Immunity and Abnormal Responses

Bio 375 Pathophysiology

Immune System

- The immune system is a major component of the body’s defenses
- It is a SPECIFIC defense, responding to particular substances:
  - Cells
  - Toxins
  - Proteins
  - Other substances that are perceived as foreign to the body

The Normal Immune Response

- Unique antigens (usually proteins) on the cell surface enable a person’s immune system to distinguish self from nonself (foreign) and thus detect and destroy unknown material
- This involves:
  - Recognition of a specific foreign invader
  - Developing a specific response to that antigen
  - Storing that specific response in memory for future reference should the invader return
Pathogenesis of Measles

Remember:

- Prior exposure necessary to prime the immune system for this defense to be effective
- Immune system is aided by general defense mechanisms such as phagocytosis and the inflammatory response
- By removing the foreign material, the immune system plays a role in preparing the area for healing

Components of the Immune System

- Lymphoid structures
- Immune cells
- Tissues concerned with immune cell development
- Chemical mediators
Antigens

- Antigens are EITHER foreign substances OR human cell markers that are unique (except in identical twins) to each individual
- They are composed of complex proteins, polysaccharides or a combination called glycoproteins
- Self antigens are coded by several genes (MHC) located on chromosome 6

MHC (major histocompatibility complex) is also known as HLA (human leukocyte antigen)

- Due to the large number of genes involved in the formation of MHC, no two people are likely to have same self antigens
- Our immune system usually tolerates self antigens
Cells of the Immune System

- Macrophages develop from monocytes
- Dendritic cells form in red bone marrow
- These large, phagocytic cells, located throughout the body, intercept and engulf foreign material and present antigens to the lymphocytes
- Lymphocytes:
  - T-cells produce cell mediated immunity
  - B-cell produce antibody mediated immunity

Development of Cellular and Humoral immunity

- T-cells are most effective against virus-infected cells, fungal and protozoan infections, cancer cells and foreign cells such as transplanted tissues
- B-cells are most effective against bacteria and viruses that are outside of cells as well as toxins produced by bacteria and parasites
- Natural killer (NK) cells require no prior exposure or sensitization and kill cancer cells and cells infected with viruses with perforin and granzyme causing apoptosis
Antibodies or Immunoglobulins

- The basic Y-structure is formed from two pairs of polypeptide chains called light and heavy
- Each antibody molecule has a region common to most antibodies called the constant region and a unique region called the variable region
- The variable regions form the antigen binding site

Structure of Basic Antibody

Types of Antibody Molecules
Complement System

- Complement system often activated during an immune reaction by IgG or IgM
- Complement system is a group of at least 20 inactive proteins (C1-C9) + others circulating in the blood
- It is activated when an antigen-antibody complex attaches to C1 and sets in motion a cascade of reactions

Complement activation eventually results in the destruction of the antigen by:
- Lysis when the cell membrane is damaged
- Phagocytosis
- Complement activation also initiates an inflammatory response.

Innate Immunity

- Natural or innate immunity is species specific
- Innate immunity involves leucocytes, macrophages, NK's, inflammation, complement and other nonspecific mechanisms that can identify and attack antigens without prior activation
- Innate immunity lacks memory
Adaptive Immunity

- Adaptive immunity requires prior exposure; the response consists of two steps:
  - A primary immune response which occurs on first exposure to a foreign antigen
  - A secondary immune response which results when a repeat exposure to the same antigen occurs; due to memory cells

Lymphocyte Specificity

- Each T- and B-cell expresses receptors for only one antigen
- Millions of different naïve lymphocytes
- When activated by an appropriate antigen, an activated lymphocyte undergoes rapid cell division to produce clone of similar lymphocytes
Types of Acquired Immunity

- Active natural immunity
- Active artificial immunity
- Passive natural immunity
- Passive artificial immunity

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Memory</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural active</td>
<td>Pathogens enter body and cause illness; antibodies form in host</td>
<td>Yes</td>
<td>Person has chickenpox once</td>
</tr>
<tr>
<td>Artif active</td>
<td>Vaccine (live or attenuated organism) is injected into person; no illness results, but antibodies form</td>
<td>Yes</td>
<td>Person receives vaccine and gains immunity</td>
</tr>
<tr>
<td>Natural passive</td>
<td>Antibodies passed directly from mother to child to provide temporary protection</td>
<td>No</td>
<td>Placental passage during pregnancy or ingestion of breast milk</td>
</tr>
<tr>
<td>Artif passive</td>
<td>Antibodies injected into person (antigen) to provide temporary protection or minimize severity of infection</td>
<td>No</td>
<td>Gamma globulin if recent exposure to microbe</td>
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</table>

Tissue and Organ Transplantation

Table 3–4

<table>
<thead>
<tr>
<th>Types of Tissue or Organ Transplants</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Ailogram (homograft)</td>
<td>Tissue transferred between members of the same species but may differ genetically—e.g., one human to another human</td>
</tr>
<tr>
<td>Isgraft</td>
<td>Tissue transferred between two genetically identical bodies—e.g., identical twins</td>
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<tr>
<td>Autograft</td>
<td>Tissue transferred from one part of the body to another part on the same individual—e.g., skin or bone</td>
</tr>
<tr>
<td>Xerograft (heterograft)</td>
<td>Tissue transferred from a member of one species to a different species—e.g., pig to man</td>
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Transplant Rejection

- Transplantation involves replacement of damaged tissue or organs by healthy ones.
- Most transplants are allografts.
- The main obstacle to successful transplants has been that the recipients immune system responds to the foreign HLA proteins of the graft and destroys or rejects it.

Rejection is a complex process and involves both cell-mediated and antibody (humoral) responses.
- Both cause inflammation and tissue necrosis.
- The rejection process eventually destroys the organ.

Survival Time for Transplants

- Survival time is increased when the tissue match is excellent.
- When the tissue is from a living donor.
- When immunosuppressive drugs are taken on a regular basis.
- Neonates and young infants can receive transplants, e.g. heart, without a good tissue match. Their immature immune systems do not respond to the foreign tissue.
**Tissue Rejection**

- One type of rejection involves the host immune system rejecting the donated tissue or organ (host-versus-graft disease) or HVGD
- Sometimes the grafted tissue contains T-cells that attack the host tissues (graft-versus-host disease) or GVHD

**Immunosuppression**

- Immunosuppressive techniques are used to reduce the immune response and prevent rejection
- Commonly, this involves drugs like cyclosporine, Imuran and prednisone
- Immunosuppressive drugs have been successful in reducing the risk of rejection, but dosage must be carefully monitored because of the high risk of infection

**Side Effects of Immunosuppression**

- Suppressing the immune system not only reduces it ability to reject grafts, but reduces it ability to:
  - Fight infection
  - Prevent cancers
- Cyclosporine can also cause gingival hyperplasia
Hypersensitivity Reactions

- HR or allergic reactions are unusual and perhaps damaging immune responses to normally harmless substances.
- There are four basic types:
  - Type I Hypersensitivity - Allergy
  - Type II - Cytotoxic Hypersensitivity
  - Type III - Immune Complex Hypersensitivity
  - Type IV - Cell-mediated or Delayed Hypersensitivity

Type I: Allergy

- Allergies are very common and appear to be increasing in incidence and severity
- A tendency toward allergic conditions is inherited
- Allergic reactions can take many forms:
  - Skin rashes
  - hay fever
  - anaphylaxis

Allergens

- The causative antigen is called an allergen; it may be
  - a food like shellfish, nuts, strawberries
  - Chemical
  - pollen like ragweed
  - Drugs like aspirin, penicillin, sulfa
Type I
Causative Mechanism

Type II - Cytotoxic Hypersensitivity

- The antigen is present on the cell membrane.
- The antigen may be a normal component or foreign
- Circulating IgG antibodies react with the antigen, causing destruction of the cell; e.g. Rh Disease of the newborn
- IgM as in transfusion reaction for ABO system
An example would the response to an incompatible blood transfusion

Type III- Immune Complex HR
- Antigen combines with antibody, forming a complex
- The complex is then deposited in tissue, often in blood vessel walls
- Complement is activated
- Causes inflammation and tissue destruction
- Glomerulonephritis and rheumatoid arthritis are examples

Immune complex reaction
Type IV-Cell-Mediated or Delayed HR

- This is a delayed response by sensitized T-cells to antigens, resulting in the release of lymphokines or other chemical mediators that cause an inflammatory response and destruction of the antigen
- Contact dermatitis or an allergic skin rash is caused by Type IV reaction to direct contact with the chemical

Type IV

- The cause may be:
  - Cosmetics
  - Dyes
  - Soaps
  - Metals like nickel
  - Rubber or latex
  - Plant toxins like poison ivy, oak, summac
  - Organ transplant rejection

Contact Dermatitis
Contact Dermatitis

Type IV

Autoimmune Disorders

- Occur when certain individuals develop antibodies to their own tissues
- Process is not certain
- Appears to be a genetic factor involved
- Autoantibodies are formed against self antigens
- Disorder may be localized or generalized
Autoimmunity

- Localized examples:
  - Hashimoto’s thyroiditis: antibodies are produced that cause destruction of thyroid tissue leading to hypothyroidism
  - Myasthenia gravis: a chronic autoimmune disease mediated by anti-acetylcholine receptor antibodies at myoneural junctions

- Systemic example:
  - Systemic Lupus Erythematosus (SLE)

SLE

- Effects primarily women
- Manifests between ages 20-40
- Familial occurrence
- Named for “butterfly” facial rash
- Chronic inflammatory disease that affects multiple systems
- Progressive disease with remissions and exacerbations

Characterized by antibodies against DNA, platelets, erythrocytes, nucleic acids, and sometimes others

- Immune complexes, especially those with DNA, are deposited everywhere in the body, activating complement and causing inflammation and necrosis
- Vasculitis (inflammation of blood vessels) develops in many organs impairing blood flow (ischemia) to many organs
**Clinical Findings Used to Assess SLE**

1. Facial rash confined to the checks
2. Discoid rash
3. Photosensitivity caused rash
4. Oral or nasopharyngeal ulcers
5. Nonerosive arthritis of at least 2 peripheral joints
6. Serositis (pleurisy, pericarditis)
7. Renal disorder (proteinuria or casts)

8. Neurological disorders (seizures/psychosis)
9. Hematologic disorders (hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia)
10. Immunologic disorders: anti-double stranded DNA antibodies, false positive test for syphilis, antiphospholipid antibodies, etc
11. Presence of antinuclear antibody (ANA)
Viruses and Immunity

- Recent research has shown that in some chronic viral infections, the body's own anti-inflammatory response blocks its immune system from attacking the virus.
- Viral meningitis, cytomegalovirus, hepatitis C and even HIV may someday be effectively attacked and killed by the immune system that has been allowed to function fully.
- High levels of IL-10 have been found in many patients with chronic viral infections. IL-10 dampens the inflammatory response and inhibits immune responses.
- Animals with chronic viral infections also have high IL-10 levels and when treated with drugs that block IL-10, their inflammatory response was reactivated and within 2 weeks they were virus free.

Immunodeficiency

- Results from loss of function, partial or total, of one or more components of the immune system.
- May be acute and short-term or chronic.
- Primary deficiencies involve a basic developmental failure somewhere in the system.
- Secondary or acquired deficiencies refer to losses from specific causes and can occur any time in life.

Primary Deficiencies

- Lack of stem cell formation in bone marrow.
- Defect in thymus function.
- Failure to produce B-cells.
- Usually result from genetic or congenital abnormality.
- Usually noted in infants and children.
- Example: X-linked hypogammaglobulinemia (low antibody production due to B-cell defect.)
Secondary Deficiencies

- Caused by infection
- Splenectomy
- Malnutrition
- Liver disease
- Use of immunosuppressive drugs
- Radiation and chemotherapy
- Stress, physical and emotional
- AIDS which affects helper T-cells (CD4)

HIV Infection of CD-4 Cells

![HIV Infection of CD-4 Cells Diagram]

- [Image description]

![Graph showing the life cycle of HIV and CD-4 cells]

- [Graph description]

- [Legend]

- [Graph x-axis: Exposures, Months, Years]
- [Graph y-axis: Normal CD4 cells, Ant-HIV, HIV]

- [Graph notes: Window period, Virus in blood, No antibodies, Mild symptoms, More antibodies form, Small amounts of virus in blood, Asymptomatic, Active infection, Decreasing CD4 count, AIDS indicator diseases, Opportunistic infections, Symptomatic, Weighing syndrome, dementia]
Using the immune system to attack melanoma cells

Table 3—8

<table>
<thead>
<tr>
<th>Deficit</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
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<tbody>
<tr>
<td>B cell (humoral)</td>
<td>Hypogammaglobulinemia (congenital)</td>
<td>Kidney disease with loss of globulins</td>
</tr>
<tr>
<td>T cell (cell-mediated)</td>
<td>Thymic aplasia</td>
<td>Hodgkin's disease (cancer of the lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>DiGeorge's syndrome</td>
<td>AIDS (HIV infection); temporary with some viruses</td>
</tr>
<tr>
<td>B and T cell</td>
<td>Inherited combined immunodeficiency syndromes (CID)</td>
<td>Radiation, immunosuppressive drugs, cytotoxic drugs (cancer chemotherapy)</td>
</tr>
<tr>
<td>Phagocytes</td>
<td>Inherited chronic granulomatous diseases (CGD)</td>
<td>Immunosuppression (glucocorticoid drugs, neutropenia); diabetes (decreased chemotaxis)</td>
</tr>
<tr>
<td>Complement system</td>
<td>Inherited deficit of one or more components</td>
<td>Malnutrition (decreased synthesis), liver disease—cirrhosis</td>
</tr>
</tbody>
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