

Normal Hematopoiesis

Hematopoietic stem cells • lineage commitment • marrow regulation

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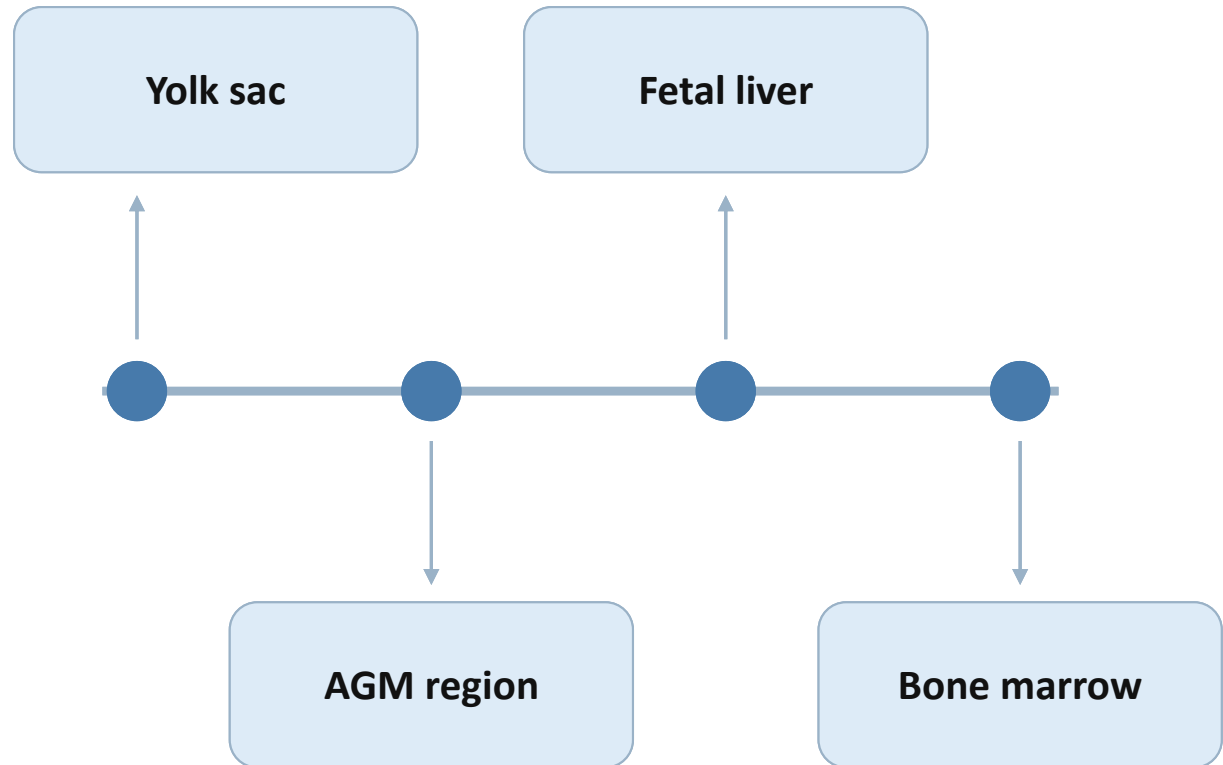
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Learning objectives

- Trace the developmental migration of blood-forming sites.
- Explain HSC pluripotency, self-renewal and lineage restriction.
- Connect growth factors to progenitor responsiveness and output.
- Interpret marrow architecture, cellularity, aspirates and biopsies.

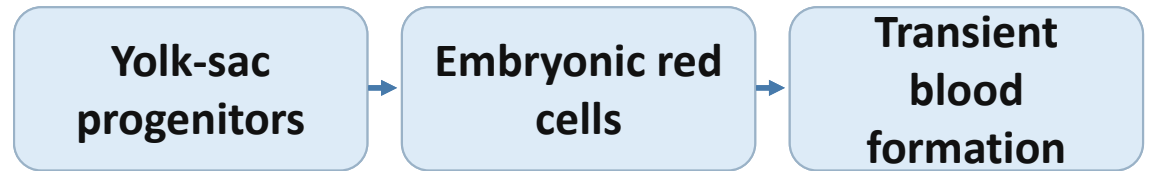
Hematopoiesis changes location during development

- The earliest blood-forming tissues are not the future adult sites.
- Stem-cell populations shift from embryonic structures to fetal liver and then marrow.
- The anatomical sequence explains changing sites of blood formation.



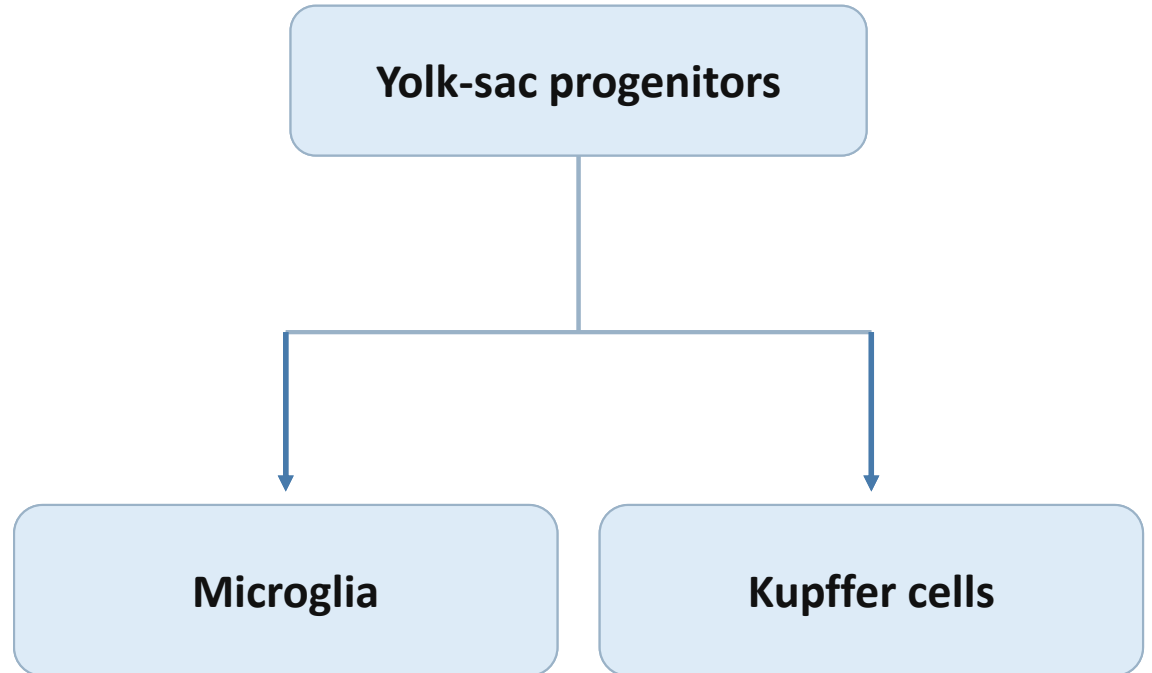
Yolk-sac hematopoiesis begins in week three

- The first blood-cell progenitors emerge in the yolk sac.
- Their contribution to circulating blood is chiefly transient embryonic erythropoiesis.
- This phase precedes the appearance of definitive HSCs.



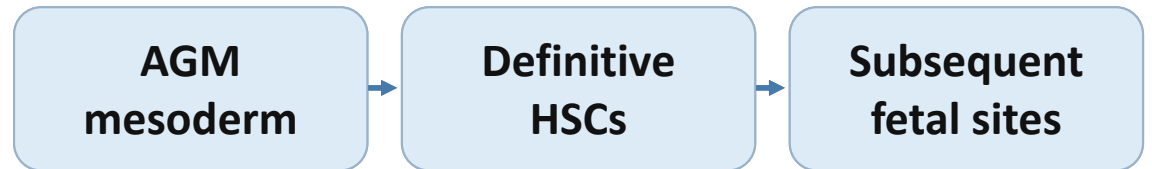
Yolk-sac progeny also supply lasting macrophages

- Yolk-sac-derived populations contribute to long-lived tissue macrophages.
- Microglia and hepatic Kupffer cells are examples cited.
- Persistent macrophage populations are distinct from transient embryonic red-cell output.



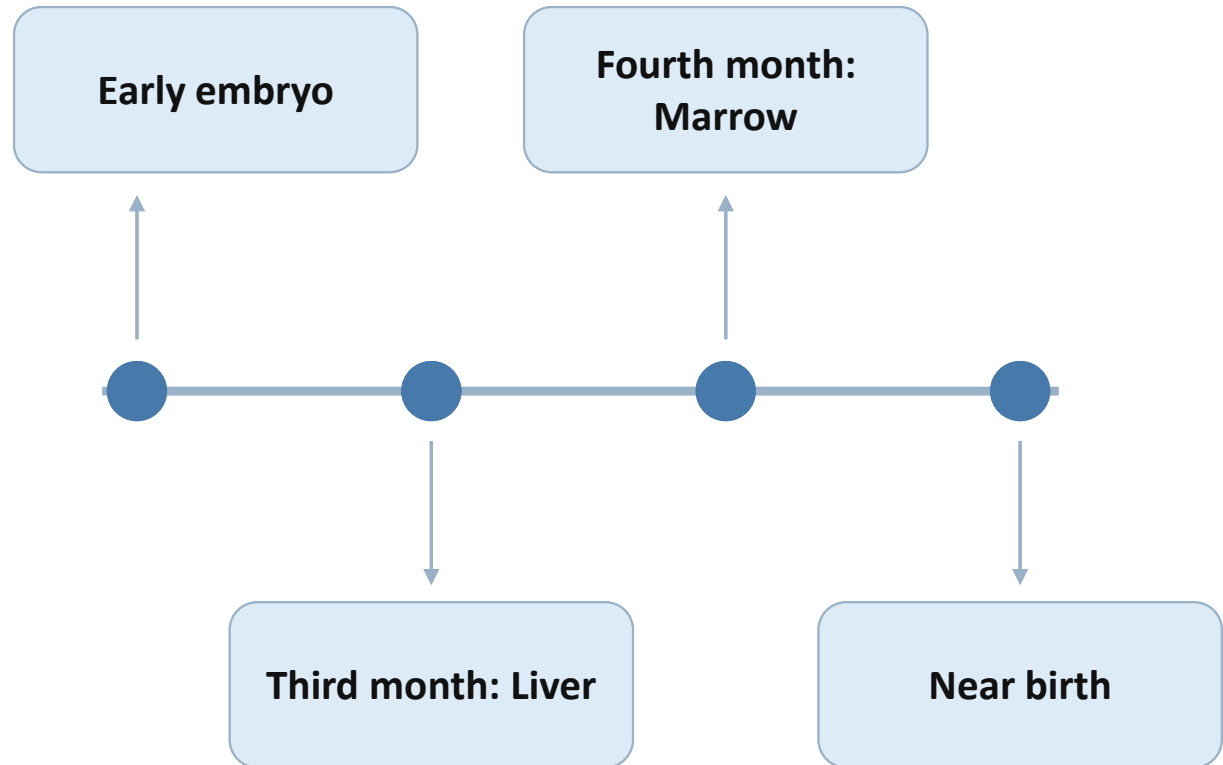
Definitive HSCs arise in the AGM region

- Definitive hematopoietic stem cells appear several weeks after yolk-sac progenitors.
- Their source is mesoderm in the intraembryonic aorta–gonad–mesonephros region.
- These HSCs are capable of sustaining later hematopoiesis.



The fetal liver becomes the main blood-forming organ

- During the third month, HSCs migrate to the developing liver.
- The liver becomes the principal hematopoietic site until shortly before birth.
- This dominance is temporary, unlike adult marrow hematopoiesis.



The fetal placenta harbors hematopoietic stem cells

- HSCs also reside in the fetal placenta.
- The physiological contribution of this pool remains uncertain.
- Cord blood collected at birth is an established transplant source of HSCs.

Placental HSC pool

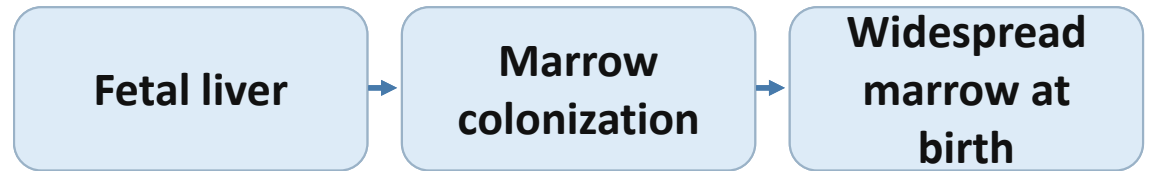
Physiologic
contribution:
Uncertain

Clinical relevance

Cord-blood
transplant source

Bone-marrow colonization begins prenatally

- By the fourth month of development, HSCs also settle in marrow.
- The shift to marrow overlaps the period of liver hematopoiesis.
- At birth, marrow throughout the skeleton is hematopoietically active.



Hepatic hematopoiesis recedes after birth

- The liver contribution falls to scattered residual foci around birth.
- These residual foci become inactive soon after birth.
- The marrow becomes the dominant normal site of blood-cell production.

Before birth

Liver is a major site

After birth

Residual hepatic foci
become inactive

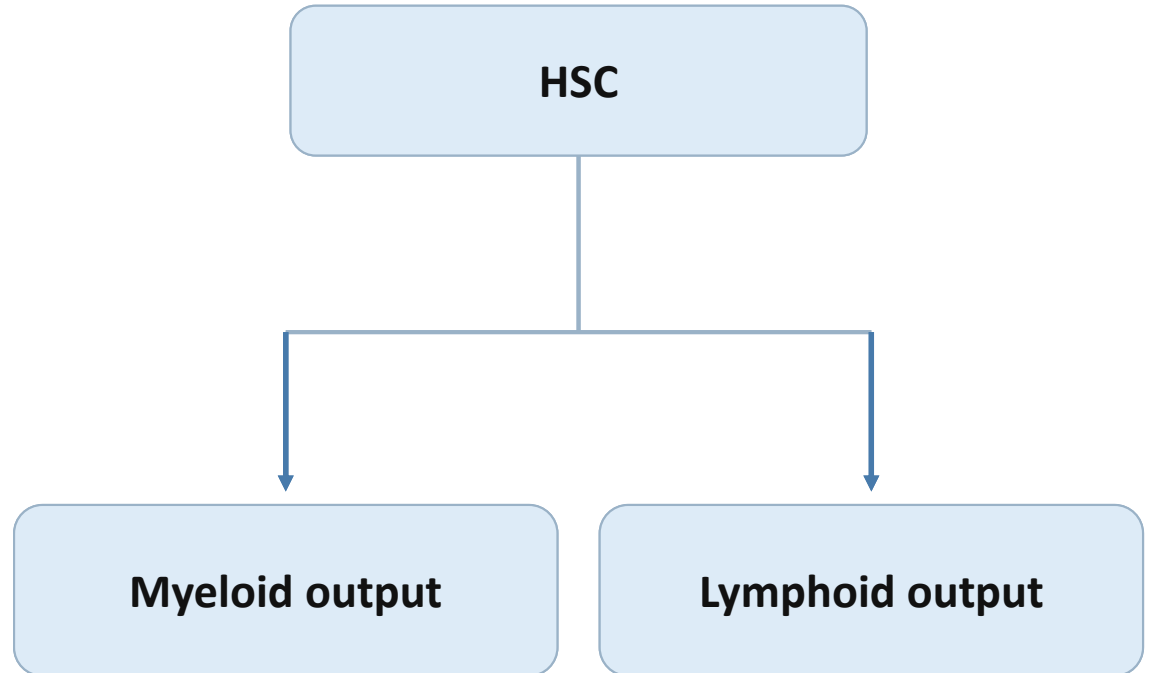
Adult hematopoiesis becomes axially restricted

- After puberty, active hematopoiesis largely ceases in distal bones.
- In normal adults, production is predominantly within the axial skeleton.
- About half of adult marrow space is hematopoietically active.

At birth	After puberty
Active marrow throughout skeleton	Activity predominantly axial

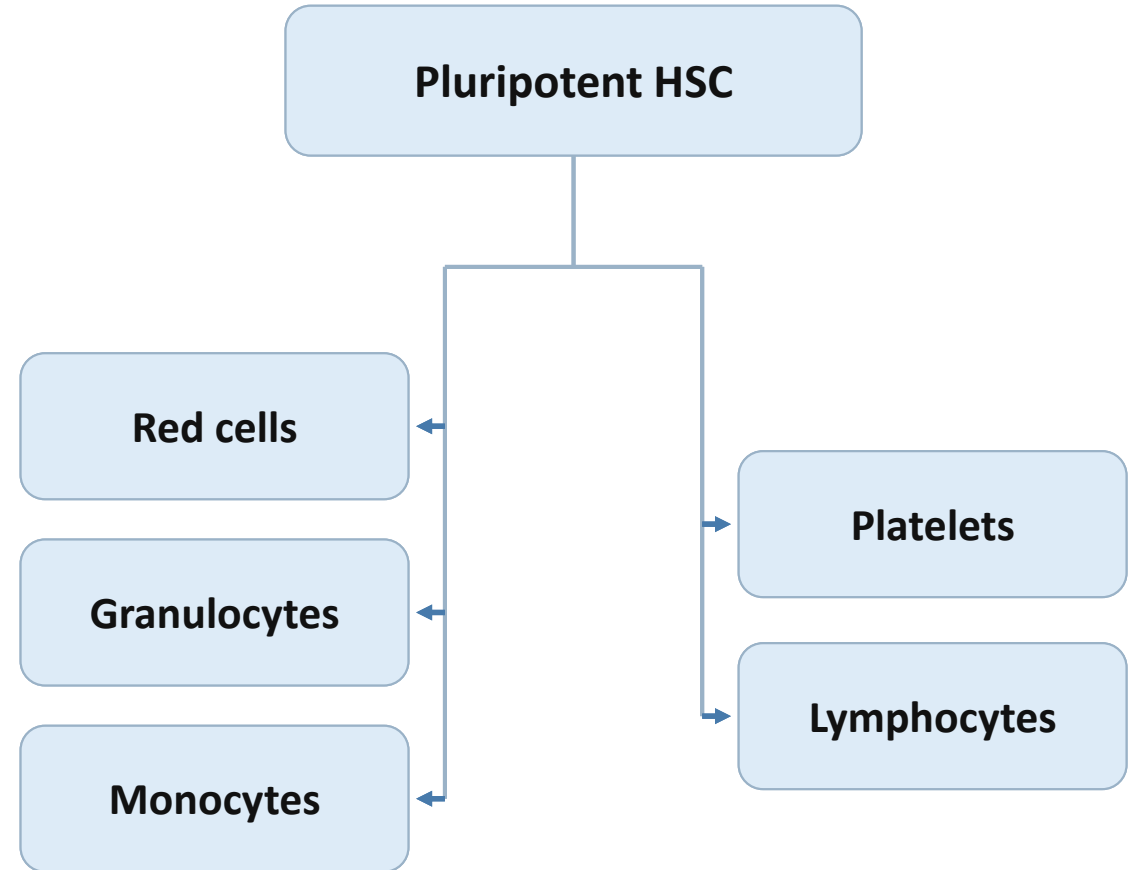
One HSC population supports all blood lineages

- Erythrocytes, granulocytes, monocytes, platelets and lymphocytes share an HSC origin.
- HSCs occupy the apex of a progenitor hierarchy.
- Diversification follows progressive restriction of cell fate.



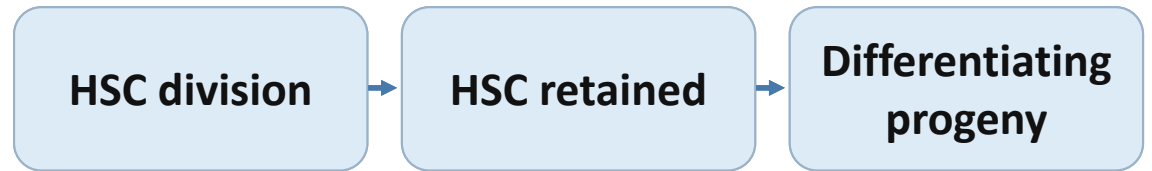
Pluripotency is the breadth of HSC fate

- One HSC can generate the major mature blood-cell lineages.
- Lineage breadth is lost progressively in downstream progenitors.
- The result is a large repertoire of mature cells from a small upstream compartment.



Self-renewal maintains the stem-cell compartment

- HSC maintenance requires a daughter cell to retain stem-cell identity.
- Self-renewal prevents exhaustion of the HSC pool.
- Differentiation can proceed in parallel with retention of stem cells.



Adult HSCs are few relative to their total output

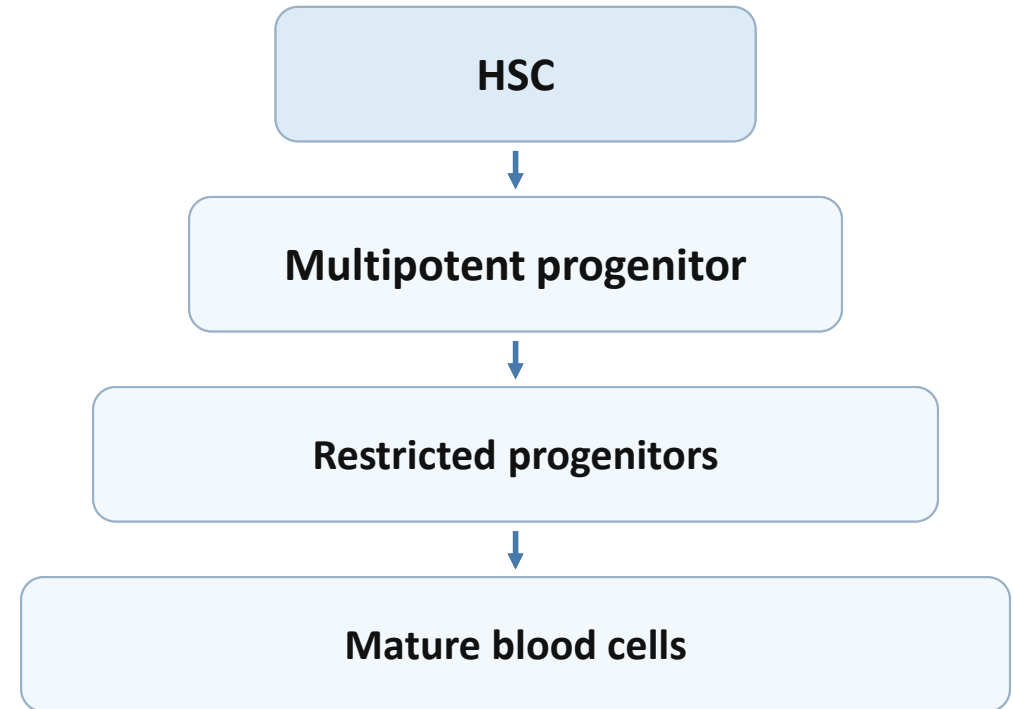
- Roughly 50,000–200,000 HSCs in normal adult marrow.
- These cells underpin the lifelong renewal of circulating blood cells.
- Their numerical scarcity makes preservation of self-renewal essential.

50,000–200,000

Estimated adult marrow HSCs

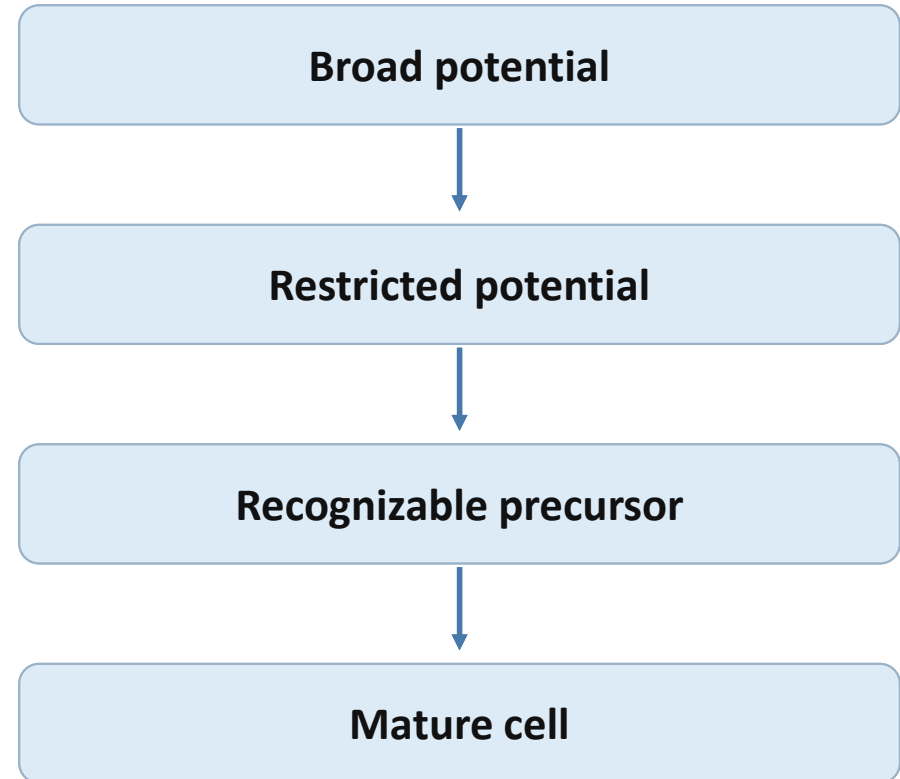
Multipotent progenitors amplify production

- Some HSC divisions give rise to multipotent progenitors (MPPs).
- MPPs proliferate more readily but have less self-renewal capacity than HSCs.
- They connect durable HSC maintenance to high-output differentiation.



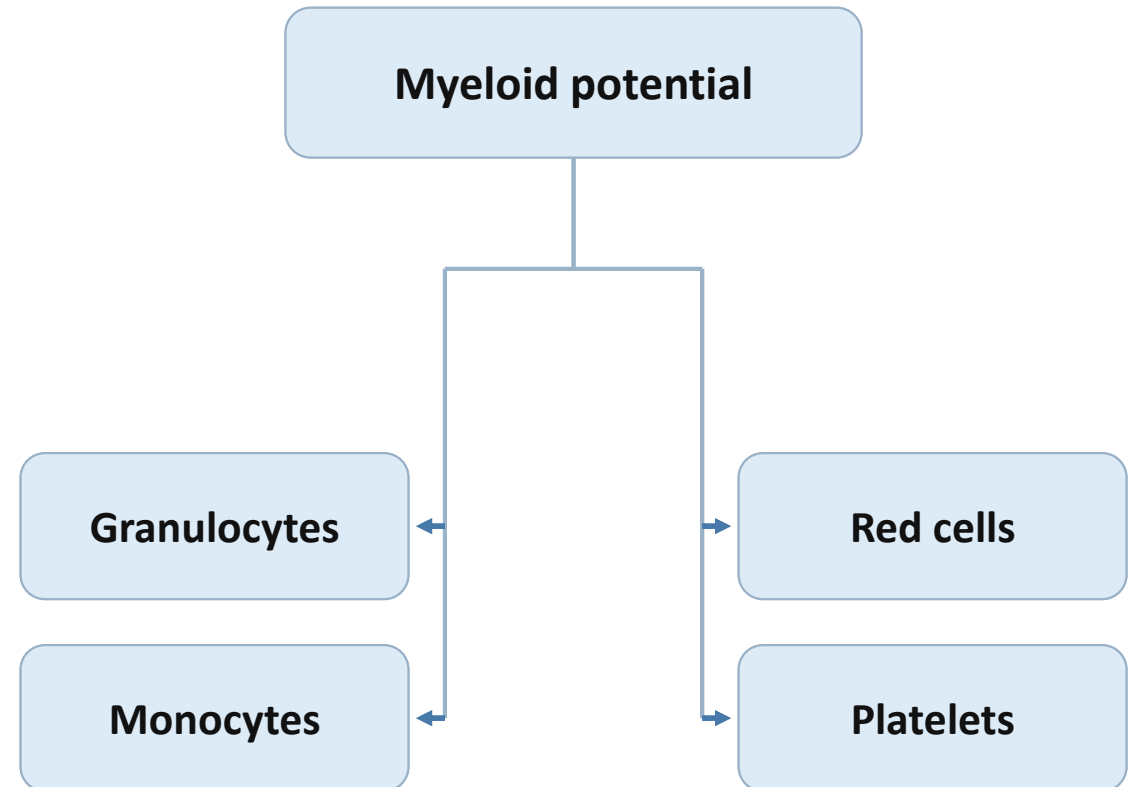
Lineage commitment is a progressive restriction

- Early progenitors still have more than one developmental option.
- Later progenitors have increasingly constrained lineage potential.
- Morphologically identifiable precursors emerge after these commitment steps.



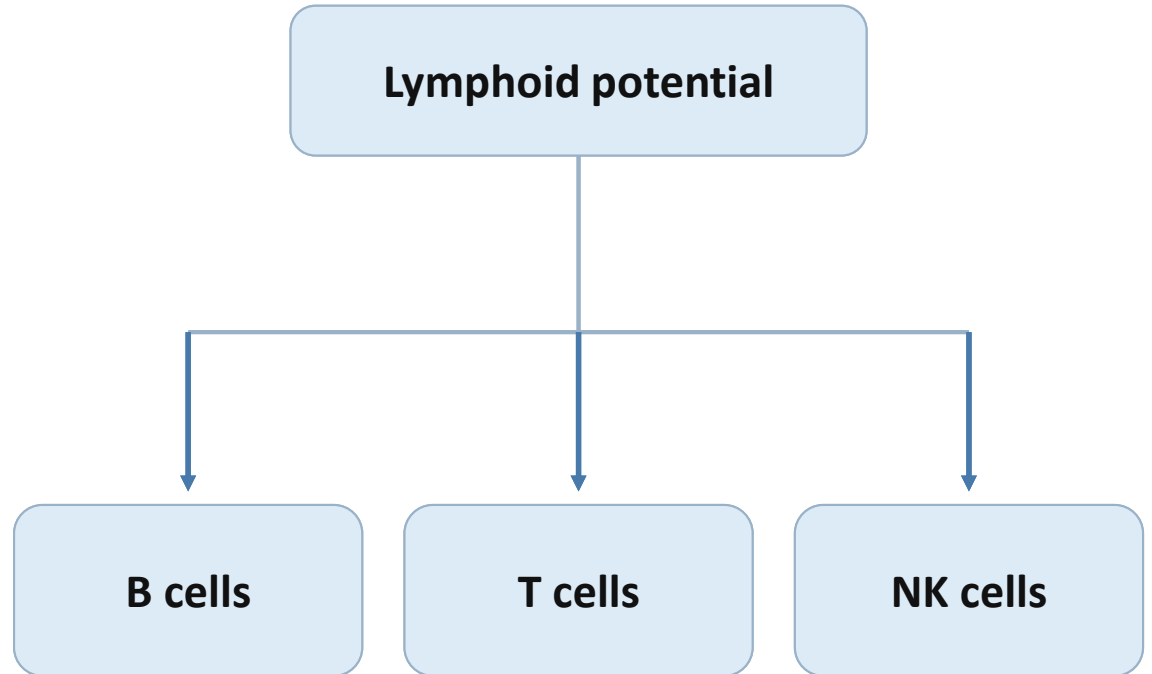
Myeloid progenitors generate several mature classes

- The myeloid pathway gives rise to granulocytes and monocytes.
- Erythroid and megakaryocytic differentiation also proceed within the myeloid arm.
- Distinct downstream precursors account for the divergent mature phenotypes.



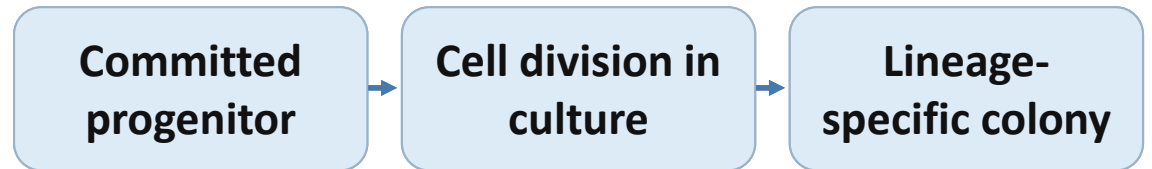
Lymphoid progenitors produce B, T and NK cells

- Early lymphoid progenitors enter distinct differentiation pathways.
- The Robbins lineage figure depicts B cells, T cells and natural killer cells.
- Committed B-, T- and NK-cell precursors precede terminally differentiated cells.



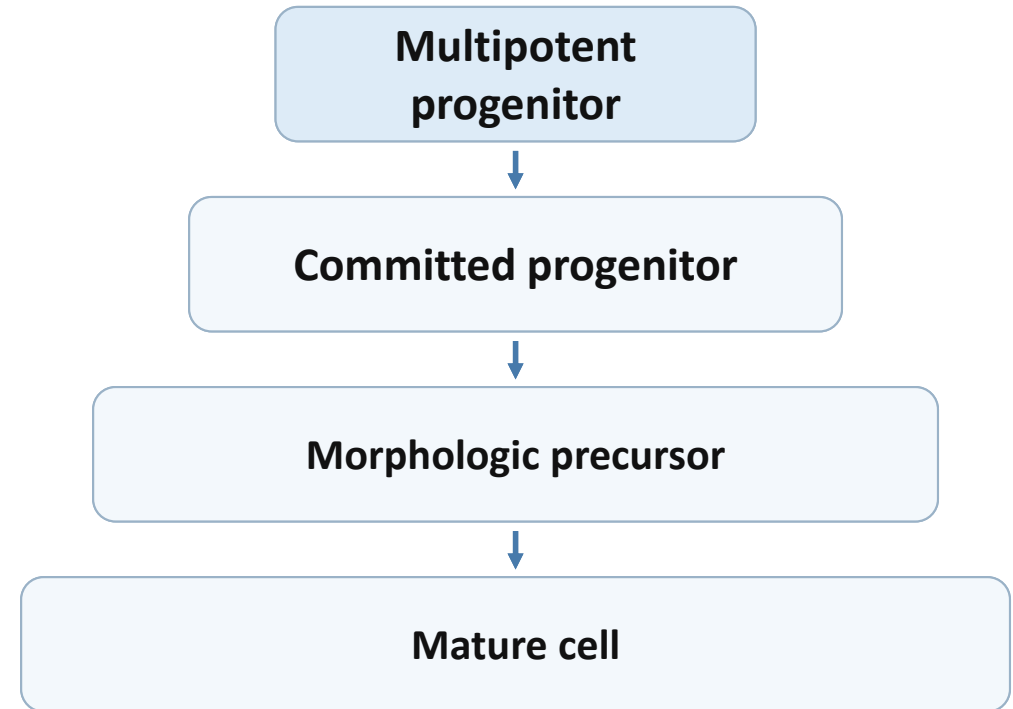
Colony-forming units identify restricted progenitors

- Some committed progenitors are defined by colonies formed in culture.
- The term CFU refers to these experimentally recognizable colony-forming units.
- Colony type reflects a progenitor's increasingly constrained differentiation capacity.



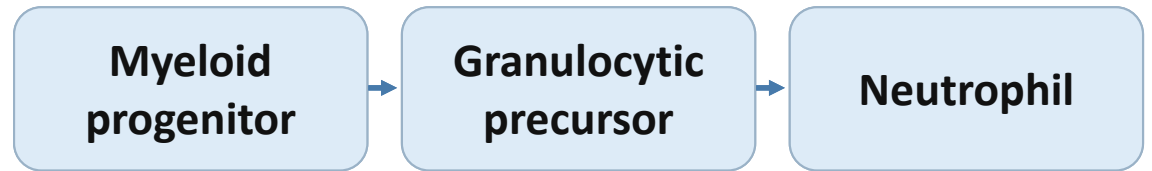
Maturing blood cells pass through recognizable stages

- Committed progenitors generate precursors with identifiable morphology.
- Examples include myeloblasts, erythroblasts and megakaryoblasts.
- These recognizable cells are closer to mature output than the upstream HSC pool.



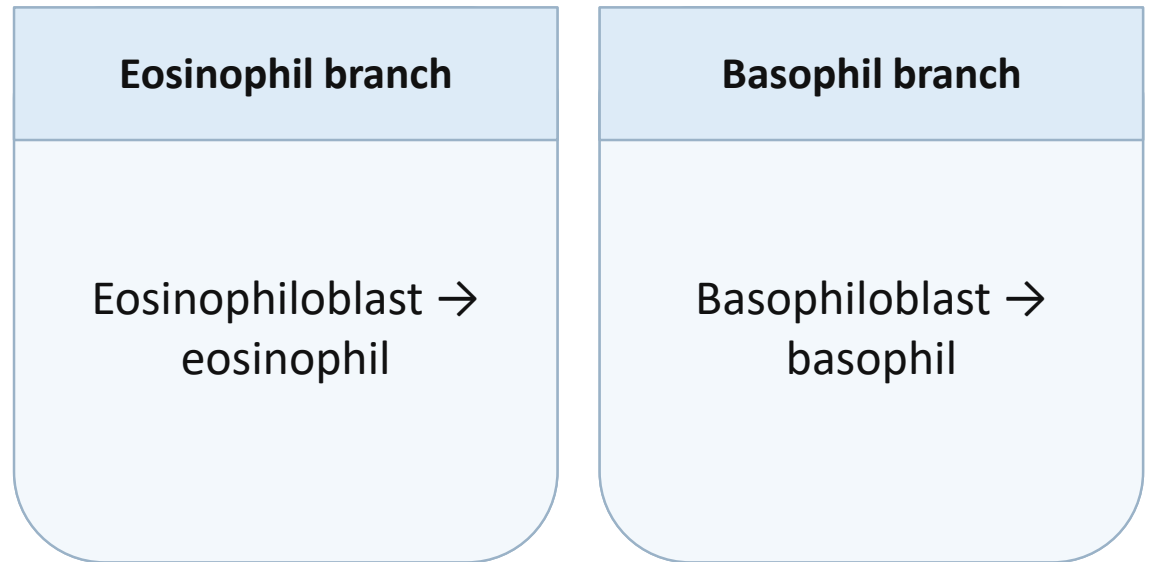
Neutrophil production proceeds through the granulocytic arm

- The source hierarchy places neutrophils downstream of myeloid progenitors.
- Myeloblasts are a morphologically recognized granulocytic precursor.
- Subsequent maturation generates circulating granulocytic cells.



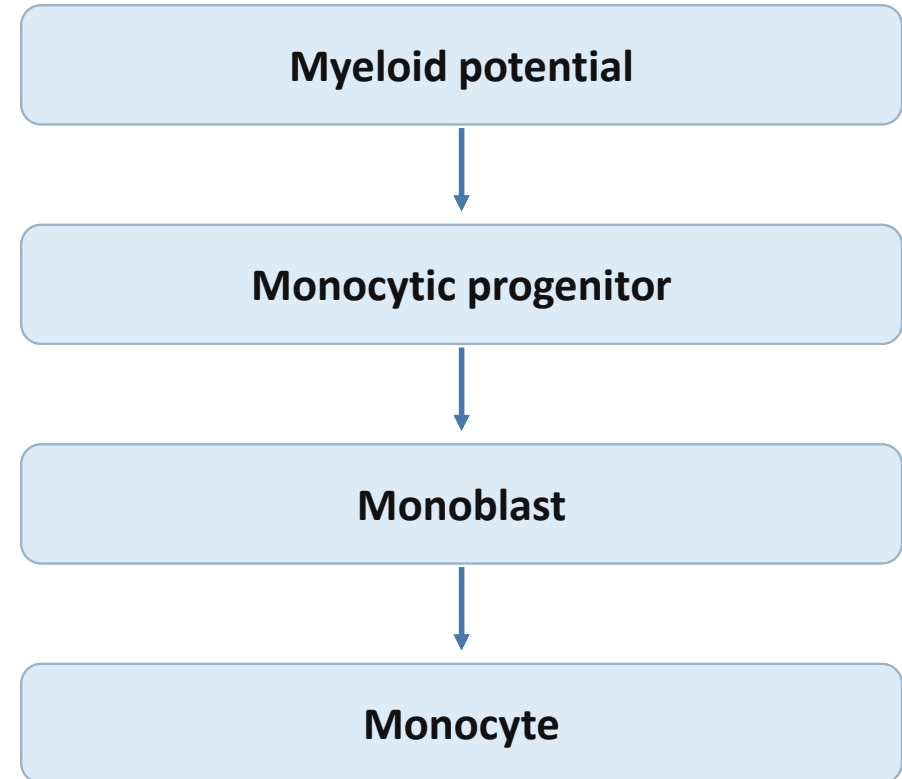
Eosinophil and basophil paths are distinct

- The lineage schematic identifies eosinophil-committed and basophil-committed precursors.
- Eosinophiloblast and basophiloblast forms precede their mature granulocytes.
- A shared early myeloid origin does not imply identical terminal differentiation.



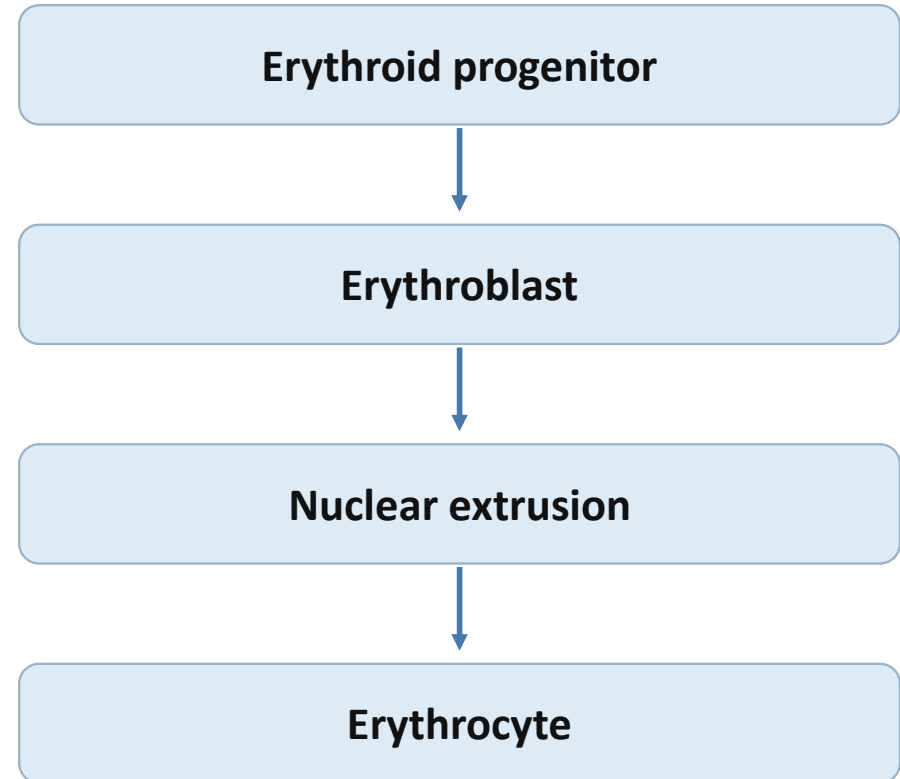
Monocyte production passes through monoblasts

- A committed monocytic progenitor lies downstream of the myeloid compartment.
- Monoblasts are the recognizable precursor depicted in the source figure.
- Their maturation yields circulating monocytes.



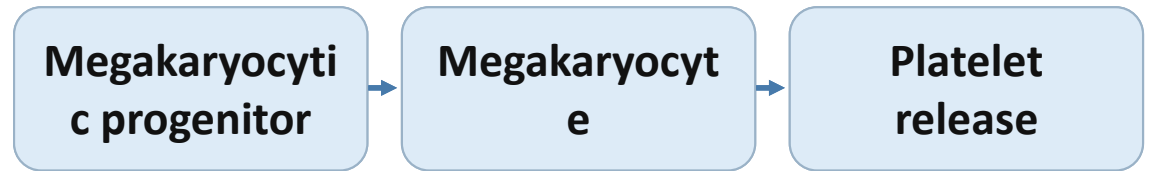
Erythroid differentiation culminates in nuclear extrusion

- Erythroid progenitors pass through erythroblast stages.
- Before release, developing red cells extrude their nuclei.
- Marrow macrophages remove the resulting nuclear remnants.



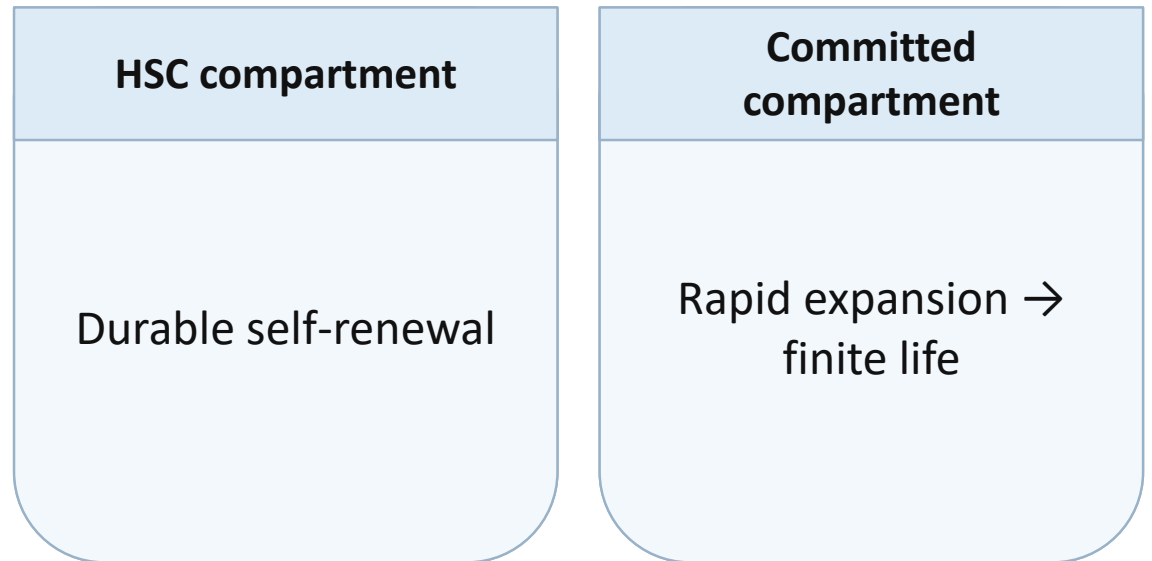
Megakaryocytic differentiation yields platelets

- Megakaryocyte progenitors generate megakaryoblasts and mature megakaryocytes.
- Mature megakaryocytes extend cytoplasmic processes toward sinusoidal blood.
- Budding processes release platelets into the circulation.



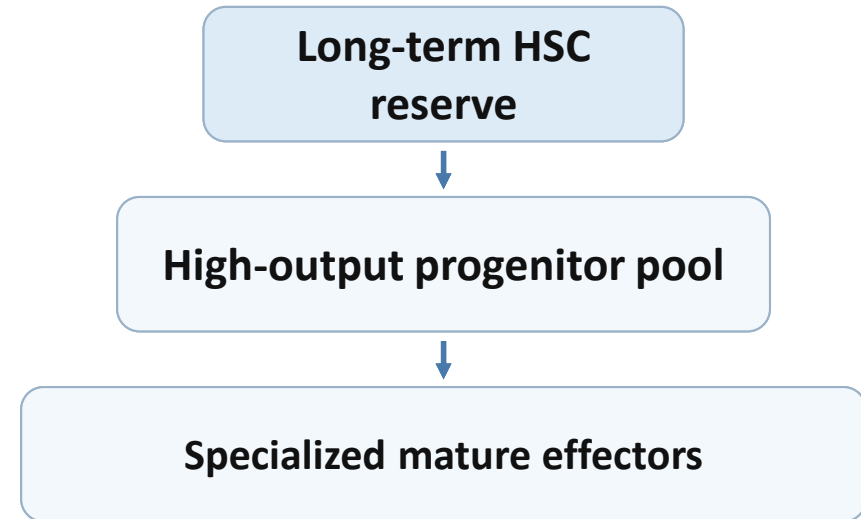
Committed progenitors trade renewal for production

- Downstream commitment progressively curtails self-renewal.
- At the same time, progenitors undergo extensive factor-responsive proliferation.
- Their amplified progeny differentiate and eventually undergo terminal cell death.



Stem cells and mature elements solve different problems

- HSCs preserve a renewable source of every blood lineage.
- Progenitors supply a rapidly expanding production compartment.
- Terminally differentiated blood cells perform specialized functions for finite lifespans.



The HSC hierarchy is a biological model, not a smear

- Most experimental evidence for the classic hierarchy comes from murine studies.
- Human hematopoiesis is believed to follow comparable principles.
- Do not apply murine-specific marker combinations figure as human diagnostic criteria.

Experimental framework

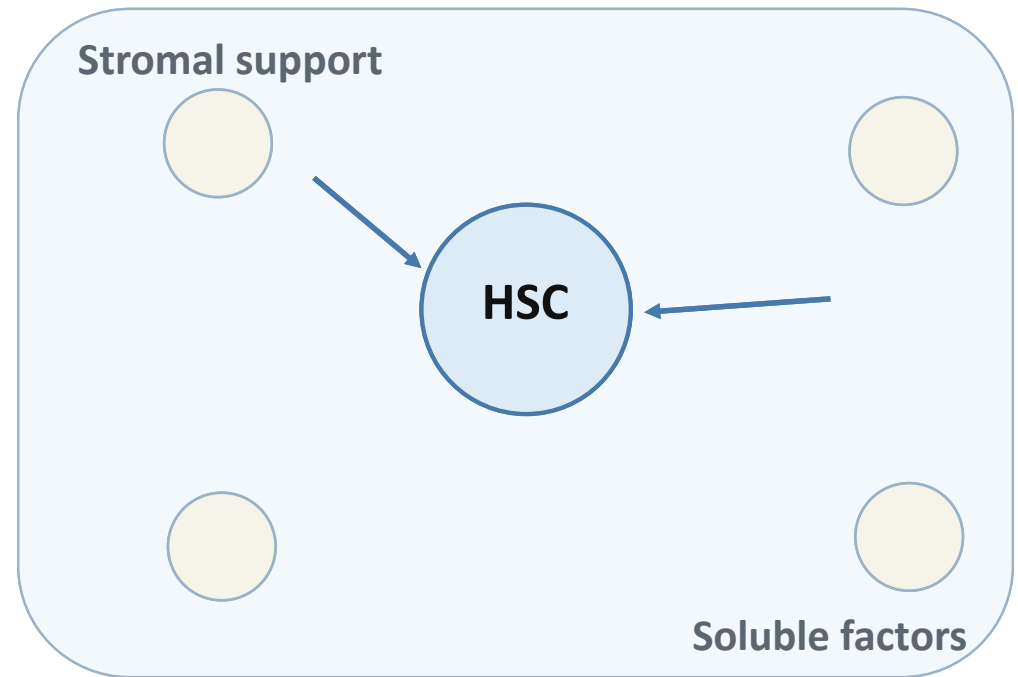
Much evidence
derives from mice

Human application

Similar overall
organization is
inferred

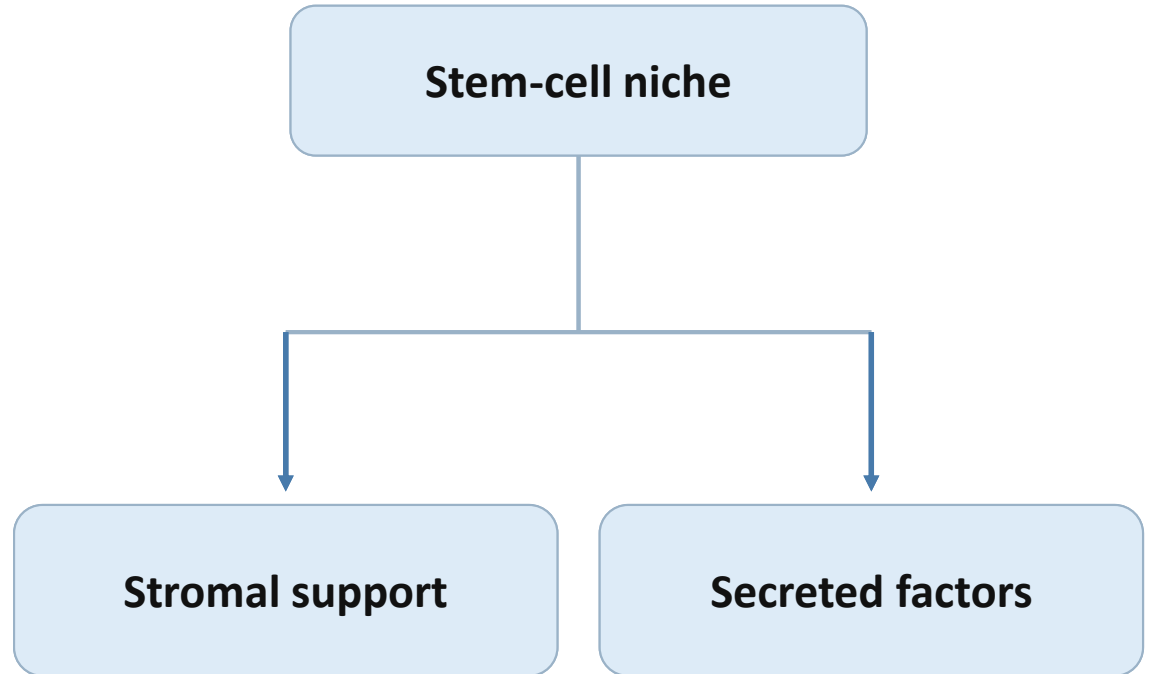
HSC self-renewal occurs within a specialized niche

- The marrow contains localized microenvironments supporting HSCs.
- The niche enables stem-cell maintenance while allowing production of progeny.
- This arrangement protects the long-lived source population.



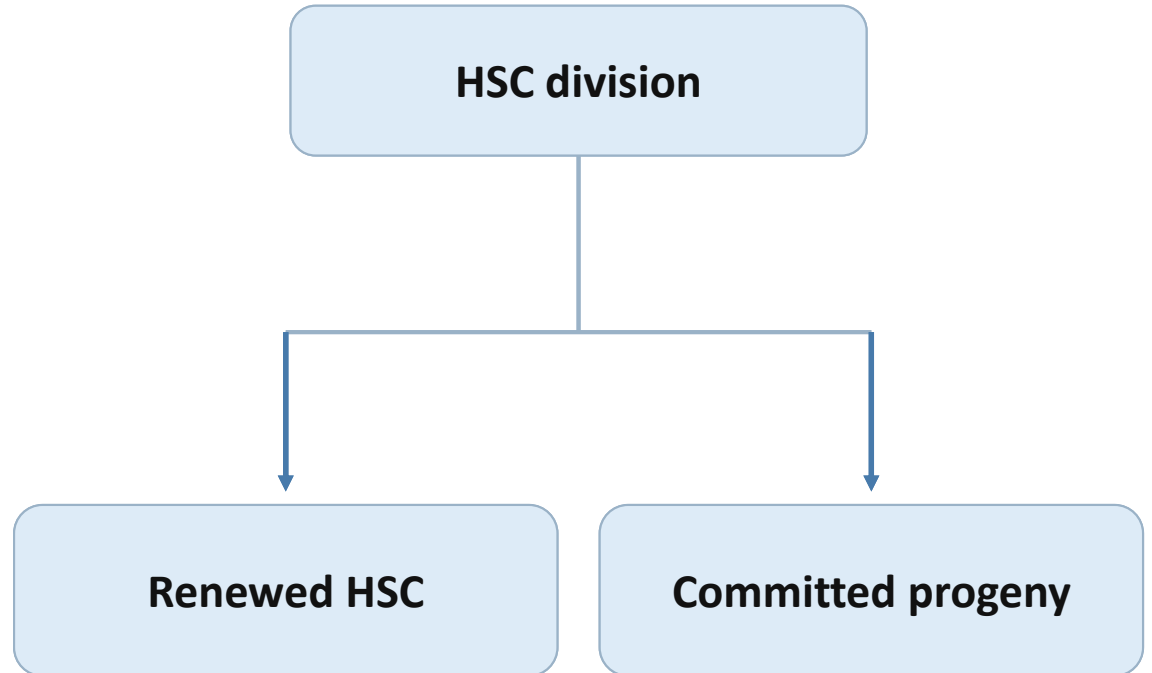
Stromal cells and secreted factors jointly support HSCs

- Niche stromal cells nurture and protect the HSC pool.
- Locally secreted factors form part of the supportive environment.
- Niche signaling is distinct from the later lineage-specific growth-factor response.



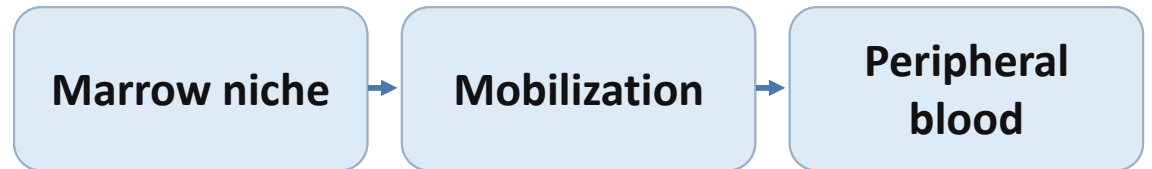
A division must preserve at least one stem-cell descendant

- HSC output cannot be sustained if every division consumes both stem-cell daughters.
- Self-renewing progeny replenish the durable reservoir.
- Another descendant may enter the progenitor differentiation pathway.



HSCs are mobile rather than fixed in marrow

- Developmental site-to-site migration demonstrates HSC mobility.
- Even after marrow residence is established, HSCs can enter peripheral blood.
- Mobilization becomes more conspicuous during hematopoietic stress.



Hematopoietic stress promotes HSC mobilization

- Severe anemia and acute inflammation are examples given in the source.
- These stresses are associated with increased circulating HSCs.
- The response links systemic need to movement of the stem-cell compartment.

Severe anemia

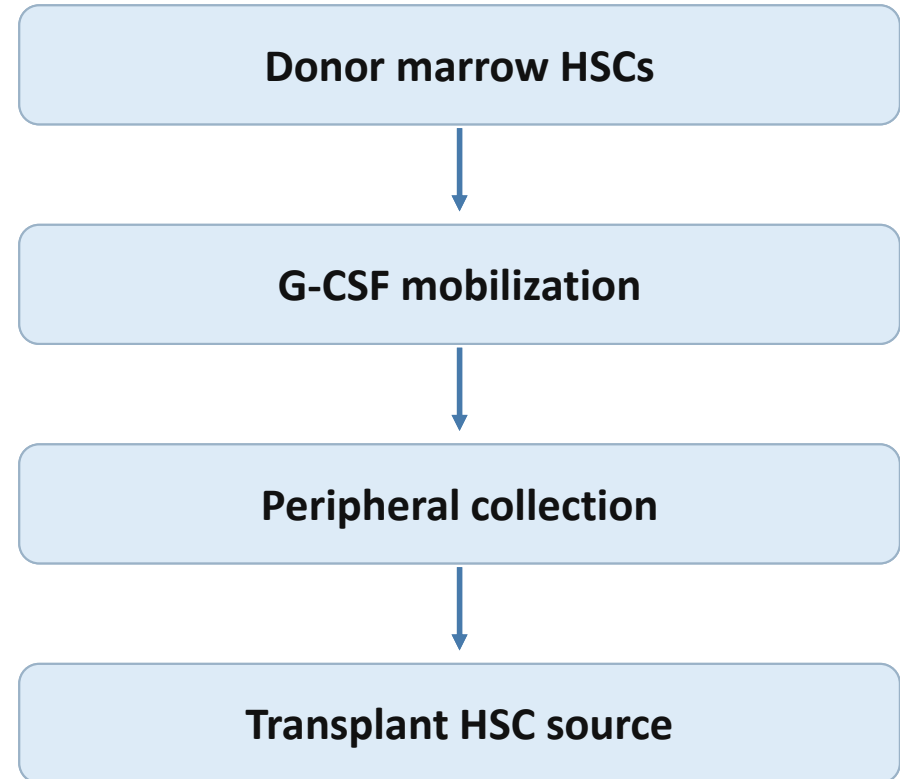
Demand for blood-cell replacement

Acute inflammation

Heightened hematopoietic stress

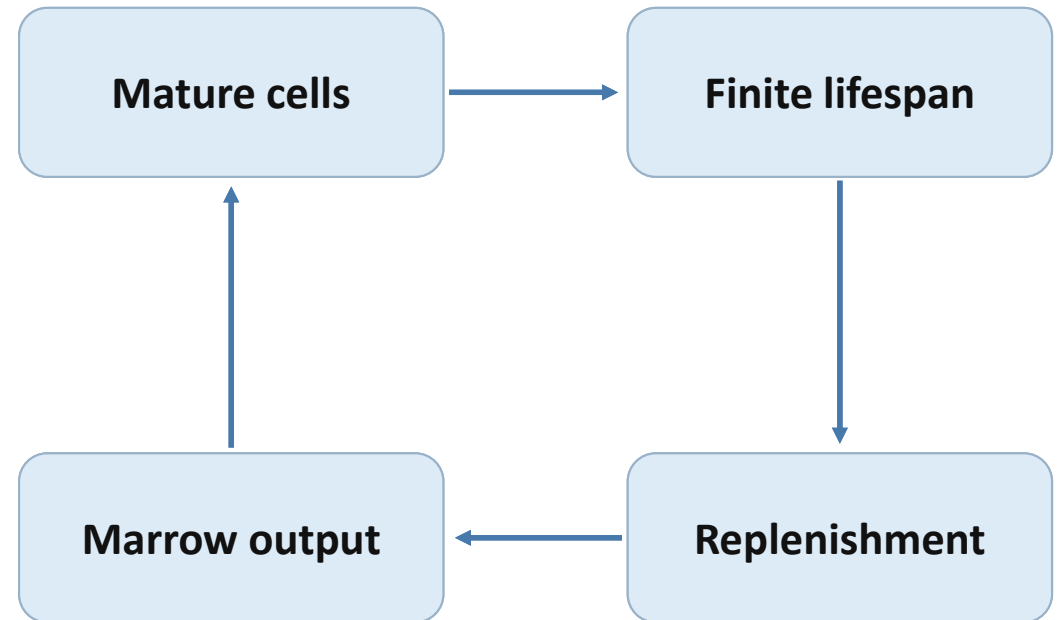
G-CSF can mobilize transplantable HSCs

- G-CSF is one of the factors capable of dislodging HSCs from their niches.
- Donors treated with G-CSF provide circulating HSCs for collection.
- Peripheral blood has become a major source for HSC transplantation.



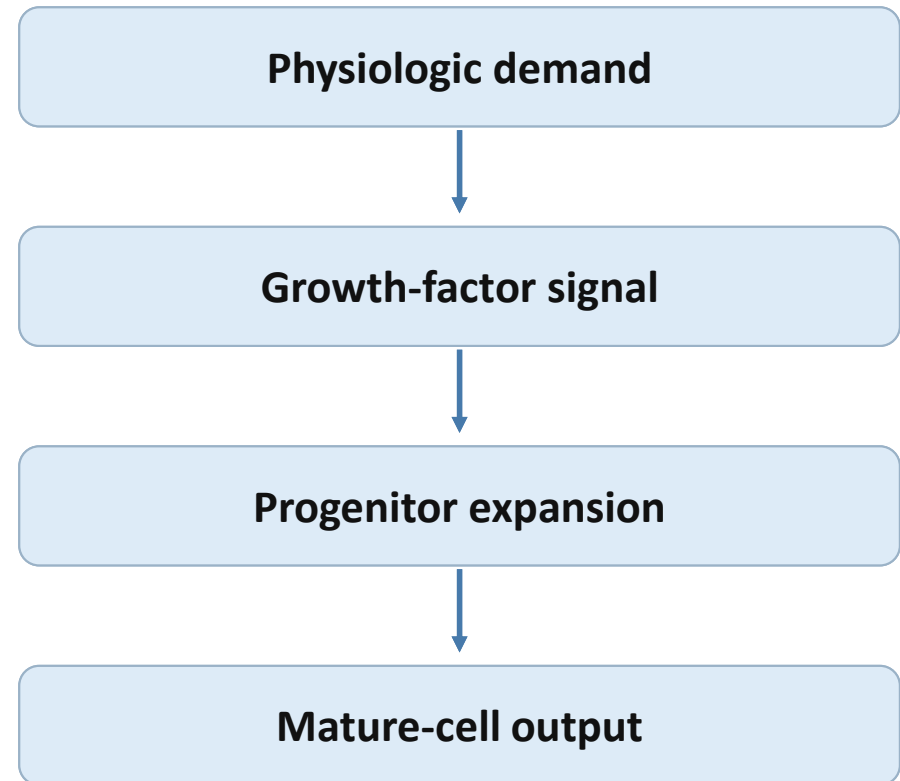
Finite cell lifespans require continuous production

- Circulating blood elements are terminally differentiated cells.
- Because they do not persist indefinitely, the marrow must continually replace them.
- The production system combines a renewing stem-cell reserve with expanding progenitors.



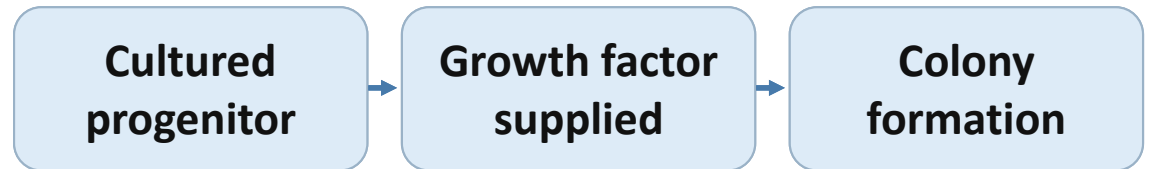
Short-term marrow responses act on committed progenitors

- Growth factors regulate the quantity of lineage output.
- Committed progenitors are especially responsive to these factors.
- The HSC pool need not directly produce every fluctuation in circulating cell count.



CSFs are named for their effect in culture

- Colony-stimulating factors support colonies of blood cells in vitro.
- The name captures the discovery method rather than a single cellular target.
- Different factors act at different levels of hematopoietic commitment.



KIT and FLT3 ligands act relatively early

- KIT ligand and FLT3 ligand support early committed progenitors.
- Their receptors occur before the most lineage-restricted maturation stages.
- They differ in target distribution from downstream lineage-specific factors.

Early progenitors

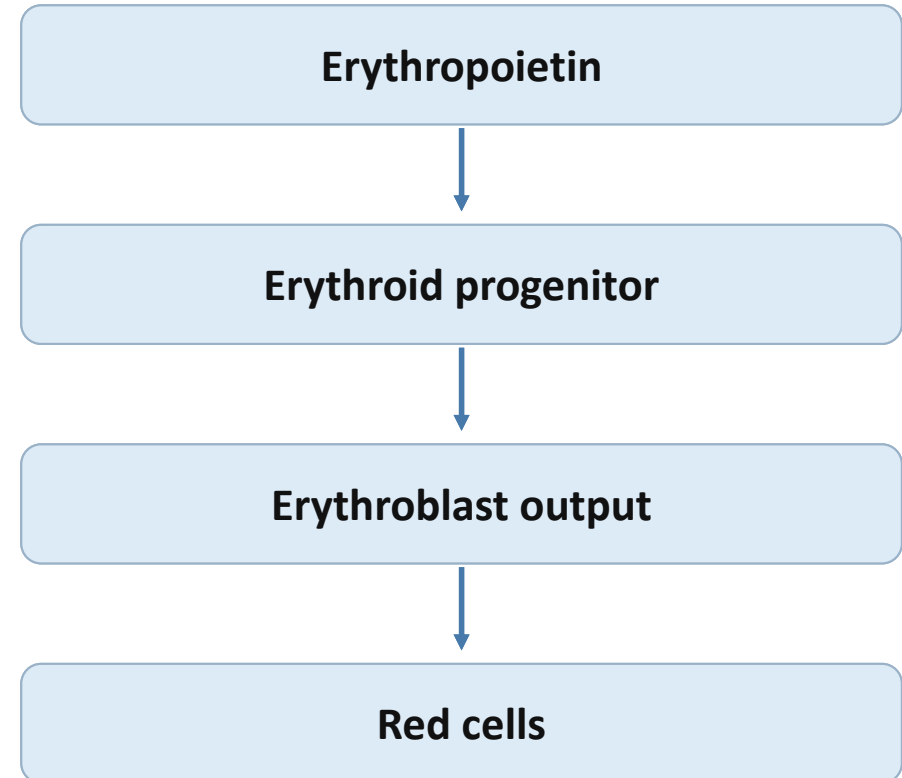
KIT ligand; FLT3
ligand

Restricted progenitors

EPO; GM-CSF; G-CSF;
TPO

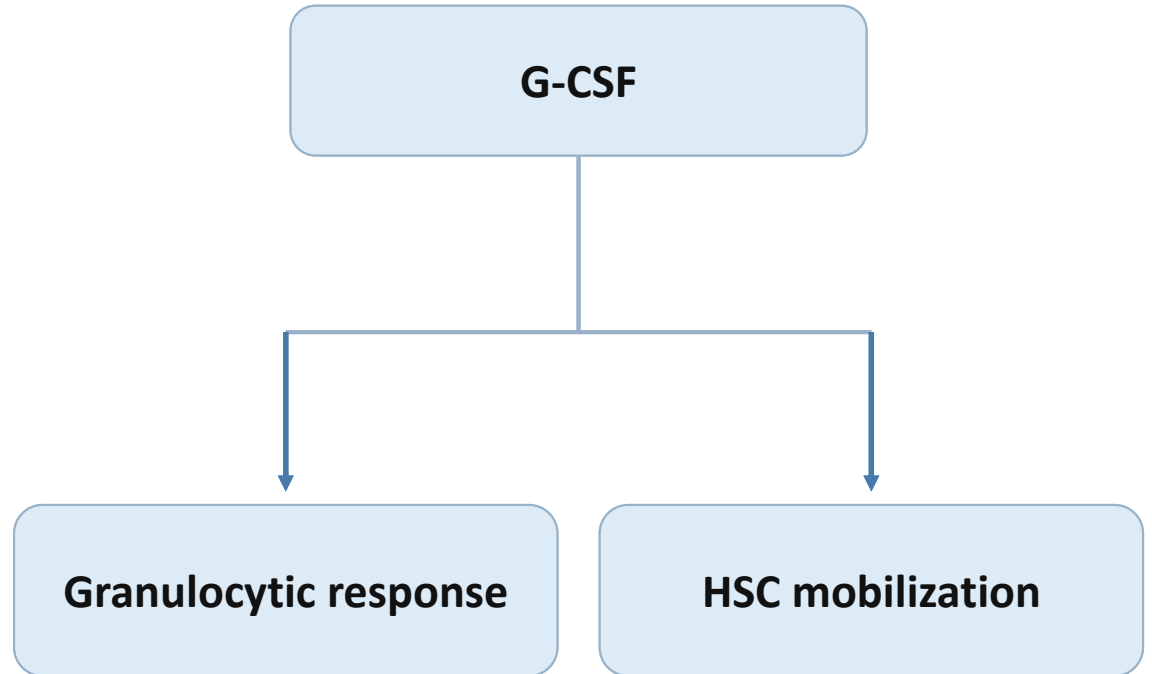
Erythropoietin supports the erythroid pathway

- Erythropoietin is a lineage-directed hematopoietic growth factor.
- Its effects are chiefly expressed through erythroid committed progenitors.
- Expansion of this compartment contributes to increased red-cell production.



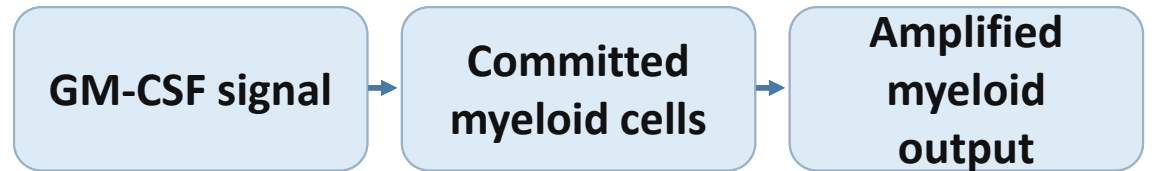
G-CSF drives granulocytic lineage responsiveness

- G-CSF is among the factors acting mainly on restricted progenitors.
- Granulocyte output can rise under cytokine and growth-factor direction.
- G-CSF additionally has a distinct role in HSC mobilization.



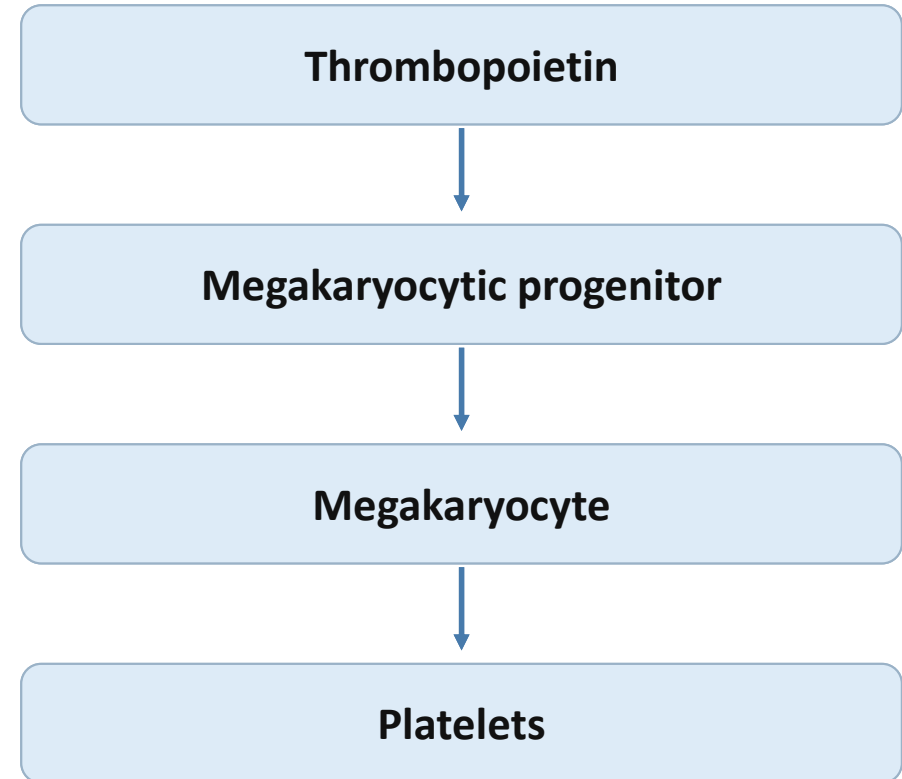
GM-CSF regulates committed myeloid production

- Granulocyte–macrophage CSF is included among lineage-related regulators.
- It acts largely through receptors on committed progenitors.
- This illustrates how growth-factor specificity accompanies lineage restriction.



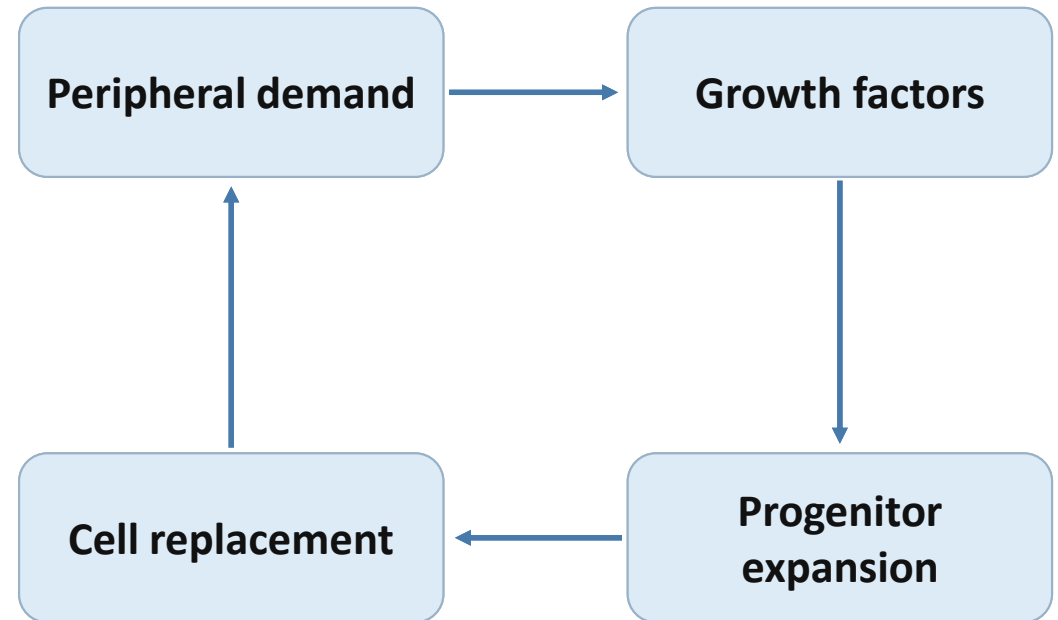
Thrombopoietin targets the platelet-producing lineage

- Thrombopoietin is listed among the principal lineage-related growth factors.
- Receptors on committed progenitors couple signaling to platelet-lineage output.
- Platelets originate from mature megakaryocytes in marrow.



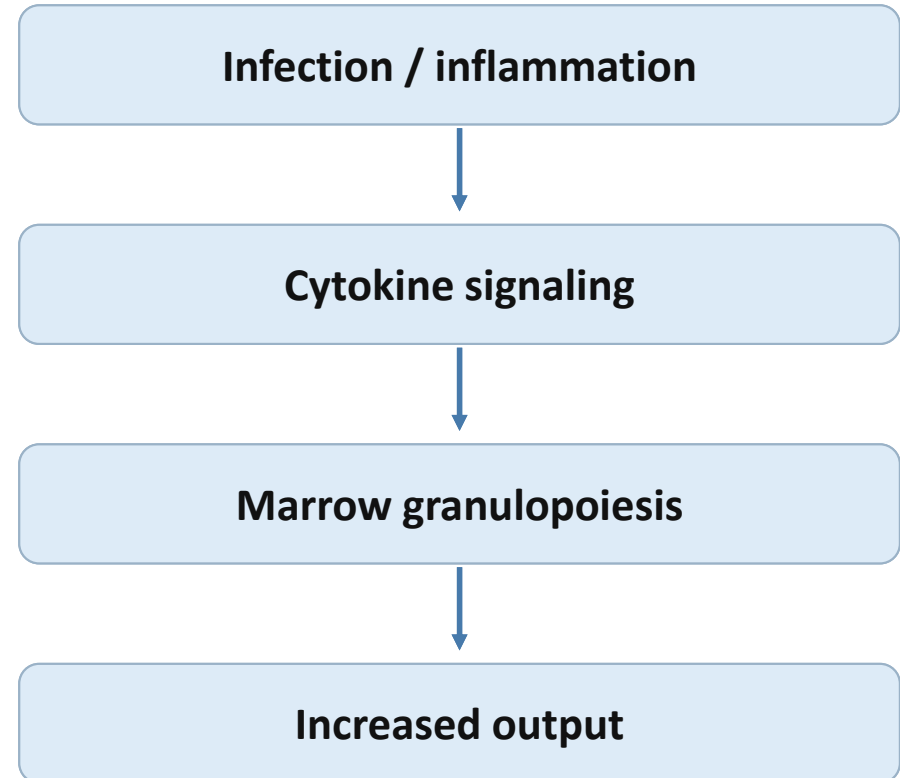
Feedback aligns production with peripheral demand

- Lineage-specific factors participate in feedback control of marrow output.
- The effective response is changed proliferation of committed progenitors.
- Such loops maintain appropriate numbers of red cells, white cells and platelets.



Inflammation can increase granulocyte production

- The marrow contributes a major cellular supply to innate host defense.
- Infectious or inflammatory signals recruit growth factors and cytokines.
- Increased granulocytic production is an adaptive marrow response.



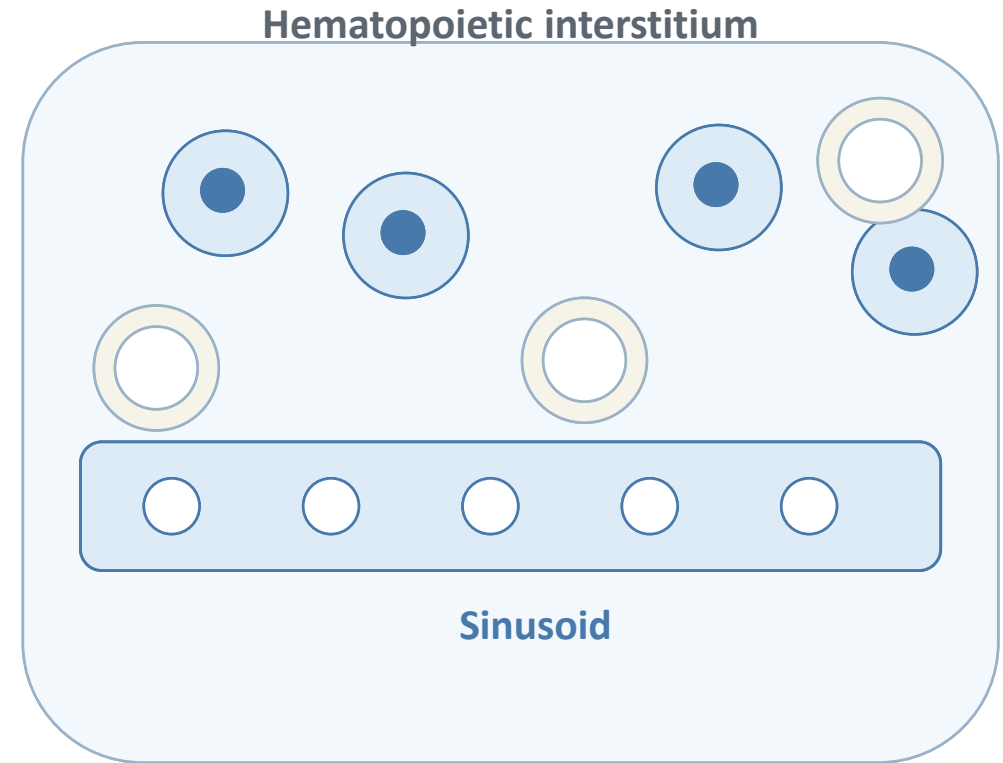
Growth factors differ by their progenitor targets

- Early progenitors respond to relatively broad-acting KIT and FLT3 ligands.
- More restricted compartments respond to EPO, GM-CSF, G-CSF and TPO.
- The stage of commitment shapes what response a factor can elicit.

Growth factor	Principal compartment	Illustrative output
KIT / FLT3	Earlier committed	Early response
EPO	Erythroid	Red cells
G-CSF / GM-CSF	Myeloid	Granulocytes / monocytes
Thrombopoietin	Megakaryocytic	Platelets

Bone marrow integrates cell growth and blood release

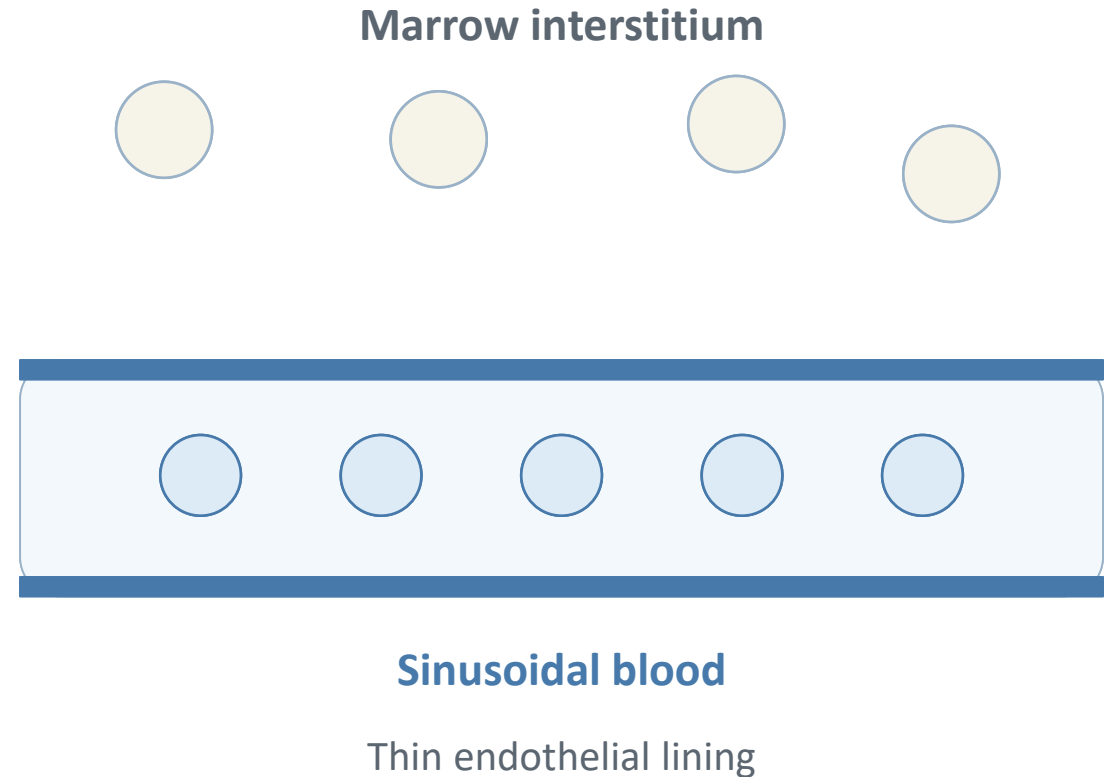
- The marrow houses proliferating progenitors and differentiating precursors.
- Its sinusoidal vasculature creates a channel for mature-cell entry into blood.
- Supportive interstitial cells and fat coexist with hematopoietic elements.



Schematic — not histology

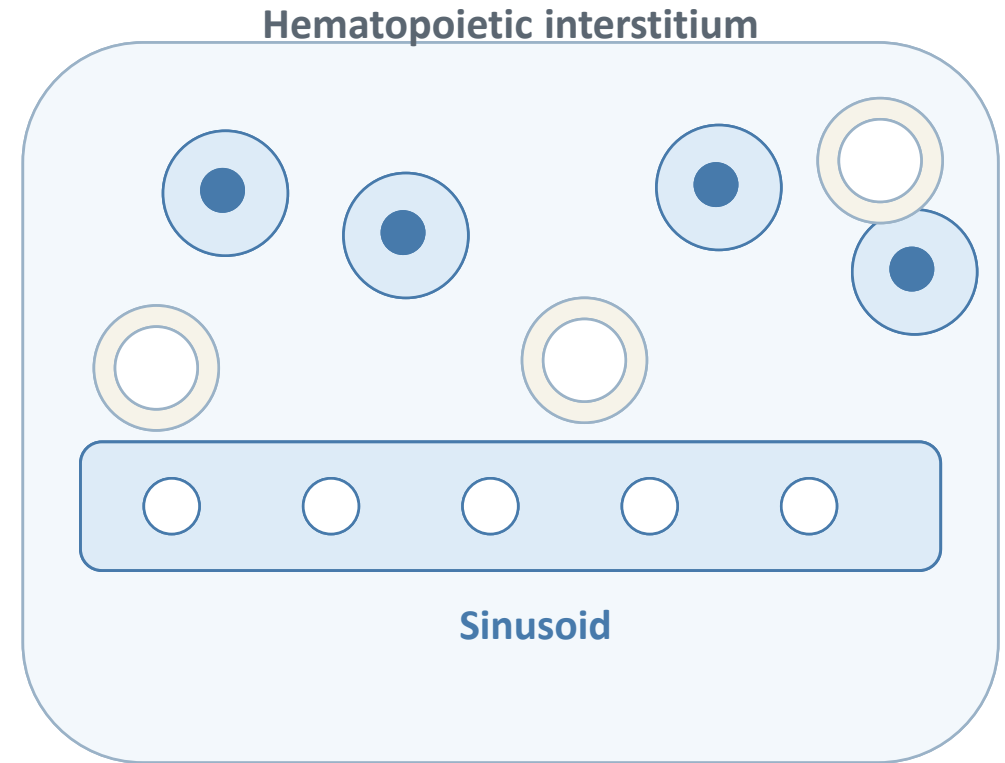
Marrow sinusoids are thin-walled vascular channels

- Sinusoids are lined by a single layer of endothelial cells.
- A discontinuous basement membrane and adventitial cells lie beneath the endothelium.
- These features are part of the marrow's specialized exchange interface.



Hematopoietic clusters occupy the interstitium

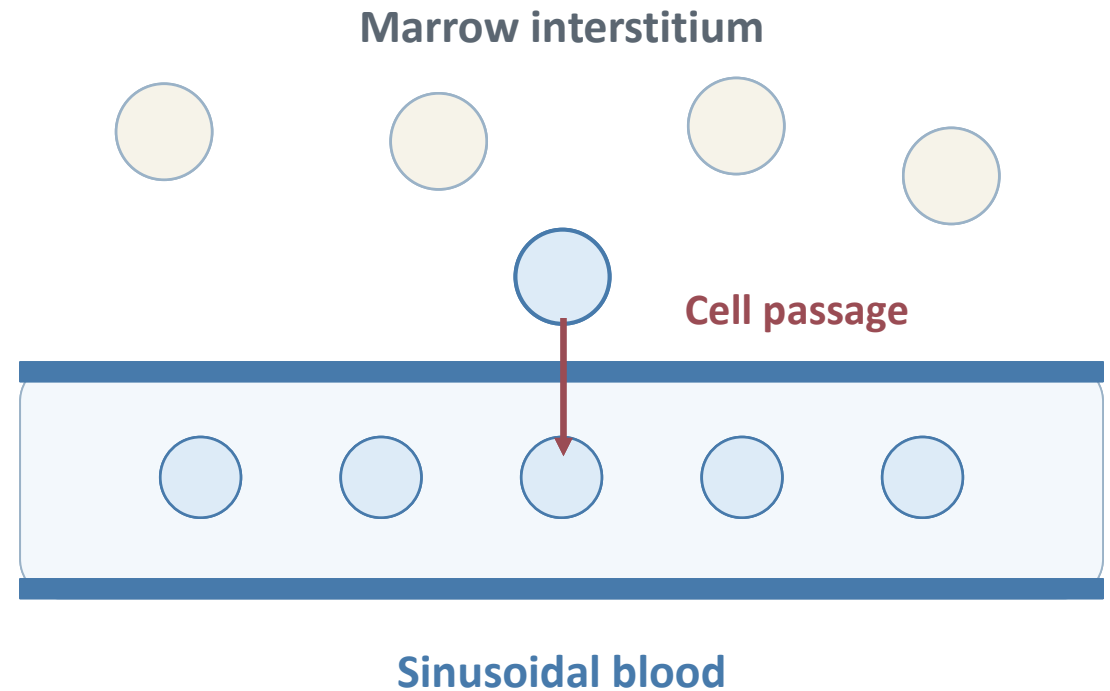
- Hematopoietic cells form interstitial clusters between sinusoids.
- Fat cells occupy spaces within the same marrow compartment.
- The balance between the two changes with marrow activity and disease.



Schematic — not histology

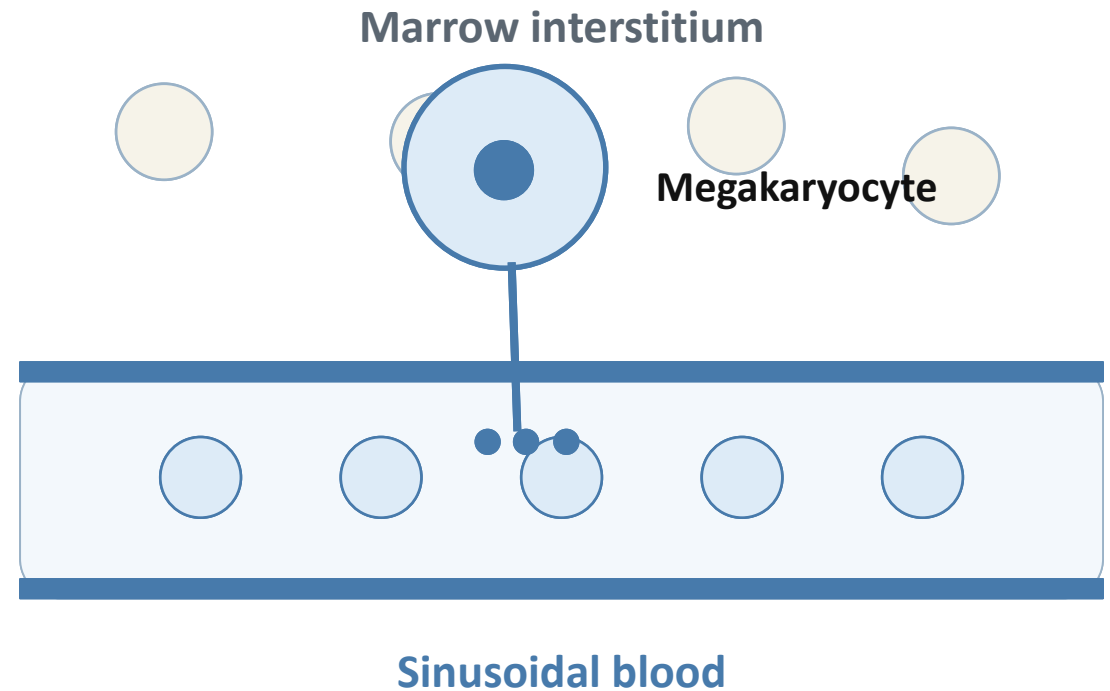
Mature cells leave marrow by crossing endothelium

- Differentiated blood cells enter sinusoidal channels.
- Transcellular migration through endothelial cells.
- Production and controlled release are therefore distinct marrow functions.



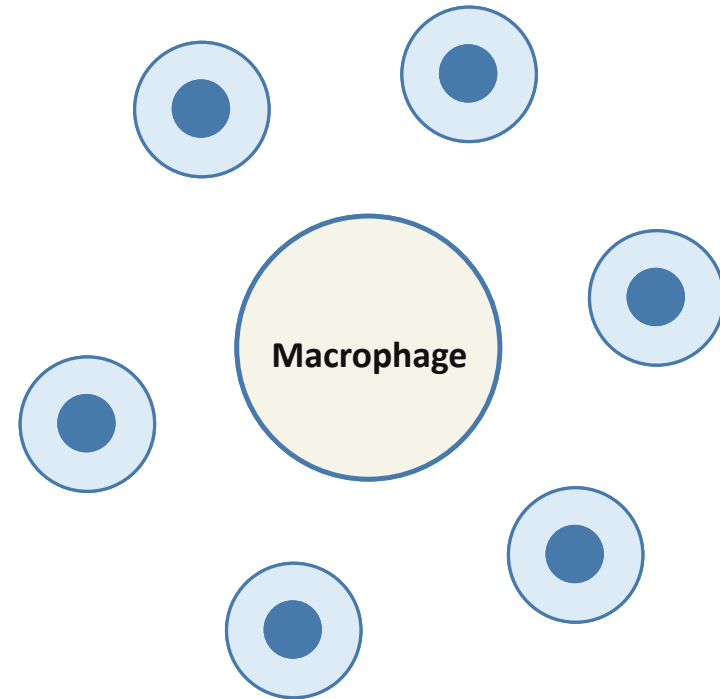
Megakaryocytes are positioned close to sinusoids

- Mature megakaryocytes lie adjacent to marrow vascular channels.
- They send cytoplasmic processes into the sinusoidal circulation.
- Platelets bud from these projections directly into blood.



Erythroblasts assemble around supportive macrophages

- Red-cell precursors often surround a central marrow macrophage.
- This spatial organization is associated with terminal erythroid maturation.
- Macrophages dispose of nuclear remnants after enucleation.

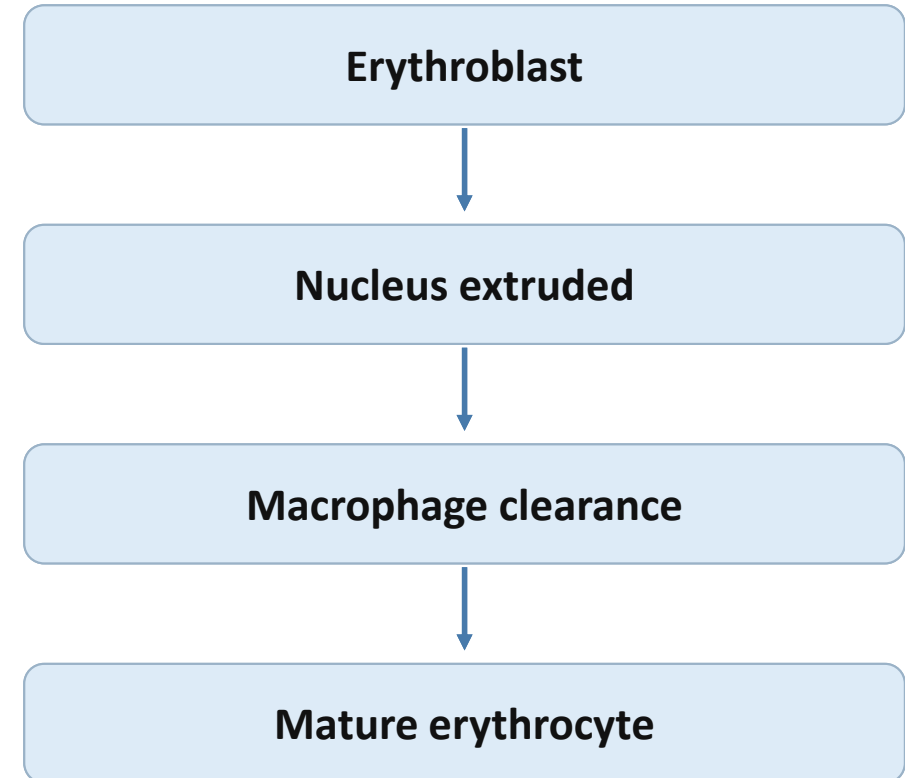


Erythroid precursors

Schematic cell grouping

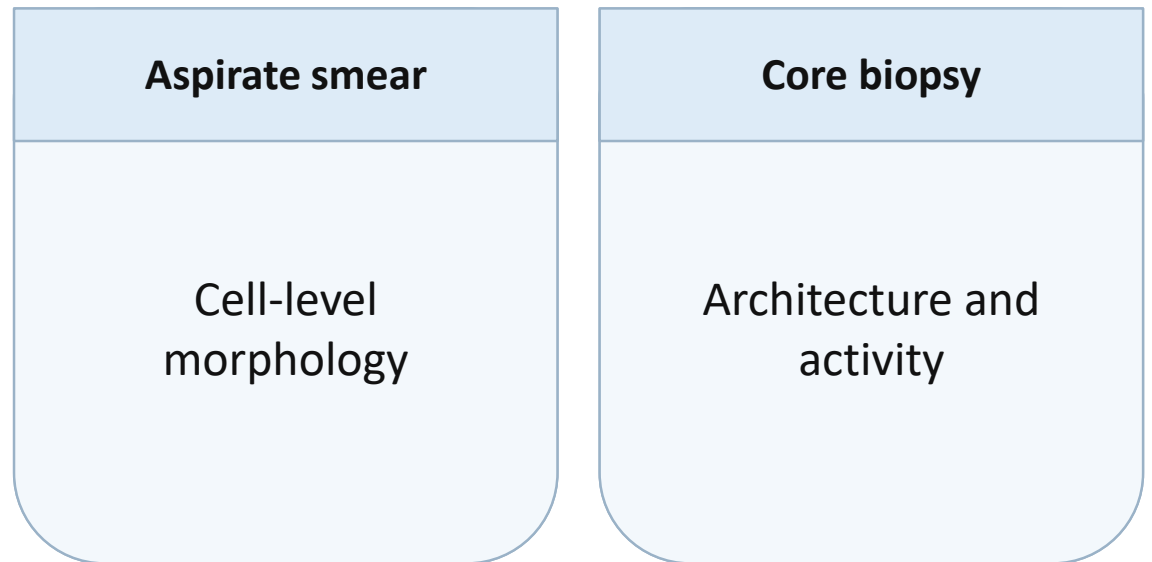
An erythroid nucleus is cleared before circulation

- Developing erythrocytes eject their nucleus before release.
- The central macrophage removes the residual nuclear material.
- This local clearance supports orderly production of anucleate red cells.



Marrow aspirates best show precursor cytology

- Aspirated marrow smears allow direct assessment of individual cell morphology.
- More mature precursor classes may be identified on morphology alone.
- This strength differs from the architectural assessment of a core biopsy.



A blast cannot be assigned lineage on appearance alone

- Immature marrow precursors of different lineages can look similar.
- Lineage-specific antibodies and histochemical markers are needed for reliable typing.
- The distinction between blast identification and lineage assignment is essential.

Mature precursor	Immature blast
Often recognizable morphologically	Lineage markers required

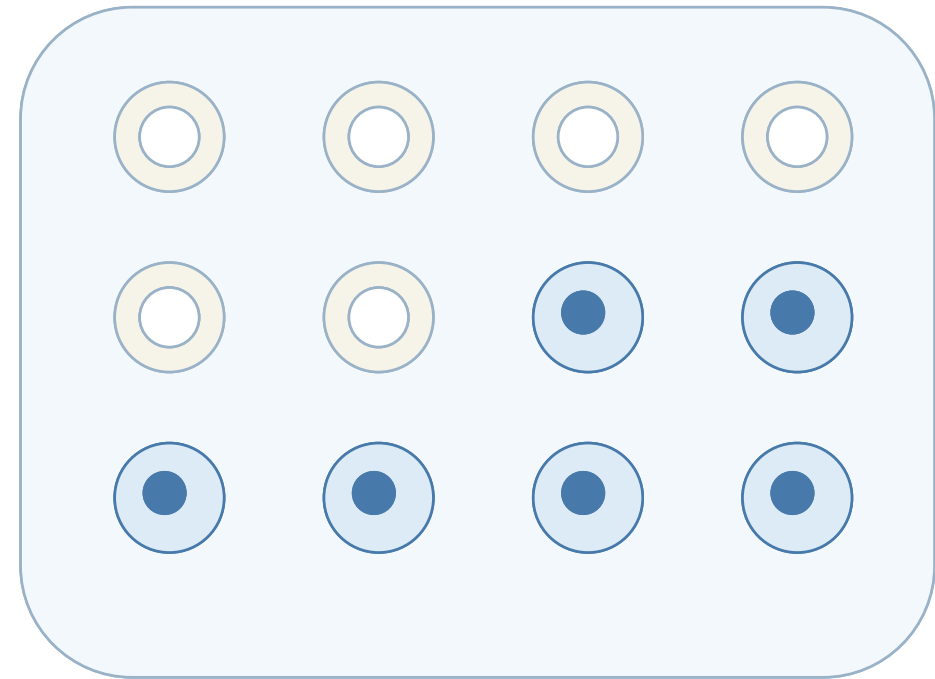
Core biopsy provides a measure of marrow activity

- A biopsy retains tissue architecture for judging cellularity.
- Cellular elements can be evaluated relative to marrow fat.
- Focal architectural disorders are more readily appreciated in a tissue core.

Aspirate	Biopsy
Dispersed cells	Tissue pattern and cellularity

Normal adult marrow contains cells and fat

- A normal adult fat-to-hematopoietic ratio of roughly 1:1.
- A biopsy reveals whether blood-forming elements occupy expected space.
- This estimate is a baseline for contrasting hypo- and hypercellular states.

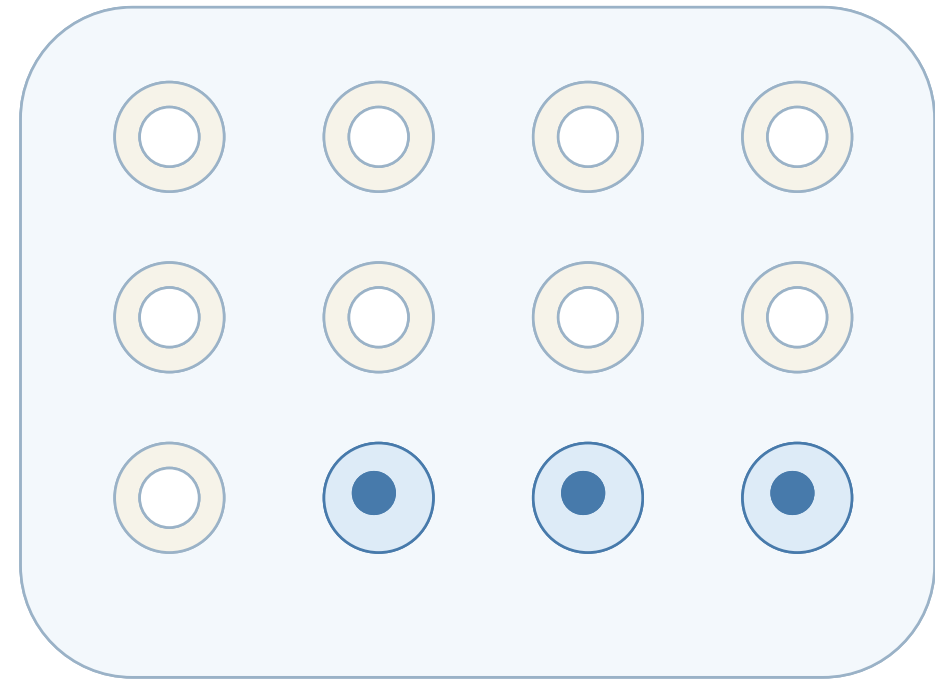


Fat $\approx$ hematopoietic elements

Relative proportions illustrated schematically; Not measured

Hypoplasia is associated with excess marrow fat

- In aplastic anemia, hematopoietic elements are markedly reduced.
- The proportion of fat cells rises as the marrow becomes hypoplastic.
- Low blood counts may thus reflect reduced marrow production rather than peripheral loss.

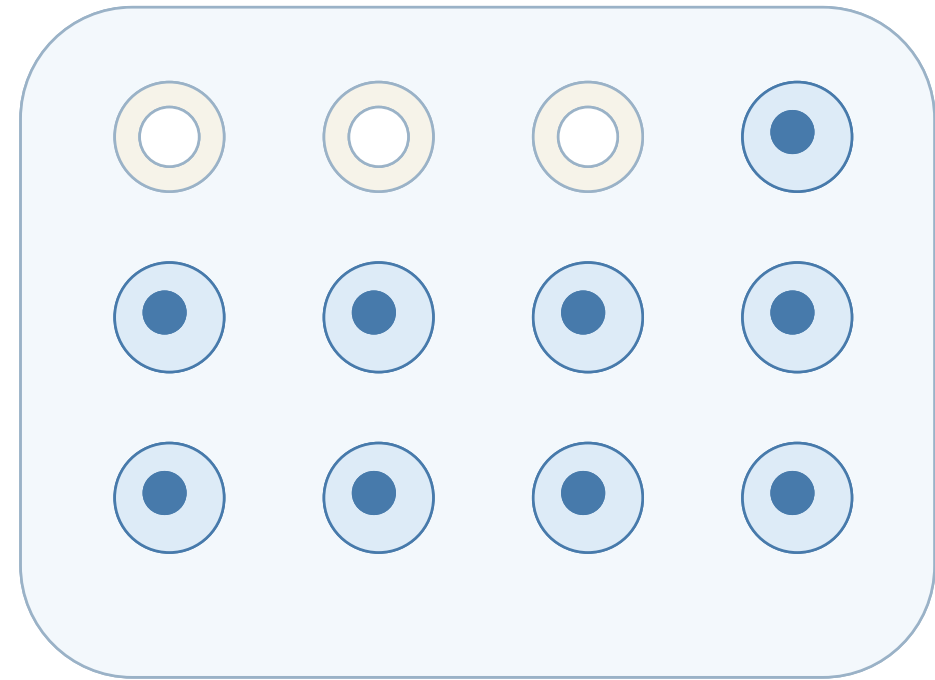


Fat predominates

Relative proportions illustrated schematically; Not measured

Compensatory hyperplasia reduces the fat compartment

- When marrow demand increases, hematopoietic cellularity may expand.
- Hemolytic anemia is one example associated with compensatory hyperplasia.
- The relative area occupied by fat consequently contracts.

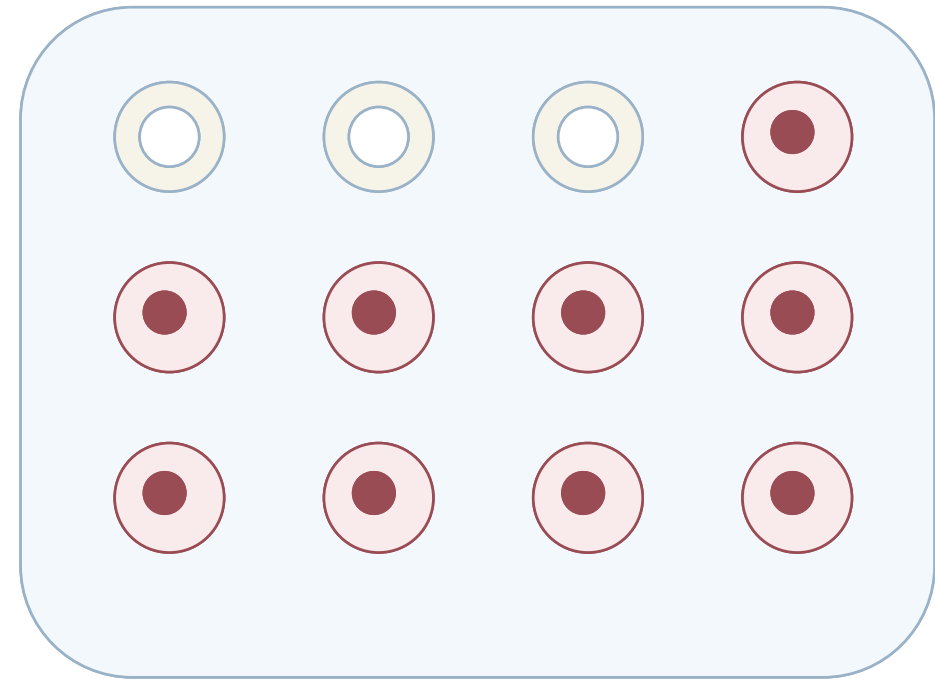


Hematopoietic elements predominate

Relative proportions illustrated schematically; Not measured

Marrow tumors can replace normal fat and cells

- Hematopoietic neoplasms may occupy large portions of marrow space.
- The normal adipose compartment may diminish or disappear.
- Clonal expansion can simultaneously impair normal marrow production.



Normal compartments displaced

Relative proportions illustrated schematically; Not measured

Fibrotic marrow may yield an unsuccessful aspirate

- Metastatic cancers and granulomatous conditions may induce local marrow fibrosis.
- An aspiration attempt can fail when tissue is fibrotic.
- A core biopsy is then better suited to seeing the underlying lesion.

Aspiration

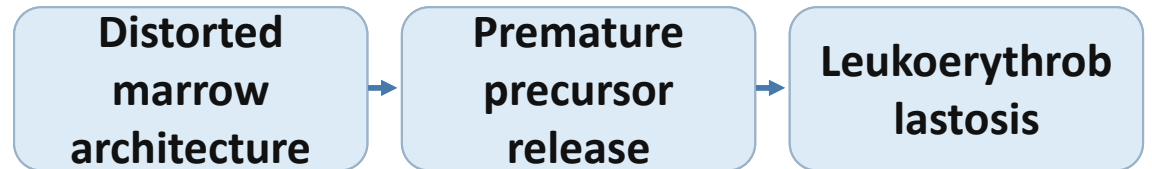
May be a dry tap

Trephine biopsy

Can reveal fibrosis or infiltration

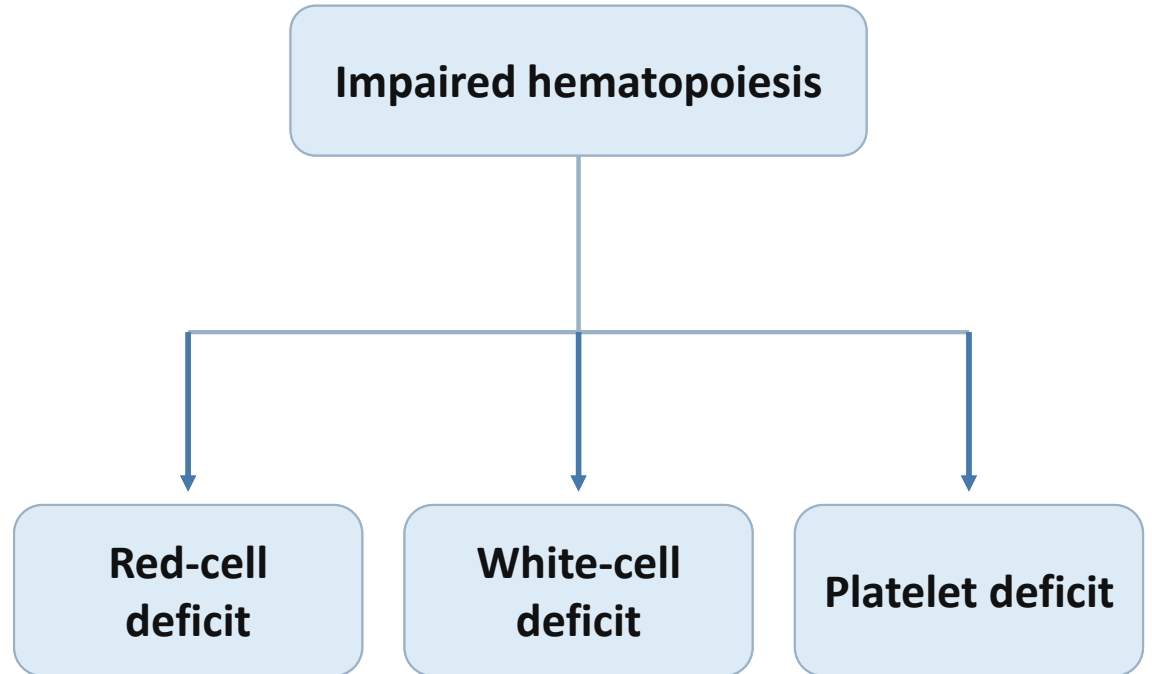
Architectural distortion can cause leukoerythroblastosis

- Marrow distortion may force immature precursors into circulation.
- Robbins calls this abnormal circulating mixture leukoerythroblastosis.
- Metastatic tumor deposits and granulomatous conditions are example causes.



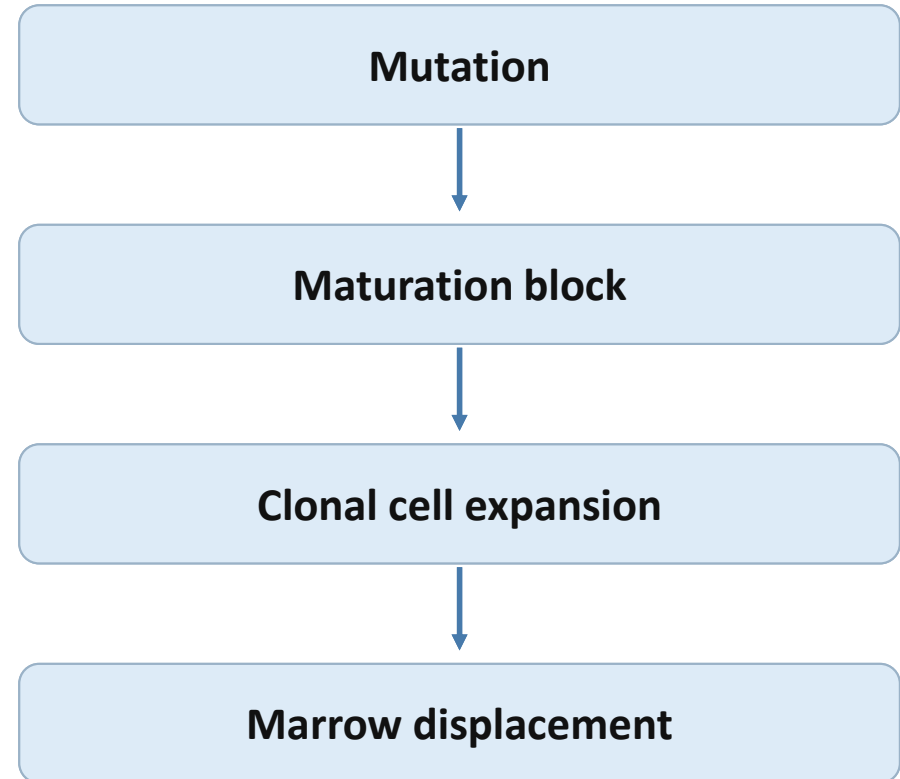
Production failure may affect one or several lineages

- Hematopoiesis may be suppressed by genetic conditions, infection or toxins.
- Nutritional deficiencies and chronic inflammation can also impair output.
- The resulting deficit may involve one or more circulating blood-cell types.



Neoplastic mutations can arrest differentiation

- Some blood-cell tumors acquire defects that block progenitor maturation.
- Immature neoplastic populations can expand without producing normal mature output.
- Such clonal expansion may replace healthy marrow progenitors.



Neoplastic cells may escape growth-factor control

- Mutations may also abrogate normal growth-factor dependence.
- Growth becomes dissociated from the physiologic feedback that limits cell production.
- This contributes to unregulated clonal expansion in marrow and beyond.

Normal hematopoiesis

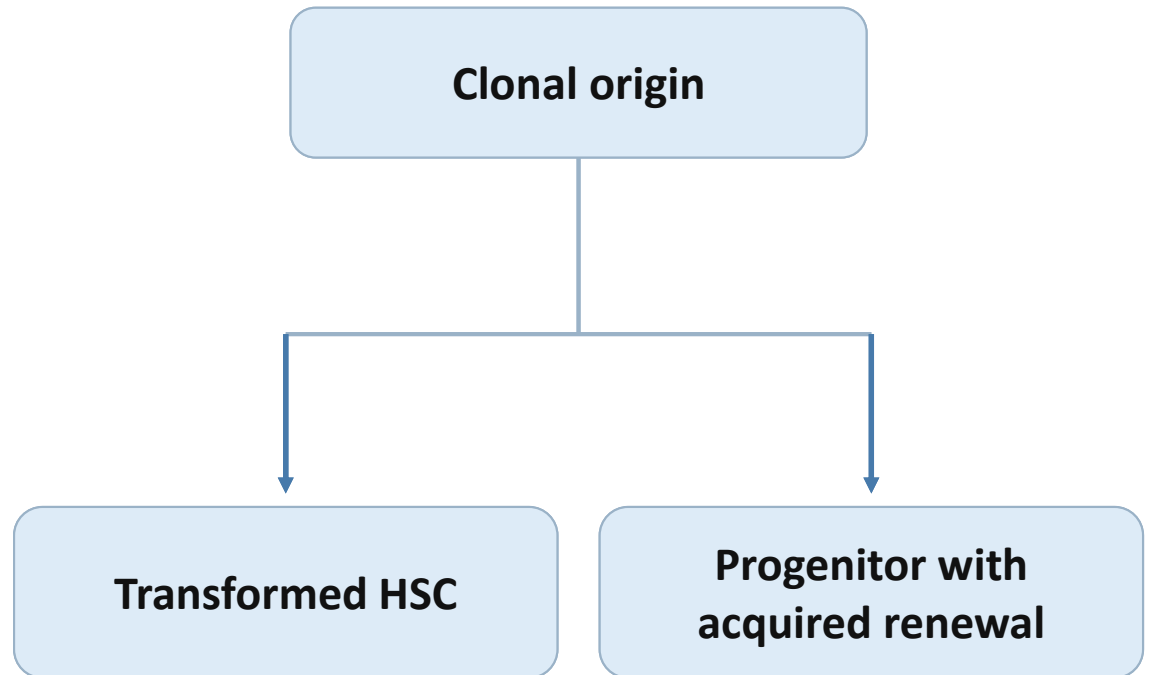
Factor-tuned,
demand-responsive

Neoplastic growth

Abnormally
autonomous
expansion

Neoplasms may begin at different hierarchy levels

- Some arise from HSCs and retain capacity for multilineage differentiation.
- Others originate in restricted progenitors that acquire abnormal self-renewal.
- The cell of origin helps explain phenotypic breadth across neoplasms.



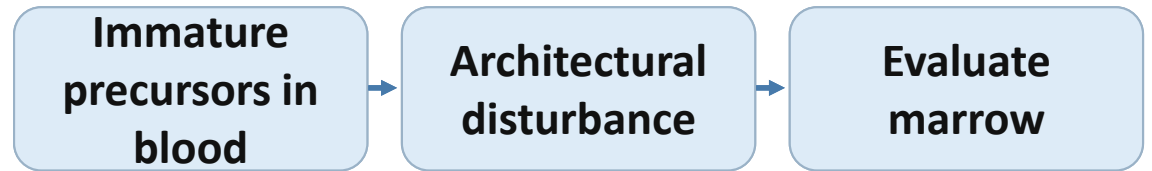
Case: Interpreting a fat-rich marrow biopsy

- A patient has reduced circulating blood counts and a markedly fat-rich marrow core.
- The tissue pattern indicates reduced hematopoietic activity.
- Aplastic anemia is a model of this hypoplastic morphology; A final diagnosis requires context.

Observed pattern	Mechanistic interpretation
Fat-rich, few hematopoietic cells	Marrow production failure

Case: Interpreting immature cells in peripheral blood

- A blood smear shows abnormal release of immature myeloid and erythroid forms.
- Consider disruption of normal marrow architecture.
- Evaluate infiltration or fibrosis with tissue sampling in the appropriate setting.



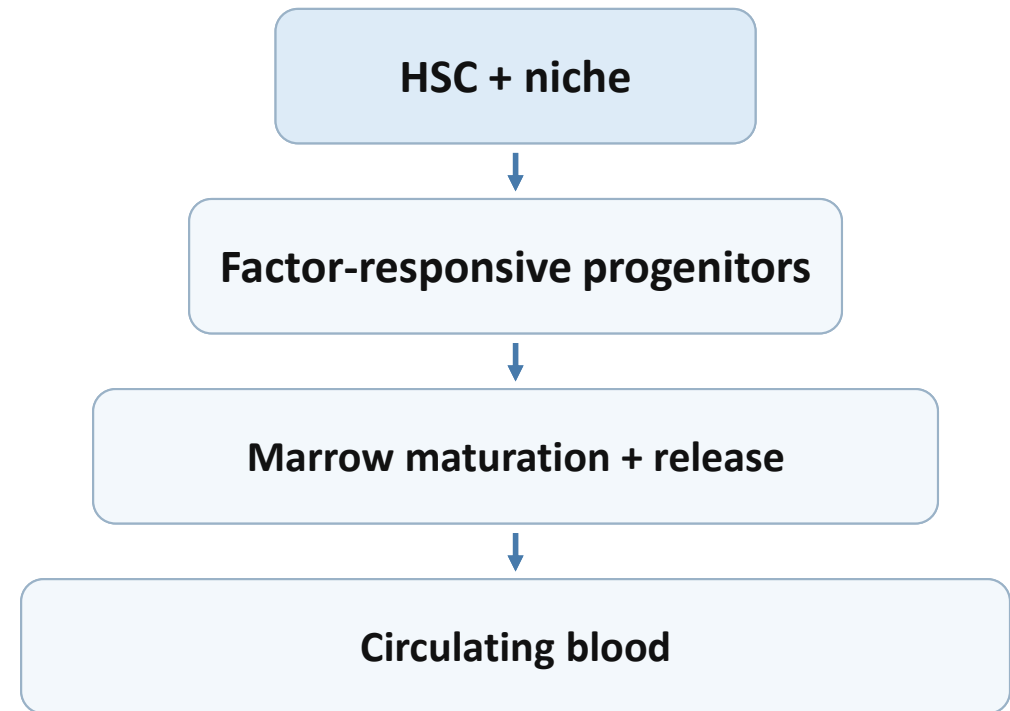
Case: Understanding a dry marrow tap

- Aspiration produces little marrow despite suspicion of infiltration.
- The result does not rule out a substantial marrow lesion.
- Fibrosis or focal infiltration is better evaluated in a core biopsy.

Aspirate	Biopsy
Nondiagnostic or absent	Architecture may reveal lesion

Hematopoiesis connects hierarchy, feedback and tissue architecture

- HSCs preserve lineage potential and long-term renewable capacity.
- Committed progenitors translate growth-factor signals into rapid cell output.
- The marrow microenvironment organizes maturation and release into blood.



Recognize three principal marrow response patterns

- Hypoplasia: Loss of hematopoietic elements and relative fat expansion.
- Hyperplasia: Increased hematopoietic elements and relative fat reduction.
- Distortion or fibrosis: Altered release and possible dry-tap aspiration.

Hypoplasia	Hyperplasia	Distortion / fibrosis
Relative fat excess	Relative hematopoietic excess	Premature release or dry tap

Explain blood-cell output by asking four questions

- Is the renewable HSC compartment preserved?
- Which progenitor lineage and growth-factor signals are active?
- Can cells mature and traverse marrow sinusoids normally?
- Does marrow architecture permit effective hematopoiesis?

HSC reserve

Lineage program

Maturation / release

Marrow architecture

Primary source and interpretation boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 13, “Normal Hematopoiesis,” pp. 531–533.
- The illustrations are original editable schematics—not diagnostic specimens or reproductions of textbook images.
- Adult ranges from the extracted Table 13.1 are omitted because unit symbols in the Markdown conversion are corrupted; consult the printed table and local laboratory ranges.