly quiescent, dividing approximately once a month. Proliferation can be activated in response to injury or injection of cytokines, such as granulocyte colony-stimulating factor (G-CSF). G-CSF also induces the exit of HSCs from their niches and mobilization of the cells into the circulation, a procedure that is used clinically to obtain HSCs from a patient's blood.

Cytokines and chemokines

Secreted proteins that stimulate cell growth, survival and differentiation.

Colony-forming assay

If seeded in semi-solid medium, blood-cell precursors form colonies in the presence of appropriate cytokines. This assay is widely used to define a cell's differentiation potential and to identify biologically active molecules.

Cancer and/or leukaemia stem cells

These are self-renewing cells capable of generating leukaemia after transplantation. They can give rise to more differentiated cells comprising the bulk of the leukaemia. Cancer stem cells, first identified in acute myeloid leukaemia, are critical targets for intervention.

Lineage priming

The promiscuous expression of myeloid–erythroid lineage associated markers in HSCs.

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