Hematopoiesis, Growth Factors, and Immunology

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Objectives

• Describe the hematopoietic system
  – How blood cells are developed
  – Role & function of blood cells
  – Growth factors that stimulate blood cell development

• Review basic function and cellular components of the immune system

• Identify new immunotherapies used to treat cancer

What Cell Type?

What Cell Type?
Origin of Blood Cells

- All blood cells have two things in common:
  - Originate from a common progenitor cell
  - Develop through a process called *hematopoiesis*

Hematopoiesis

- Process of blood cell formation
  - Red Blood Cells
  - Platelets
  - White blood cells

- Greek origin
  - “Haima”: blood
  - “Poiesis”: to make

Bone Marrow Microenvironment

- Vessels
- Marrow Sinuses
- Marrow Stroma
  - Supportive structure
  - Regulatory proteins
- Cells

Hematopoiesis

- Includes the processes of:
  - Cellular proliferation
    - An increase in the number of cells as a result of cell growth and division
  - Cellular differentiation
    - Process by which a cell changes from a generic cell to a specialized cell
  - Stem cell maturation

Pluripotent Stem Cell

- Hematopoietic cell
- Source of all cells
  - “Uncommitted”
  - Progenitor
- Self renewing
- Location
  - Marrow
  - Peripheral Blood (CD34+)
- Migratory properties

Differentiation

Commitment

Proliferation

STEM CELL SELF-REPLICATION/Differentiation

Pluripotent Stem Cell

Myeloid Stem Cell

Lymphoid Stem Cell

MYELOID LINEAGE

Pluripotent Stem Cell

Myeloid Stem Cell

Megakaryocyte

Monocyte

Neutrophil

Eosinophil

Basophil

LYMPHOID LINEAGE

Pluripotent Stem Cell

B Lymphocyte

T Lymphocyte
Commitment

- **Myeloid Lineage**
  - Erythrocyte
  - Platelet
  - Granulocyte
    - Neutrophil
    - Basophil/mast cell
    - Eosinophil
  - Monocyte / macrophage
  - Dendritic cell

- **Lymphoid Lineage**
  - B lymphocyte
  - T lymphocyte
  - Natural Killer Cell (NK)

Cytokines

- **Mediators of the immune system**
- **Molecules that:**
  - Enhance communication
  - Induce growth and differentiation of lymphocytes and other cells within the immune system
- **“Messengers” of the immune system**
  - Released by cells throughout the body
  - Bind to surface receptors of target cells
  - Provide communication between cells of immune system

Examples of Cytokines

- Interferons (IFNs)
- Interleukins (ILs)
- Hematopoietic growth factors
  - Erythropoietin (EPO)
  - Granulocyte colony-stimulating factor (G-CSF)
  - Granulocyte macrophage colony-stimulating factor (GM-CSF)
- Tumor necrosis factor (TN)
- Chemokines

Erythropoiesis Feedback Mechanism

- Erythropoietin (EPO)
- Cytokine (protein signaling molecule) for erythrocyte precursors
- Produced by the kidneys
Erythrocytes

- Functions:
  - $O_2/CO_2$ Transport and exchange
  - Acid Base Balance
- Normal:
  - M: 4.7 – 6.1 million cells/mm$^3$
  - F: 4.2 – 5.4 million cells/mm$^3$
- Production:
  - 2.5 billion/kg/day
- Life span:
  - Approximately 120 days

Erythropoietic-Stimulating Agents (ESA’s)

- Mechanism of action:
  - Stimulates erythropoiesis via same mechanism as endogenous erythropoietin (EPO)
- Indications:
  - Chemotherapy-induced anemia
  - Anemia due to chronic kidney disease in patients on dialysis and not on dialysis
- Agents
  - Epoetin alfa (*Procrit®, Epogen®*)
  - Darbepoetin (*Aranesp®*)

Platelets

- Function:
  - Hemostasis
- Normal:
  - 150,000 – 400,000 cells/mm$^3$
- Production:
  - 2.5 billion/kg/day
- Life span:
  - 7 - 10 days

Thrombopoietic Growth Factor Oprelvekin (IL-11, Neumega)

- Indications:
  - To prevent severe thrombocytopenia and reduce the need for platelet transfusions in patients with nonmyeloid malignancies receiving chemotherapy with a high risk of severe thrombocytopenia
- Route of Administration
  - Subcutaneous
- Nursing considerations:
  - Dosing should begin 6-24 hours after completion of therapy
  - Discontinue when post-chemotherapy platelet nadir >50,000 and 2 days before next chemotherapy cycle
Leukocyte Function

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Function</th>
<th>When Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>Phagocytosis</td>
<td>Bacterial Infection</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Allergic reaction</td>
<td>Parasitic Infections</td>
</tr>
<tr>
<td>Basophil</td>
<td>Allergic reactions</td>
<td>Inadequate inflammatory response</td>
</tr>
<tr>
<td>Monocyte</td>
<td>Phagocytosis</td>
<td>Fungal infection</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>Immunity</td>
<td>Viral infections, Opportunistic infections, Cancer</td>
</tr>
</tbody>
</table>

Neutrophils

- Phagocytic cells
  - Early responder to infection
  - When low: susceptible to bacterial infection
- Capacity for infection fighting/defense
  - Advantage
    - Limited stimuli provoke a response
    - Early response in large numbers
    - Effective killing bacteria, digest debris (healing)
  - Disadvantage
    - Unable to recognize many injurious agents
    - Cannot modify response (i.e. doesn’t “learn”)

Normal Values
- 60%-80% of total WBC count (1800-7700 cells/mm³)
- Life span: 7-12 hours (circulating neutrophils)
- Production:
  - Normal adult bone marrow produces approximately 1 X 10¹¹ neutrophils each day

Banded neutrophil (Band)
- Less mature

Polymorphonuclearcyte (Poly)
- Also called segmented neutrophil (Seg)
- Poly = Seg = Neutrophil (mature)
Granulocyte Colony-Stimulating Factors (G-CSFs): Cytokines

- Filgrastim (Neupogen®)
- tbo-filgrastim (Granix®)
- Filgrastim-sndz (Zarxio™)

Route of administration:
- Subcutaneous (filgrastim & tbo-filgrastim)
- IV (filgrastim only)

Nursing considerations:
- First dose should be administered at least 24 hours after chemotherapy
- Avoid use 24 hours before chemotherapy is administered

Pegfilgrastim (Neulasta®)

Route of administration:
- Subcutaneous

Nursing Considerations:
- Longer half life than filgrastim or tbo-filgrastim
- 1 dose equivalent to 10-11 daily injections of G-CSF
- Administer as single 6 mg injection once per chemotherapy cycle
- Do not administer in the period beginning 14 days before or until 24 hours after administration of myelosuppressive chemotherapy

Antigen Presenting Cells (APC’s)

- Help lymphocytes recognize antigens on foreign cells (including cancer cells)

- Include:
  - Monocytes
  - Macrophages
  - Dendritic cells

Monocytes

- Respond to inflammation & infection
  - Present fragments of pathogens to T-cells (so that they can be recognized and destroyed)

- Survival:
  - In circulation short (8-72 hours)
  - When they enter the tissues and become macrophages, life span may extend up to 3 month

- Precursors for macrophages and dendritic cells
  - Will further differentiate into these cell types as the need arises
Macrophages

- Greek: big eaters:
  - From makros “large” + phagein “eat”
  - Found in tissue
  - Commonly referred to as “scavengers” or antigen-presenting cells
  - Seize and engulf foreign materials and then present these antigens to lymphoid-derived cells (T lymphocytes and B lymphocytes)

Dendritic Cells (DCs)

- Travel from tissue to secondary lymphoid organs to present antigens to T-lymphocytes and B-lymphocytes
- Results in T-cell and B-cell activation
- Effective in stimulating both antiviral and antitumor immune responses

Lymphocytes

- Derived from lymphoid stem cell lineage
- Key for all immune responses
- Two types
  - B Lymphocytes
  - T Lymphocytes
- Make up 20% of total white blood cell count

B Lymphocytes

- Mature in Bone marrow
- Function
  - Multiply on recognition of a specific antigen
  - Further differentiate into plasma cells
  - Produce one of 5 types of immunoglobulins (IgG, IgA, IgM, IgE, IgD)
**T Lymphocytes**

- Produced in the bone marrow
- Migrate to the thymus gland for development
- Play a major role in immune surveillance
- Before antigen recognition by T cells, antigens are processed by antigen-presenting cells (APCs) displayed on the cell surfaces as peptides

**T Cell Types**

<table>
<thead>
<tr>
<th>Type</th>
<th>Functions</th>
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| Helper T cells (Th) | • Assist other white blood cells in immunologic processes  
|                    | • Also known as CD4+ T cells (express CD4+ on cell surface)                                |
| Cytotoxic T cells (Tc) | • Destroy virus-infected cells and tumor cells, also implicated in transplant rejection  
|                    | • Also known as CD8+ cells                                                                  |
| Memory T cells      | • Subset of antigen-specific T cells that persist long-term after an infection has resolved  
|                    | • Quickly expand to large numbers upon re-exposure to original antigen (provide immune system with “memory” to past infections) |
| Suppressor T cells  | • Major role to shut down T-cell mediated immunity toward the end of an immune reaction  
|                    | • Also called “regulatory T cells”                                                          |

**Null Cells/Natural Killer Cells**

- Separate lineage of lymphoid cells
- Contain substances called perforin, serine proteases, and enzymes that create a hole in the membrane of the cell resulting in cell death
- Activity increased with the addition of cytokines such as interleukin-2 (IL-2), IL-12, and interferon gamma
- Function:
  - Identification and destruction of virus-infected cells and certain tumor

**Immune System Function**

- Protect against foreign invaders
- Maintain homeostasis
- Provide surveillance
- Immune response:
  - Coordinated action of the immune system
  - Goal: Target invading microbes, infected cells, and tumor cells while ignoring healthy tissue


Immune System Components

- Nose
- Thymus
- Bone Marrow
- White blood cells
- Tonsils
- Lymph nodes
- Spleen
- Lymphatic vessels

Mechanisms of Cancer Development

- Evade checkpoints and cell signals to stop or for apoptosis
- Form blood vessels to develop source of food and energy (angiogenesis)
- Invade other tissues and spread throughout body (metastasis)
- Evade the immune system and avoid destruction

Immunosurveillance

- Immune system identifying and controlling tumor cells (Vesely, & Schreiber, 2013)
- A theory that the immune system patrols the body not only to recognize and destroy invading pathogens, but also host cells that become cancerous
- Immune escape:
  - Loss of recognition by cells within the immune system, which leads to tumor escape and cell proliferation (Devita, et al, 2011)
Immunotherapy

• Treatment that restores or enhances the immune system’s natural ability to fight diseases, including cancer
• Described as a way to “fire up the immune system’s response to cancer” (Ledford, 2015, p. 24).
• Immunotherapy works by:
  – Stopping or slowing the growth of cancer cells
  – Stopping cancer from spreading to other parts of the body
  – Helping the immune system recognize cancer cells and increase its effectiveness at eliminating cancer cells

Types of Immunotherapy: Active or Passive

• Passive:
  – Enhances preexisting immune response
  – Usually administered to initiate antitumor effect but do not result in immunologic memory (require repeated administration to be effective)
  – Short-term response
  – Examples: Monoclonal antibodies
• Active:
  – Engages the immune system
  – Capitalize on immune system’s ability to remember foreign invaders; longer-term, more durable response
  – Examples: Cancer vaccines

Types of Immunotherapy: Specific versus Non-Specific

• Specific:
  – Capitalize on tumor markers or tumor-associated antigens to specifically target and kill cancer cells
  – Examples: monoclonal antibodies
• Non-specific:
  – Do not target cancer cells alone but rather stimulate a large immune response
  – Often given adjuvantly to other anticancer treatment drugs
  – Examples: cytokines, interleukins, and checkpoint inhibitors

Immunotherapy Strategies To Treat Cancer

• Non-specific immune stimulation
• Adoptive cell transfer
• Immune-checkpoint blockade
• Vaccine strategies
• Monoclonal antibodies
• Cytokines
Non-Specific Immune Stimulation

- Used to give a general boost to the immune system
- Activate antigen-presenting cells by using cell signaling molecules (cytokines)
  - Interferon alfa-2b (*Intron® A*)
  - Aldesleukin (IL-2, *Proleukin®*)
- Activated cells alert other immune cells – such as T cells

Adoptive Cell Transfer

- [https://www.youtube.com/watch?v=Hivji9V9l-8](https://www.youtube.com/watch?v=Hivji9V9l-8)
- Approach that enhances the natural cancer-fighting ability of the body’s T cells by:
  - Removing immune system cells
  - Growing and/or making changes to them outside the body (activating cells using cytokines)
  - Re-infusing them back into the patient
- Not currently FDA approved, in clinical trials

Immune Checkpoint Blockade

- [https://www.youtube.com/watch?v=v9NBUEu3PG0](https://www.youtube.com/watch?v=v9NBUEu3PG0)
- Immune checkpoints play a key role in immune responses
  - Dampen down the immune response to prevent collateral damage to normal, healthy tissue
- Checkpoint inhibitors can be used to “release the breaks” allowing the immune system to respond appropriately to the cancer
  - This is a “negative signaling approach

Commonly Expressed Checkpoints

- Checkpoints commonly expressed on the surface of immune cells include the following:
  - Programmed cell death protein 1 (PD-1)
  - Programmed death ligand 1 (PD-L1)
  - Cytotoxic T lymphocyte-associated protein 4 (CTLA-4)
**Immune Checkpoint Inhibitors/Modulators**

- **Ipilimumab (Yervoy®)**
  - Targets a blockade molecule: cytotoxic T-lymphocyte antigen 4 (CTLA-4)

![Ipilimumab Diagram](image)

**Programmed death receptor-1 (PD-1) Inhibitors**

- **Pembrolizumab (Keytruda®)**
- **Nivolumab (Opdivo®)**

**Vaccine Strategies**

- [https://www.youtube.com/watch?v=WHZBqwZgXyE](https://www.youtube.com/watch?v=WHZBqwZgXyE)
- Currently one approved “vaccine” to treat cancer
  - Classified as an “autologous cellular immunotherapy” for treatment of certain types of prostate cancer
- **Provenge®** (sipuleucel-T)
  - FDA approval in 2010 to treat certain types of metastatic prostate cancer
  - Antigen presenting cells taken from patient
  - Matured outside the body and loaded with tumor antigens
  - Cells are reintroduced to the patient
  - The antigen stimulates other immune cells and helps them to recognize the tumor

**Monoclonal Antibodies & Hematopoietic Growth Factors (Cytokines)**

- **Monoclonal antibodies**
  - Special type of protein designed to target antigens, or markers, located on the surface of cancer cells
  - Antibodies locate antigens and recruit immune cells to attack
  - [https://www.youtube.com/watch?v=XL5Q7b1nYbE](https://www.youtube.com/watch?v=XL5Q7b1nYbE)

**Hematopoietic Growth Factors (Cytokines)**

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Immunotherapy Strategies To Treat Cancer

- Non-specific immune stimulation
- Adoptive cell transfer
- Immune-checkpoint blockade
- Vaccine strategies
- Monoclonal antibodies
- Cytokines


Which of the following best describes what cytokines do?

a. They bind to surface receptors of target cells and act as regulators of cell growth or as mediators of defense functions
b. They are capable of non-specific tumor cell killing
c. They are sedentary cells located in the spleen
d. They facilitate the attachment of a natural killer cell and other cytotoxic cells.

Each of the following is an important function of the body’s immune system except:

a. Protecting the body against injury from foreign substances
b. Preserving the body’s internal environment
c. Preventing the growth of aberrant cells that might develop into neoplasms
d. Providing support and nourishment to the body’s genetic machinery

THANK YOU!

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