Transplantation: Stem Cells

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Aims

• to understand the basics of hematopoiesis

• to understand the basic principles of hematopoietic stem cell transplantation
Outline

• Hematopoiesis

• Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Hematopoietic Cell Production

- 70-140 x 10⁶/Min
- 180 x 10⁶/Min
- 180 x 10⁶/Min
- 4 x 10¹⁵/70 years
Hematopoiesis

- Monocyte/Macrophage
- Neutrophil
- Eosinophil
- Mast Cell
- Platelets
- Erythrocyte
- T-Lymphocyte
- B-Lymphocyte

<table>
<thead>
<tr>
<th>Multipotent HSC</th>
<th>Committed HPC</th>
<th>Lineage-specific HPC</th>
<th>End Cells</th>
</tr>
</thead>
</table>

Hematopoiesis

- 100-200 billions
  76-140 millions/minute

- 250 billions
  180 millions/minute

- 250 billions
  180 millions/minute

- 4 x 10^{15} / 70 years
Stem Cells

Zygote — Totipotent Cells
   can develop to a whole organism

Blastocyst:
Embryonic Stem Cells — Pluripotent Cells
   can develop all tissue types of an organism

Organs:
Hematopoietic Stem Cells — Multipotent Cells
   can develop all cell types of a certain tissue

Stem Cell Characterisation

SELF-RENEWING HSCs

CD54

CD48

CD205

c-kit

Adhesion receptors

Drug efflux pumps

COMMITTED PROGENITORS

CD34

CD205

HLA-DR

CD33

CD133

Adhesion receptors

Drug efflux pumps

Lineage markers

Gabriela M. Baerlocher 27.04.2017
Stem Cell Assays

Stem Cell Concept
Stem Cell Regulation

Stochastic Model

Instructive Model

Intrinsically properties of the stem cell cytokines have only permissive role

Extrinsically hematopoietic cytokine signaling influences cell fate

Hematopoietic Environment

non-hematopoietic cellular components of the environment

non-cellular matrix molecules and their complex supportive structures
Hematopoietic Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Site of Production</th>
<th>Prominent Action(s)</th>
<th>Definitional Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic growth factor</td>
<td>Endothelial cells</td>
<td>Erythropoiesis</td>
<td>Erythropoiesis</td>
</tr>
<tr>
<td>Interleukin-13 (IL-13)</td>
<td>Mast cells</td>
<td>Growth and differentiation of monocytes</td>
<td>Monocyte differentiation and activation of mast cells</td>
</tr>
<tr>
<td>Interleukin-15 (IL-15)</td>
<td>Monocytes</td>
<td>Proliferation and differentiation of hematopoietic cells (HSCs)</td>
<td>Proliferation and differentiation of hematopoietic cells (HSCs)</td>
</tr>
<tr>
<td>Flt3 ligand (FL)</td>
<td>B cells</td>
<td>Colony-stimulating activity</td>
<td>Colony-stimulating activity</td>
</tr>
<tr>
<td>Stem cell factor (SCF)</td>
<td>T cells</td>
<td>Proliferation and differentiation of hematopoietic cells (HSCs)</td>
<td>Proliferation and differentiation of hematopoietic cells (HSCs)</td>
</tr>
<tr>
<td>Interleukin-22 (IL-22)</td>
<td>T cells</td>
<td>Antiviral and immune regulation</td>
<td>Antiviral and immune regulation</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony-stimulating factor (G-CSF)</td>
<td>Myeloid progenitors</td>
<td>Proliferation and differentiation of hematopoietic cells (HSCs)</td>
<td>Proliferation and differentiation of hematopoietic cells (HSCs)</td>
</tr>
</tbody>
</table>

HSC Mobilization and Homing

**Steady State**
- Endothelial cell
- Erythrocyte
- Neutrophil
- CD34+ blood stream cell
- Stromal cell

**Mobilization**
- G-CSF
- SCF
- VLA-4
- VLA-5

**Homing**
- G-CSF
- SCF
- VLA-4
- VLA-5

**KEY**
- VCAM-1
- ICAM-1
- G-CSF
- Hyaluronic acid
- CD44
- Fibronectin
- VLA-4
- SDF-1
- SCF
- RHAMM
- CD44
- Collagenase

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Outline

• Hematopoiesis

• Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Allogeneic Transplantation
Autologous Transplantation

Milestones in HSCT
Indications for HSCT

INDICATIONS FOR AUTOLOGOUS BLOOD AND MARROW TRANSPLANTATION IN NORTH AMERICA 2002

Multiple myeloma  NHL  AML  Hodgkin's disease  ALL  MDS/ Other  CML  Neuroblastoma  CLL  Breast cancer  Other cancer  Non-malignant disease

Outline

• Hematopoiesis

• Hematopoietic Stem Cell Transplantation
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  - autologous
Allogeneic Transplantation

Indications for Allo-HSCT

Box 94-1. Diseases Treated by Stem Cell Transplantation (SCT)

- Severe inherited and acquired hemolytic anemias
- Congenital erythrocytic hypoplasia
- Pelagre Disorders
- Glomerular and thalassemia intermedia
- Congenital aplastic anemia or thrombocytopenia
- Metabolic Disorders
- Neutropenia associated with type I (Niemann-Pick type V (Mauriac-Lamy))
- OSA (severe aplastic anemia, Leukodystrophy)
- Congenital disorders types 1, 2, and 3 (Gaucher)
- Not Corrected by SCT: Variable or No Significant Benefit—Not Standard Indications for SCT
- Niemann-Pick type II (type II sphincterioses), type III (West-Zeiss disease), type IV
- Osteopetrosis
- Neutropenia
- Transient myelopetrotic reticulopathies
- Thalassemia syndromes
- Secondary myelofibrosis
- Myelodysplastic syndromes
- Aplastic anemia
- Solid cell anemia
- Hemoglobin E syndromes
- Hereditary spherocytosis
- Pure red cell aplasia
- Hemoglobin H disease
- Paroxysmal nocturnal hemoglobinuria
- Hypertrophic cardiomyopathy
- Mitochondrial diseases
Allogeneic Transplantation

Donor  HLA  Recipient/Patient

Indications

Human Leukocyte Antigens (HLA)

Schematic representation of HLA class I and II loci in the MHC that comprises >200 genes on the short arm of chromosome 6. The corresponding number of antigens (as defined by serology) and alleles (as defined by nucleotide sequence) are indicated for each locus.

http://medweb2.unige.ch/immunologie/
Human Leukocyte Antigens (HLA)

http://medweb2.unige.ch/immunologie/

Allogeneic Transplantation
Sources of Stem Cells

**Bone Marrow**
- Donation requires surgery under general anesthesia; growth factors
- Larger dose of stem cells; rapid engraftment
- After a formal search is begun, takes average of 4 months to transplant, if a donor is available
- Donor may be available to give a second transplant or to donate T-cells if necessary
- Must be used fresh
- Latent viral infection in the donor common (CMV > 50%)
- Severe GVHD common
- Generally requires a perfect match between donor and recipient for 6/6 HLA-A, -B, and DRB1 antigens

**Peripheral Blood**
- Donation requires apheresis and growth factors
- Larger dose of stem cells; rapid engraftment
- After a formal search is begun, takes average of 4 months to transplant, if a donor is available
- Donor may be available to give a second transplant or to donate T-cells if necessary
- Can be stored frozen for over 10 years
- Latent viral infection in the donor common (CMV > 50%)
- Severe GVHD common
- Generally requires a perfect match between donor and recipient for 6/6 HLA-A, -B, and DRB1 antigens

**Cord Blood**
- Donation poses no risk to mother and infant
- Smaller dose of stem cells; slower engraftment
- When a match is found, can take only a few days for confirmatory and special testing and shipment to the Transplant Center
- Donor is not available for a second transplant
- Can be stored frozen for over 10 years
- Latent viral infection in the donor rare (CMV < 1%)
- GVHD less frequent and usually less severe
- HLA-mismatched cord blood transplants are possible, making it easier to find a suitable match

Decision Tree for Allo-HSCT

Diagram showing decision criteria for transplant selection and management.
Stem Cell Selection

Stem Cell Freezing
Stem Cell Thawing

Stem Cell Transplantation
Allogeneic Transplantation

Sources of Stem Cells
Cell Processing/Transplantation

Indications
Conditioning Regimens

Conditions for Allo-HSCT
Allogeneic Transplantation

GVHD

- presence of immunologically competent cells in the graft
- the recipient is unable to mount an effective response to destroy the transplanted cells
- the donor and recipient express different histocompatibility antigens
Allogeneic Transplantation

Donor  HLA  Recipient/Patient

Sources of Stem Cells  Cell Processing/Transplantation

Indications  Conditioning Regimens  Preventing GVHD  Engraftment/Hematopoietic Recovery

Kinetics of Cell Recovery after Allo-HSCT

LYMPHOCYTES

NK

B CELLS AND IMMUNOGLOBULINS

PLATELETS

NEUTROPHILS

3 weeks  3 months  3 years

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Allogeneic Transplantation

Sources of Stem Cells
Cell Processing/Transplantation

Donor HLA Recipient/Patient

Indications
Conditioning Regimens
Preventing GVHD
Engraftment/Hematopoietic Recovery
Complications

Complications after Allo-HSCT

A) Immediate
- Idiopathic (IP)
- Acute (GVHD)
- Chronic GVHD
- Infection
- Pro-Tx rejection

B) Late effects
- Organ toxicity
- Infusion

KEY
- IP = Idiopathic pneumonia
- GVHD = Graft-versus-host disease
- Tx = Transplant

HLA-ID.SSB
100 200 3 years 20 years

B) UNRELATED
- Rotaplas
- Other
- Organ toxicity
- Infusion

untitled.png
Outline

• Hematopoiesis

• Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Autologous Transplantation

Patient

Indications

Therapy
Indications for Auto-HSCT

Autologous Transplantation
HSC Mobilization

Autologous Transplantation

Patient

Indications
SC Mobilization/Transplantation

Therapy
High-dose Regimens
High-dose Regimens

### TABLE 95–1. Agents Used in High-Dose Therapy Regimens with Dose-Limiting Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose-Limiting Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-body irradiation</td>
<td>Mucositis, hepatitis, pneumonitis</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Mucositis, hepatitis, pneumonitis</td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>Pneumonitis, hepatitis</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Thiota    pe</td>
<td>Encephalopathy, mucositis</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Ifosamide</td>
<td>Cystitis, encephalopathy</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Neuropathy, hepatitis, renal failure</td>
</tr>
</tbody>
</table>

**Autologous Transplantation**

- Complications
- Indications
- SC Mobilization/Transplantation
- Therapy
  - High-dose Regimens
  - Patient
Complications after Auto-HSCT

Summary

- Hematopoiesis occurs in a specialized bone marrow microenvironment, composed of cellular and non-cellular elements critical to localization and control of blood cell production.

- Hematopoietic stem cells can be defined by the expression pattern of specific cell surface proteins, cell cycle quiescence, and telomerase activity.

- The process of stem cell mobilization and homing are governed by modulation of interactions between primitive hematopoietic cells and their microenvironment.
Summary

• Allogeneic bone marrow transplantation involves transfer of stem cells and lymphocytes from bone marrow, peripheral blood, or umbilical cord blood.

• Bone marrow transplantation is used to treat a wide spectrum of hematologic malignancies and non-malignant hematologic disorders as well as rare inborn errors of metabolism and storage diseases.

• Progress in understanding allograft immunology and stem cell biology and the introduction of new antimicrobial and immunosuppressive agents over the last 30 years has resulted in continuing improvement in transplant outcome.

• Major limitations are availability of suitably matched donors, complications of GVHD, slow recovery of immune function, and recurrence of advanced malignant diseases after transplant.

Summary

• Autologous hematopoietic stem cell transplantation is based on the dose-response relationship of many chemotherapy agents and radiation: the greater the dose, the greater the response. Infusion of autologous stem cells allows for substantial dose escalation of these agents.

• Successful autologous stem cell transplantation requires proper patient selection, adequate stem cell harvest, processing and storage, appropriate high-dose therapy, intravenous stem cell reinfusion and supportive care and follow-up.

• Autologous stem cell transplantation improves survival for selected groups of patients with multiple myeloma, non-Hodgkin's and Hodgkin's lymphoma, acute myeloid leukemia and germ cell cancer.
http://edweb2.unige.ch/immunologie/

Clinical Hematology by N.S. Young, S.L. Gerson, K.A. High
Mosby, Elsevier