Hematopoiesis, Growth Factors, and Immunology
Kelley Blake MSN, RN, AOCNS, OCN
UW Medicine/Valley Medical Center

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 how the immune system is used to treat cancer

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
  • “Poieses”: to make

Bone Marrow Microenvironment

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

Bone Marrow Cellularity

4 Year Old Child 80 Year Old Adult

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

Stem Cell Self-Replication/Differentiation

Myeloid Lineage
**Lymphoid Lineage**

- B lymphocyte
- T lymphocyte
- Natural Killer Cell (NK)

**Myeloid Lineage**

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

**Commitment**

**Hematopoiesis**

**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
  - Cytokine (protein signaling molecule) for erythrocyte precursors
  - Produced by the kidneys

Erythrocytes

- Functions
  - O2/CO2 Transport and exchange
  - Acid Base Balance
- Normal
  - M: 4.7 – 6.1 million cells/mm3
  - F: 4.2 – 5.4 million cells/mm3
- 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

- **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/mm³

- **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

| Leukocyte Type | Function | Limitation
|---------------|----------|-------------
| Neutrophil    | Phagocytosis | Bacterial Infection
| Eosinophil   | Allergic reaction, Defense against parasites | Parasitic Infections
| Basophil      | Allergic reactions, Inflammatory reactions | Inadequate inflammatory response
| Monocyte      | Phagocytosis, Immunity | Fungal infection, Viral infections, Opportunistic infections, Cancer
| Lymphocyte    | Phagocytosis | Bacterial Infection

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”)
Neutrophils

- 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

Granulocyte Colony-Stimulating Factors (G-CSFs): Cytokines

- Filgrastim (Neupogen®)
- Tbo-filgrastim (Granix®)
- Filgrastim-sndz (Zaroxio®)

- Route of administration
  - Subcutaneous (filgrastim & tbo-filgrastim)
  - IV (filgrastim only)
- Nursing considerations
  - First dose should be administered at least 24 hours after chemotherapy

Polymorphonuclearcyte (Poly)

- Also called segmented neutrophil (Seg)
- Poly = Seg = Neutrophil (mature)

Banded neutrophil (Band)

- Less mature

Granulocyte Colony-Stimulating Factors (G-CSFs): Cytokines

- Pegfilgrastim (Neulasta®)

- Route of administration
  - Subcutaneous
- Nursing considerations
  - Longer half life than filgrastim or tbo-filgrastim
  - Administer as a 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

Granulocyte Colony-Stimulating Factors (G-CSFs): Cytokines

- Oncpro on-body injector (Neulasta®)

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
dthat 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
months
- Precursors for macrophages & dendritic cells
  - Will further differentiate into these cell types as
the need arises

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

Macrophages

- Greek: big eaters
  - From makros “large” + phagein “eat”
  - Found in tissue
  - Commonly referred to as
“scavengers” or antigen-presenting
  - Seize and engulf foreign materials
  - When they enter the tissues and become
macrophages, life span may extend up to 3
months
- Precursors for macrophages & dendritic cells
  - Will further differentiate into these cell types as
the need arises

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

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
months
- Precursors for macrophages & 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
  - Seize and engulf foreign materials
  - When they enter the tissues and become
macrophages, life span may extend up to 3
months
- Precursors for macrophages & dendritic cells
  - Will further differentiate into these cell types as
the need arises

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

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
months
- Precursors for macrophages & 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
  - Seize and engulf foreign materials
  - When they enter the tissues and become
macrophages, life span may extend up to 3
months
- Precursors for macrophages & dendritic cells
  - Will further differentiate into these cell types as
the need arises

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>Function</th>
</tr>
</thead>
</table>
| 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 reactions
|                 | • 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

- Antibodies
- T Lymphocytes
- B Lymphocytes
- Phagocytes:
  - Natural Killer Cells
  - Granulocytes
  - Macrophages
- Skin
- Mucous Membranes
- Enzymes
- Natural Microbial Flora
- Complement Protein

Learned, Specific Immunity

Innate, Non-Specific Immunity

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

**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
• 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=Hivji9V9i-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)
• 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 (Yervoy®) Package Insert, 2017. Bristol Myers

Immune Checkpoint Inhibitors/Modulators

- Programmed death receptor-1 (PD-1) Inhibitors
  - Pembrolizumab (Keytruda®)
  - Nivolumab (Opdivo®)

Vaccine Strategies

- [https://www.youtube.com/watch?v=WHZBgwZgXyE](https://www.youtube.com/watch?v=WHZBgwZgXyE)
- 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=XL3Q7binY8E](https://www.youtube.com/watch?v=XL3Q7binY8E)

**Hematopoietic Growth Factors (Cytokines)**
- Granulocyte colony-stimulating factors (G-CSF)
  - Filgrastim (Neupogen®)
  - Tbo-filgrastim (Granixa®)
  - Pegfilgrastim (Neulasta®)
- Erythropoiesis-stimulation factor: EPO
  - Epoetin alfa (Procrit®, Epogen®)
  - Darbepoein (Aranesp®)

Question

- Which of the following best describes what cytokines do?
  - They bind to surface receptors of target cells and act as regulators of cell growth or as mediators of defense functions
  - They are capable of non-specific tumor cell killing
  - They are sedentary cells located in the spleen
  - They facilitate the attachment of a natural killer cell and other cytotoxic cells

Thank you!

Kelley Blake MSN, RN, AOCNS, OCN
UW Medicine/Valley Medical Center
Kelley_blake@valleymed.org