Inflammation, Immunity and Related Disorders

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Class 2 Objectives
• Upon completion of this lesson, the student will be able to
  – differentiate the immune function across the lifespan.
  – determine the different effects of inflammation.
  – describe the four mechanisms of hypersensitivity.
  – contrast the concepts of autoimmunity, infection, and immunosuppression.
  – determine gene-environment interactions that can result in cancer.
  – evaluate the signs and symptoms, as well as laboratory findings, for various types of cancers.

Immunity
• Innate: Native or Natural Resistance
  • Not produced by an immune response
  • One type of “natural immunity” that exists at birth
    – Species specific
      • For example, we are not prone to infectious agents that cause illness in other species (e.g. canine distemper)
Immunity

- **Acquired**: formed after birth
  - Produced by an immune response
  - **Active**: following an exposure to antigen or immunization
  - **Passive**: does not involve the host’s immune response
    - T lymphocytes or preformed antibodies are transferred to host
    - Temporary - such as tetanus, rabies exposure, snake bite

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Immune Response

- **Key Cells are “Lymphocytes”**
  - Recognize micro-organisms
  - 2 types develop in bone marrow
    - **T - Cells**: lymphokine, macrophages, cytotoxic, helper, suppressor,
      - Mature in **thymus** and move to the **spleen**
    - **B - Cells**: (10-20% of lymphocytes)
      - Mature in **bone marrow** and move to the **spleen**
      - Infection causes maturation into Plasma Cells
      - Plasma Cells secrete antibodies
        » antigen receptors

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Immune Responses

- **Cell Mediated Immunity (CMI)**
  - **T - Cells** (“helper” & “killer”) fight invading microbes and destroy infected cells
  - To boost CMI the immune system produces cytokines (soluble molecules)
    - govern the development of antigen-specific immunity
    - Interferon, Interleukin-2, Interleukin 12
    - Interferon elicits uninfected neighboring cells to produce antiviral proteins
  - CMI is paramount in fighting infections caused by viruses & microbes hiding inside cells
Immune Responses

- **Hummoral Immunity:**
  - Immune system depends on the production of antibodies made by mature, antibody secreting B - Cells
  - To strengthen this response the immune system releases cytokines
    - Interleukin-4, IL 6, IL-10
  - T - Cells (CMI) are essentially responsible for stimulating antibody production by B - Cells

Immune Function

- **Fetal**
  - Last trimester: fetus is able to produce an immune response to various infections
  - IgG is not sufficient and maternal transfer occurs
    - Figure 6-21, p. 193
- **Neonate**
  - IgG is near adult levels and then drops by 5-6 mos.
  - Human infant is immunologically immature at birth

Immune Function

- **Elder**
  - Immunologically at risk d/t declined function with age
  - Decreased T-cell and specific antibody function
  - Increased autoantibodies that attack normal tissue
    - Infections, cancers and autoimmunity take place
Acute Inflammatory Response

- Occurs when first line of defense is broken by cellular injury
- Injury can be caused by:
  - trauma or surgery
  - chemical agents
  - temperature extremes
  - invasion of micro-organisms
  - oxygen/nutrient deprivation (ischemic damage)
  - genetic/immune defects (e.g. autoimmune)

Acute Inflammatory Response

- A biochemical and cellular process that occurs in vascular tissues due to cellular injury
- Non-specific elimination of micro-organisms
  - Inflammation may precede an immune response or be caused by one
  - Occurs physiologically in the same manner whether initial or second exposure to antigen

Acute Inflammatory Response

- Hemodynamic changes in microcirculation:
  - Momentary constriction followed by prolonged vasodilation of arterioles and venules
  - Vascular permeability increases d/t histamine release
Acute Inflammatory Response

- Cellular changes occur:
  - WBCs adhere to inner walls of blood vessels
    - mast cells, neutrophils, eosinophils, macrophages
  - Chemotaxis: movement of neutrophils to the site
    - granulocytes = neutrophils, eosinophils, basophils
    - monocytes
    - macrophages: “Big Eaters”

- Following phagocytosis, exudates are formed:
  - Serous: watery
  - Fibrinous: thick & clotted
  - Membranous: sticky
  - Purulent: present with abscess or cellulitis
    - Hemorrhagic or Sanguinous: bleeding
  - Removal of cellular debris
  - Protein deposition for tissue healing

- Chemical mediators:
  - Histamine released from mast cells & basophils
  - Plasma factors: kinins and clotting factors
  - Prostaglandins: stimulate inflammatory response
  - Cytokines: enhance inflammatory response
  - Interferons: stimulate immune cell production & enhances the body’s defenses against viral & parasitic infections
  - Tumor necrosis factor (TNF): produced by macrophages in response to infection with gram-negative bacteria
Inflammatory Response

http://www.micro.msb.le.ac.uk/MBChB/1b.html

Manifestations of Inflammation

- **Local Symptoms:**
  - rubor (redness)
    - > blood flow to area
  - tumor (swelling)
    - > capillary permeability
  - calor (heat)
    - > blood flow to area
  - dolor (pain)
    - stretching of nerves by swelling

- **Systemic Changes:**
  - Fever
  - Leukocytosis
  - Increase in circulating plasma proteins

- **Septic Shock:**
  - < BP, > HR, > RR
  - infection

- **Scar tissue formation**

Chronic Inflammation

- Can occur as a distinct process without much acute inflammation
- Some micro-organisms have cell walls that are very high in lipid & wax content, making them relatively insensitive to degradation by phagocytes
  - These bacteria continue to stimulate inflammation (e.g. tuberculosis & syphilis)
Resolution and Repair

- Healing:
  - Minor injury:
    - return to normal structure & function
  - Extensive damage:
    - infection with abscess or granuloma formation
    - repair takes place
- Repair:
  - Replacement of destroyed tissue with scar tissue
    - fill in the wound
    - cover, seal, or shrink the wound

Wound Healing

- Primary Intention:
  - minimal tissue loss
  - wound edges are close together
  - no infection & little scarring
- Secondary Intention:
  - wounds requiring a lot of tissue replacement
  - heal from bottom upward
  - extensive scarring
  - staphylococcus may be present

Dysfunctional Wound Healing

- May occur at any phase of wound healing
  - insufficient repair (e.g. dehiscence)
  - excessive repair
  - infection
- Etiological Causes:
  - Diabetes Mellitus, anti-inflammatory agents
  - Hypoxemia, hypovolemia, poor nutrition
  - Age (infants vs. elders)
Inflammatory vs. Immune

- **Inflammatory response**
  - nonspecific
  - occurs in the same manner whether an initial or second exposure

- **Immune response**
  - antigen specific
  - has a memory

Why does one get a flu attack each year?

Molecular model of hemagglutinin, the protein on the surface of the influenza virus that is recognized by the host immune system. The yellow dots represent amino acids, which get randomly changed, requiring new antibodies to be made. Source: D. M. Hillis, Science, 286, 1999, 1866-1867

Hypersensitivity

- **Immediate**
  - Most immediate: within minutes of exposure
    - Anaphylaxis: systemic
      - shock, antibiotics
      - airway obstruction
      - Shock, death
    - Allergy
      - Mast cell degranulation
      - Asthma, eczema, urticaria
      - Vasodilation
      - > vascular permeability

- **Delayed**
  - Memory T-Cell mediated response
  - Skin irritant
    - poison ivy or oak
    - adhesive tape
    - suntan
    - PPD response
    - Graph rejection
  - Inflammation
    - clinical manifestation
Mechanisms of Hypersensitivity

- **Type 1 (IgE)**
  - Mast cell activity
  - Seasonal allergies, milk, citrus, wheat
  - Some genetic basis

- **Type 2 (tissue specific)**
  - Destruction of target cell from an antibody that is attacking an antigen on the cell membrane
  - Hemolytic anemia's
  - Reactions to wrong blood type
  - Rh disease
  - Antibodies made against organs

- **Type 3 (Immune Complex)**
  - Complexes that are formed within the circulation, in response to another invasion
  - Glomerulonephritis, arthritis

- **Type 4 (Cell-mediated)**
  - Only reaction not mediated by antibody
  - Sensitized T lymphocytes
  - Graph rejection, PPD reaction, poison ivy or oak
  - Insulin dependent DM
  - Thyroid destruction

Autoimmunity

- **Self/ Non-Self Discrimination is altered**
  - Immune response is inappropriately directed at self
  - Autoantigens
  - Alteration of antigens on cell bodies
  - Alteration of function or immunocompetent cells

- **Diseases:**
  - Type 1 Diabetes Mellitus
  - Systemic Lupus, Rheumatic Fever
  - Multiple Sclerosis

Infection

- **The success of a pathogen is dependent upon**
  - Virulence and portal of entry

- **Gram negative are most problematic**
  - Trick the phagocytes
  - Harm vessels by forming clots
  - E-coli and meningococciemia are very aggressive pathogens
  - Can move from local site to sepsis
  - Compromised host is at extreme risk
  - Sepsis to death can occur from gram negative or positive
Immunosuppression

- Immune deficiency can be
  - Primary: Inherited
    - X-Linked: A Gamma-Globulinemia
    - SCID: Severe Combined Immunodeficiency
  - Secondary: Acquired
    - Neoplasia of Immune System
      - Hodgkin’s Disease: Neoplasm of Lymphoid Cells
      - AIDS: A depletion syndrome of the T-Cells
    - Use of corticoid steroids
    - Iatrogenic immunodeficiency:
      - Caused by RX for Neoplasias

HIV & AIDS

- HIV infects CD4 cells preferentially
- CD4 surface markers serve as anchors for HIV
- HIV is a "retrovirus" and its genetic information is carried in the form of RNA
  - Produces reverse transcriptase
  - Converts RNA to DNA
  - Viral DNA is incorporated into the Host’s genome
- < T-Cells: leads to opportunistic infections manifested in AIDS (HIV+ & CD4 < 200)
Current Issues Related to AIDS

- Protease inhibitors and Transcriptase Blocking
  - Two types of interventions that attack replication
- Problems
  - Retroviral mutation rate is very high
  - Mutants become drug resistant
  - Reduction of serum concentration of viral load does not equate "cured," oft infected T-cells hiding in reservoirs and are not measured by lab analysis
- Drug compliance and clients’ misunderstanding of their infection has produced a new era of HIV infection as a consequence of high-risk sex behaviors.

Biology of Cancer

http://biology.berkeley.edu/orl/index.shtml

- Cancer cells do not respond to "social control"
- Two characteristics of cancer cells
  - Autonomy and anaplasia
- Origins of cancer
  - Mutations in genes involved in DNA repair
    - XP gene; BRCA1, 2; malfunction of p53 (regulator of cellular responses to DNA damage)
  - Hereditary, oncogenic viruses and bacteria

Tumor Grading

- Grade 1: well differentiated
  - Resembles tissue of origin
- Grade 2: moderately differentiated
  - Increased variation in size and shape
- Grade 3: poorly to very poorly differentiated
  - A lot of variation in size and shape;
- Grade 4: no resemblance to original tissue
  - Size and shape vary greatly
Tumor Classification

- Cell type
- Tissue origin: e.g. “meningioma”
- Degree of aggression: benign or malignant
- Degree of differentiation
- Anatomic site
- Function

Tumor Cell Markers

- Cancer cells produce biological substances that can be detected on tumor plasma membranes or in the blood, spinal fluid or urine
- Detection through analysis can help
  - Screen, diagnose, mark tumor progression
- These “biologic markers” include
  - Hormones, enzymes, genes, antigens, antibodies
- Not used alone as a diagnostic test of cancer

Carcinogenesis

- The development of a cancerous tumor involves the evolution of cellular changes (phenotypic & genotoxic)
  - e.g. normal epithelium to invasive malignancy
  - Can take several years to progress
- Phases include
  - Initiation (DNA mutation)
  - Promotion (cells continue to change with exposure)
  - Tumor formation (local invasion and metastasis)
Environmental Risks

- Tobacco use is carcinogenic and is an essential cause of cancer
  - Twenty carcinogens in tobacco smoke
  - Increases the chance for bladder, pancreas, kidney, larynx, oral cavity, esophageal, and lung cancer
  - Teens account for 85-90% of new smokers
  - Passive smoke: children are most vulnerable
  - Inhaled chemicals are carcinogenic
    - benzene (cleaning fluids), sulfur dioxide (smog)

Dietary Influences

- There are advantages:
  - Inhibit carcinogens
    - Vitamins A, C, E; Cruciferous vegetables; soy; green tea
  - Block carcinogens from accessing DNA target
    - Plant phenols; Coumarins; Green tea
  - Inhibit promotion and progression
    - Retinols, protease inhibitors, carotenids
- And disadvantages:
  - Vitamin C (antioxidant) render cancer treatments less effective
  - Beta carotene in lung cancer made it worse

Tumor Invasion & Staging

- Local spread after tumor cells detach
- Malignant tumor secretes degrading enzymes that destroys normal tissue
- Cancerous cells have faulty anchors (fibronectin) that allows them to break away from cells
- Wandering cancer cells allow them to invade blood or lymph and metastasize to other parts
- Most common route of spread is the lymph
- Angiogenesis: tumor cells thrive on new blood supply
- Stage: size (T); local invasion (N); degree of mets (M)
Manifestations of Cancer

- Anemia: r/t chronic bleeding, bone marrow suppression, chemo, dietary intake
- Cachexia: includes anorexia, early satiety, wt. loss, asthenia, altered protein, carbohydrate, and lipid metabolism
  - A common cause of death in cancer patients (80%)
- Fatigue: caused by sleep deprivation, level of activity, depression, and treatments
- Pain: not present in early phases; however, 60-80% of terminally ill clients experience pain
  - Psychogenic, cultural, physiologic components

Treatment of Cancer

- Look for treatment for specific cell type, location of tumor, and stage.
  - Combination Rx: surgery, radiation, and chemo
- Goal of chemo is to reduce # of cells
  - Affects cell cycle (see table 11-6, p. 348)
- Radiation: a direct shot at the cancer mass
  - Avoid normal tissue
- Surgery: very successful if no distant mets
- Immunotherapy: interferons, antigens, monoclonal antibodies…a future endeavor?

References