THE IMMUNE SYSTEM AND LEUKOCYTE FUNCTION

PLAYERS IN IMMUNITY THE INNATE PARTY

The Innate Party	the Adaptive Party
The "Professional" killer cells (trap the MO) phagocytes =neutrophils, monocytes, macrophages natural killer cells Enzymes from within the cells=lysozymes (kill the MO) Inflammatory -related serum proteins Complement /C-reactive protein / Lectins Antimicrobial peptides (AMPs) =defensins, cathelicidins Cell receptors =DAMPs, TLRs, PAMPs Cytokines, histamine, leukotrienes, chemokines, platelet-activating factor, kinins	Cellular (cytotoxic=cell killing) or humoral (in body fluids) B and T lymphocytes; natural killer cells Dendritic cells and macrophages (Antigen presenting cells) Major Histocompatibility complex molecules Primary and Secondary Lymphoid tissues Provides long term immunity against invaders MORE specific response but delayed (few days) Specificity and memory

LEUKOCYTES STARTING POINTS

1. Occurs via stepwise maturation of CD34+ STEM CELLS
2. Arise from stem cells in bone marrow
3. Hematopoietic stem cells differentiate into 2 lineages
4. Myeloid and lymphoid
5. Decreased/increased production from marrow or accelerated destruction
6. Non-neoplastic or neoplastic syndrome encompass dysfunction
7. Leukocytes
    a. granulocytes or agranulocytes
        i. Granulocytes = neutrophils, basophils, and eosinophils
        ii. Agranulocytes =lymphocytes, monocytes, and macrophage
    b. phagocytes or immunocytes
8. Deficiency in QUANTITY (leukopenia) or increased quantity (leukocytosis)
9. Leukocytosis (>10K) and leukopenia (<5K)
10. Disruption of function

GRANULOCYTES

- Have many membrane bound granules within the cytoplasm
- Enzymes can kill MOs and catabolizing debris during PHAGOCYTOSIS
- Also have powerful biochemical mediators w/ inflammatory and immune functions triggered to release by specific stimuli
- Have amoeboid movement (diapedesis) which helps move through BV walls

NEUTROPHILS

1. 55% of total leukocyte count takes 14 days from early precursors to maturation
2. Function:
    a. Primary defense against bacterial infection
    b. Phagocytosis and digests microorganisms
    c. Responds to several sources of chemotaxis
        i. Macrophage released Interleukin
        ii. Basophil and Mast Cell released Histamine
        iii. C-reactive Induced Complement Activation
3. Nucleus with 3 to 5 lobes connected by thin chromatin
    a. Cytoplasm with fine granules

EOSINOPHILS

1. 1-4% of total leukocyte count
2. Forms in bone marrow from myeloblasts
3. Function:
    a. Response to Allergy and parasitic infections
    b. Responds to mast cell, basophil chemotactic factors
    c. Ingest antigen antibody complexes using pattern recognition receptors
4. Secondary granules have toxic chemicals that are highly destructive to parasites and viruses
    a. major basic protein, eosinophil cationic protein, eos- peroxidase, and eos -derived neurotoxin
5. Pro-inflammatory release leukotrienes, prostaglandins, platelet activating factor, and cytokines (IL-6, IL-1, TNF –a, GM-CSF)
6. Also contain anti- inflammatory enzymes (histaminase)

BASOPHILS

1. <1% of total leukocyte count
2. Forms in bone marrow from myeloblasts
3. Function:
    a. Allergic Response
    b. Similar mechanism of action to mast cells
    c. Related to delayed hypersensitivity response
    d. Triggered by IgE binding to antigen
    e. Releases inflammatory mediators
        i. Preformed mediators (Histamine, Bradykinin)
        ii. New Mediators (Prostaglandins, Leukotrienes)
        iii. Chemotactic factors attract neutrophils and eosinophils

4. Stimulation of basophils synthesis of vasoactive leukotrienes and cytokines IL-6 IL-10 (by Th-1 and Th2 that favor B-cell differentiation) IL-4 guides B-cell into secrete IgE

MAST CELLS

1. Originate from different precursor cells than eosinophils, basophils, or neutrophils, have similar action to basophils
2. Reside in vascularized connective tissue just beneath epithelial surfaces
3. Function:
    a. Central role in inflammation
    b. Vascular endothelial cells, smooth muscle cells, circulating platelets and leukocytes
    c. Involved in healing
        i. Fibroblasts
4. Activation leads to increased permeability of BV and smooth muscle contraction
5. Widely distributed throughout connective tissue
6. Mediate inflammatory response
7. Store chemical mediators
    a. Histamine
    b. Interleukins
    c. Proteoglycans
    d. Heparin
8. Involved via either degranulation or synthesis
9. Activated by
    a. Tissue trauma
    b. Complement proteins C3a and C5a
    c. Cross-linking cell surface IgE by antigen
10. Activate other mediators
    a. Leukotrienes
    b. Prostaglandins
    c. Platelet activating factor

MONOCYTES

1. Monocytes and macrophages >>> mononuclear phagocyte system
    a. AKA reticuloendothelial system (RES)
2. Largest normal blood cell w/ horseshoe shaped nucleus
3. Migrate to variety of tissues and mature into tissue macrophages or dendritic cells; other monocytes are circulating macrophages
4. Dendritic cells have arm like projections that extend into tissues and look like “neurons”
5. Once they leave circulation they do not return, can live months to years –exact turnover is unknown

MACROPHAGES

1. Macrophages are the “cleaners”
2. present in 2-3 days after inflammation/neutrophils begin- higher concentrations in Adaptive immunity/chronic inflammation
3. Source: monocytes in the blood
4. FUNCTION:
    a. resolution and healing, continued active inflammation, abscess, or chronic inflammation
    b. remove old debris and damaged cells and large molecular substance from the circulation
    c. Tissue repair
5. Secrete cytokines & growth factors
6. Ingest organisms via phagocytosis and destroy (using lysosomes) the material in secondary granules (o2 independent killing)
7. Activate other cells, especially T-cells
8. Eliminate microbes, particulate matter, and senescent cells

DENDRITIC CELLS

1. Are the major antigen-presenting cells
2. Antigen presenting and antigen processing
3. begin life as unprogrammed innate state
4. serve essential role in adaptive immunity
5. represent a key link between the innate and adaptive systems

AGRANULOCYTES

- Monocytes, macrophages, and lymphocytes
- Fewer granulocytes in cytoplasm
- Monocytes and macrophages have larger and fewer digestive vacuoles than granulocytes
- lymphocytes DO NOT have any enzymes to digest

LYMPHOCYTES

1. 36% of total leukocyte count
2. Present in circulation and lymphoid organs
3. Primary response for immune response
4. Most transiently circulate then reside in secondary lymphoid tissues as mature T-cells, B-cells, or plasma cells
5. Life span days, months years
6. Develop from precursors in generative (primary) lymphoid tissues
7. Each B and T cells and its progeny (clone) express a SINGLE antigen receptor
8. Total pop of lymphocytes = 10^{12} Can recognize tens –hundreds of millions of antigens
9. Encoded in DNA sequences

B-LYMPHOCYTES

1. Immature B cells produced in bone marrow
    a. undergo immunoglobulin arraignment
    b. become naïve b cells that express IgM and IgD
2. B-cell activation occurs
3. Become plasma cell or memory cell

T-CELLS: CELL-MEDIATED/CELLULAR IMMUNITY

1. Bone marrow as progenitor T cells migrate to and develop in thymus
2. TCR undergoes rearrangement
3. progenitor cells "evolve" into either
    a. CD4 (t-helpers) or CD8+ (Cytotoxic T-cells)
4. Use TCR as "surveillance" for antigens and recognizes MHC molecules
5. Recognition of antigens on surface of macrophages
    a. Elimination of virally infected cells tumors or foreign bodies
    b. Release of cytotoxins
    c. Delayed hypersensitivity reactions

NATURAL KILLER CELLS

1. Resemble large granular lymphocytes
2. Develop in marrow found in peripheral blood and spleen mainly
3. Kill some in vitro cancer cells and some virus infected cells w/o being induced by previous exposure to antigen
4. t-cytotoxic cells MUST be activated by antigen- differentiation
5. Have capacity to activate T-cells, phagocytes and produce variety of cytokines that can regulate immune response
6. Unique innate immune cells with specialized features
7. Kill some in vitro cancer cells and some virus infected cells w/o being induced by previous exposure to antigen
8. (t-cytotoxic cells MUST be activated by antigen- differentiation)
9. Have capacity to activate T-cells, phagocytes and produce variety of cytokines that can regulate immune response

ANTIGEN-PRESENTING CELLS

1. Highly specialized hunter cells that capture ANTIGEN and present it and display it to the lymphocytes of the adaptive immune system
2. Dendritic cells
3. B-lymphocytes
4. Macrophages

LYMPHATIC SYSTEM

1. Primary and Secondary Lymph tissues
2. Structure/function
    a. Closely integrated and all are linked to hematological and immune systems
    b. Lymphoid organs are merely aggregations of tissue
    c. Primary
        i. thymus and bone marrow
    d. Secondary
        i. spleen, lymph nodes, tonsils, and Peyer patches (sm intestine)
3. Are sites of proliferation, residence, differentiation and function of lymphocytes and mononuclear phagocytes (monocytes and macrophages)

SPLEEN

1. major lymphopoietic organ- 25% of the total lymphoid mass of the body +RES can react and enlarge quickly after the onset of infection or inflammation.
2. function -remove particulates (opsonized bacteria, antibody-coated cells) from the blood stream
3. Pts w/ splenectomies are susceptible to bacterial sepsis, especially with encapsulated organisms.
4. spleen also serves as a quality control mechanism for red cells, removing senescent and/or poorly deformable red cells from the circulation; also removes circulating red cells (its "pitting" function), such as nuclear remnants (Howell-Jolly bodies), insoluble globin precipitates (Heinz bodies), and normally occurring endocytic vacuoles

LYMPHATIC DRAINAGE AND NODES

1. Collect interstitial fluids from tissues and transport it as lymph through vessels of increasing size and dump into thoracic duct
2. 1-way system that returns lymph fluid via vessels to the CV system for eventual elimination of toxic byproducts by end organs, such as the liver, kidney, colon, skin, and lungs
3. Provide filtration of the lymphatic fluid
4. NODES
    a. PRIMARY site of antigen –lymphocyte encounter
    b. cortex contains follicles w/ lymphocytes. At the center of the follicles is an area called germinal centers that predominantly host B-lymphocytes while the remaining cells of the cortex are T-lymphocytes.

THYMUS

1. bilobed lymphoid organ located in the superior mediastinum of the thorax, posterior to the sternum.
2. After puberty, decreases in size; it is small and fatty in adults after degeneration.
3. Function
4. processing and maturation of T lymphocytes

5. While in the thymus, T lymphocytes do not respond to pathogens and foreign organisms.
6. Also produces thymosin, a hormone that helps stimulate maturation of T lymphocytes in other lymphatic organ

LYMPHADENOPATHY (LAD)

1. Enlarged lymph nodes
    a. size, consistency, fixation
    b. Painful versus painless
2. Inflammation cause lymph node hyperplasia of regions within the node
    a. many potential causes
    b. Although biopsy is sometimes the best way to reach a definitive diagnosis, it should be used judiciously
3. HX and focused P.E >> lead to a DD of peripheral lymphadenopathy, which will then inform the need for further evaluation (laboratory evaluation, imaging, and/or biopsy)

ALTERATIONS IN LEUKOCYTE AND LYMPHOID FUNCTION

LEUKOCYTOSIS

1. Increased circulating neutrophils
2. Caused by:
    1) infection, or tissue necrosis
        i. Induces release of marginated pool from marrow neutrophils including bands (immature forms)
    2) 2) high cortisol state – impairs leukocyte adhesion leading to release of marginated pool of neutrophils

WBC DIFFERENTIAL

1. Monocytosis >> inc circ monocytes
    a. chronic inflammation
2. Eosinophilia >> inc circ eosinophils
    a. allergic reactions, parasitic, Hodgkin lymphoma
3. Basophilia >> inc circ basophils
    a. Chronic myeloid leukemia
4. Lymphocytic leukocytosis >> inc circ lymphocytes
    a. Viral infections
    b. Pertussis

LEUKOMOID REACTION

1. an increase in the white blood cell count, which can mimic leukemia.
2. The reaction is actually due to an infection or another disease and is not a sign of cancer.
3. PREMATURE RELEASE OF IMMATURE WBC's in response to depletion of mature WBC demand exceeds supply
    a. AKA "left shift"
4. As infection decreases the balance restored and shift back to normal occurs

LEUKOPENIA/NEUTROPENIA

1. decrease in circulating neutrophils
    a. <1500 cells/microL in most clinical laboratories
2. Neutrophils = most abundant WBCs in peripheral blood
    a. mature neutrophils are also called polymorphonuclear cells (PMNs) based on the characteristic segmentation of the nucleus
3. Absolute neutrophil count – # of neutrophils + bands
    a. ANC = WBC (cells/microL) x percent (PMNs + bands) ÷ 100
    b. Classified as
        i. Mild – ANC ≥1000 and <1500
        ii. Moderate – ANC ≥500 and <1000
        iii. Severe – ANC <500

ETIOLOGY OF LEUKOPENIA

1. Inherited/congenital DO
    a. BEN-Benign Ethnic neutropenia
    b. Familial neutropenia
    c. Congenital neutropenia
2. Acquired DO
    a. Infection
    b. Medications
    c. Nutritional
    d. Autoimmune DO
    e. Rheumatological DO
3. hematological malignancies

LYMPHOCYTOSIS

1. Abnormal increases lymphocyte count
2. May be transient infection or one of several other benign or malignant conditions
3. Consider malignant proliferation vs. reactive
4. Reactive include:
    a. Viral:
        i. CMV, Mumps, Rubella, Measles, Influenza
        ii. Hepatitis, Adenovirus, Coxsackie virus, Poliovirus

b. Bacterial:
    i. Pertussis, Cat-scratch fever, toxoplasmosis
c. Other drug hypersensitivity reactions, stress, thymoma

LYMPHOCYTOPENIA

1. Abnormal decreases in the lymphocyte count
2. may be transient infection or one of several other benign or malignant conditions
    a. infection, iatrogenic causes, systemic disease, and congenital immunodeficiency disorders
3. Examples include
    a. Malignancy -Hodgkin lymphoma
    b. SLE
    c. TB
    d. Aplastic anemia
    e. High cortisol state
    f. Cytotoxic chemotherapy and/or radiation therapy

LYMPHEDEMA

1. DEFINE: Chronic, progressive swelling of tissue with protein-rich fluid; Lymphoscintigram, the most accurate way to diagnose lymphedema visualizes a radiolabeled marker as it moves through the lymphatic system
2. Can be either because of developmental (primary lymphedema) or acquired (secondary lymphedema) disruption of the lymphatic system
    a. Extremities are most affected, followed by genitalia
    b. Most cases are 2/2 nematode infection (filariasis is endemic particularly Africa or Asia, malignancy, or cancer-related treatment
3. ETIOLOGY/EPIDEMIOLOGY
    a. Cancer treatments (esp. breast cancer) lymph node dissection, lymphatic hypoplasia, parasitic nematodes, injury to lymph
    b. 140-250 million worldwide
    c. Primary lymphedema –children rare 1.15/100000
    d. Male =female ratio
        i. Male presents in infancy
        ii. Females in adolescence
    e. Secondary lymphedema 2/2 malignancy
4. PATHO: The lymphatic system returns interstitial fluid and proteins to the circulatory system. Particulate matter and microorganisms are filtered at lymph nodes for immunologic presentation. Dysfunction of channels or nodes leads to lymph accumulation in the superficial interstitial space. Lymphatic stasis leads to fat hypertrophy with associated thickening of

subcutaneous tissue, as well as immunologic dysfunction. Elevated concentrations of interstitial protein cause inflammation and fibrosis, leading to a cycle of further damage

5. KEY FEATURES:
    a. Painless unilateral swelling of extremity or genitalia
    b. Positive Stemmer sign
    c. Limp heaviness or weakness
    d. Nonpitting edema
    e. Skin changes

6. DIAGNOSTIC WORKUP
    a. Lymphoscintigram
    b. MRI or CT scan of affected limb
    c. U/S
    d. Blood smear
    e. Genetic testing