Transplantation:  
Stem Cells

4540-FS2017-0: Selected Topics in Clinical Immunology  
23.05.2019, 16:15 -17:00h

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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

Hematopoiesis

Multipotent HSC → Committed HPC → Lineage-specific HPC → End Cells

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

[Diagram showing stem cell characterisation with markers and self-renewing properties]
Stem Cell Assays

Stem Cell Concept

Nature 2003; 423: 231-233
Stem Cell Regulation

Stochastic Model

Instructive Model

Intrinsically properties of the stem cell
extrinsically hematopoietic cytokine signaling influences cell fate

cytokines have only permissive role

Hematopoietic Environment

hematopoietic stem and progenitor cells and their progeny
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(s) of Production</th>
<th>Predominant Action(s)</th>
<th>Deficiency(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>Monocytes, macrophages</td>
<td>Proinflammatory</td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td>Erythroblasts, myeloid</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-3</td>
<td>Erythroblasts, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-5</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-7</td>
<td>Erythroblasts, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-9</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
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<tr>
<td>IL-11</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
<tr>
<td>IL-12</td>
<td>Macrophages, mast cells</td>
<td>Colony-stimulating factor</td>
<td></td>
</tr>
</tbody>
</table>

HSC Mobilization and Homing

**TABLE 1:** Hematopoietic Cytokines

**STANLEY STATE**
- Endothelial cell
- Erythrocyte
- Neutrophil
- CD34+ blood
  - Blood vessel
  - Stromal cell
- SKELETAL MARROW
  - Osteoblast
  - Endostium

**MOBILIZATION**
- CAM-1
- VLA-4
- CXCRI4
- G-CSF
- CXCRI4
- VLA-4

**HOMING**
- Basal membrane
- VLA-4
- CXCRI4
- G-CSF
- Neutrophil

**KEY**
- VCAM-1
- CXCR4
- C-kIT
- CD44
- Hyaluronic acid
- MMP9
- Cathepsin G
- Neutrophil elastase
Outline

- Hematopoiesis
- Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Allogeneic Transplantation
Autologous Transplantation

Milestones in HSCT
Indications for HSCT

Outline

- Hematopoiesis
- Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous
Allogeneic Transplantation

Donor

Recipient/Patient

Indications

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

- Severe inherited and acquired hematologic disorders
- Congenital erythropoietic porphyria
- Severe combined immune deficiency disease (SCID), SCID with adenosine deaminase deficiency, Wiskott-Aldrich syndrome, tyrosine kinase deficiency, severe T-cell defects
- Chronic granulomatous disease, congenital neutropenia, Chédiak-Higashi syndrome, other rare granulocytic disorders
- Chronic myeloproliferative disorders

Bone Marrow Disorders
- Aplastic anemia
- Fanconi's anemia
- Dyskeratosis congenita
- Schwachman-Diamond syndrome
- Fanconian anemia

Red Cell Disorders
- Thalassemia syndromes
- Sickle-cell anemia
- Diamond-Blackfan anemia
- Pure red cell aplasia
- Pernicious anemia/hemolytic anemias
- Uremic anemia
- Spherocytic anemia

- Metabolic Disorders
- Macropolyserenolysin type 1 (Fukuyama-type muscular dystrophy)
- Crigler-Najjar syndrome type 1
- Osteogenesis imperfecta
- Congenital disorders of glycosylation type 1, 2, and 3 (Ghosh)

- Not Corrected by SCT

- Variable or No Significant Benefit—No

- Standard Indications for SCT
- Macropolyserenolysin type 1 (Fukuyama-type muscular dystrophy)
- MPS type I (Haberl syndrome), type III (Sanfilippo disease), type IV (Morgan syndrome)
- Osteogenesis imperfecta

- No Benefit
- Hypophosphatemic rickets/osteodystrophy
- Type 1A glucose-6-phosphate dehydrogenase deficiency
- Type 1A glycosyltransferase deficiency (Pompe's disease)
- Neurofibromatosis
- Infantile global cell leucodystrophy (Krabbe's disease)
Allogeneic Transplantation

Donor    HLA    Recipient/Patient

Indications

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.

Human Leukocyte Antigens (HLA)

Class II

Antigens

Class I

Alleles

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)

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
Allogeneic Transplantation

Donor  HLA  Recipient/Patient

Sources of Stem Cells
Cell Processing/Transplantation

Indications

Stem Cell Collection

Control Panel
Removed Plasma
Blood Withdrawn
Albumin Bottles
Blood and Albumin Returned
Stem Cell Selection

Stem Cell Freezing
Stem Cell Thawing

Stem Cell Transplantation
Allogeneic Transplantation

Donor

Sources of Stem Cells

Cell Processing/Transplantation

HLA

Recipient/Patient

Indications

Conditioning Regimens

Conditions for Allo-HSCT

<table>
<thead>
<tr>
<th>Conditioning regimen for SCT method in order of intensity</th>
<th>Intensities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced (Bu, TBI, etc.)</td>
<td>Low dose cyclophosphamide (Cy)</td>
</tr>
<tr>
<td>Standard (Cy)</td>
<td>High dose TBI</td>
</tr>
<tr>
<td>Enhanced (Bu, TBI, etc.)</td>
<td>High dose TBI, high-dose melphalan (Melph), additional conditioning (e.g., busulfan, methotrexate)</td>
</tr>
</tbody>
</table>

*Cy = Cyclophosphamide, Bu = Busulfan, TBI = Total Body Irradiation, Melph = Melphalan, Busulfan = Busulfan, Melph = Melphalan, TBI = Total Body Irradiation*
**Allogeneic Transplantation**

- **Donor**
  - Sources of Stem Cells
  - Cell Processing/Transplantation

- **Recipient/Patient**
  - HLA

- **Indications**
  - Conditioning Regimens
  - Preventing GVHD

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**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

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*Nature Reviews Immunology 2007, 7:340-52*
Allogeneic Transplantation

Sources of Stem Cells

Cell Processing/Transplantation

Donor

HLA

Recipient/Patient

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

20,000/cu mm

500/cu mm

Allogeneic Transplantation

Donor HLA Recipient/Patient

Sources of Stem Cells
Cell Processing/Transplantation

Indications
Conditioning Regimens
Preventing GVHD
Engraftment/Hematopoietic Recovery
Complications

Complications after Allo-HSCT

Infection
Organ toxicity
Relapse
Chronic GVHD
Acute GVHD
Mortality after transplant
Pre-Tx status

A

HLA-ID SIB

Relapse
Organ toxicity
Infection
IPh

16%
34%
17%
8%
14%

UNRELATED

Relapse
Organ toxicity
Infection
IPh

16%
22%
17%
21%
9%

B

KEY
IPh = Interstitial pneumonia
GVHD = Graft-versus-host disease
Tx = Transplant

Gabriela M. Baerlocher 23.05.2019
Outline

• Hematopoiesis

• Hematopoietic Stem Cell Transplantation
  - allogeneic
  - autologous

Autologous Transplantation

Patient

Indications

Therapy
Indications for Auto-HSCT

Autologous Transplantation
HSC Mobilization

Autologous Transplantation
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>Thiopeta</td>
<td>Encephalopathy, mucositis</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Ifosfamide</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**
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
Literature

http://edweb2.unige.ch/immunologie/

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