Chapter 19: Disorders of the Immune System

1. Hypersensitivity
2. Autoimmunity
3. Transplant Rejection

1. Hypersensitivity

What is Hypersensitivity?
Hypersensitivity is an immunological state in which the immune system “over-reacts” to foreign antigen such that the immune response itself is more harmful than the antigen.

All types of hypersensitivity involve:
• the adaptive immune response
  • i.e., highly specific reactions via T or B cells
• prior exposure to the antigen
  • the initial exposure sensitizes the individual but does NOT cause a hypersensitive reaction
  • hypersensitivity is only seen on secondary exposure
Types of Hypersensitivity

Hypersensitivity following secondary exposure to antigen comes in 4 basic forms:

* Type I: allergic reactions ("immediate" hypersensitivity)
  - IgE mediated and very rapid (2-30 minutes)

* Type II: cytotoxic reactions
  - cell damage due to complement activation via IgM or IgG

* Type III: immune complex reactions
  - cell damage due to excess antibody/antigen complexes

Type IV: delayed cell-mediated reactions
  - cell damage involving T cells & macrophages

* Types I-III are all antibody-mediated, Type IV is not!

Type I: Allergic Reactions

Allergic (anaphylactic) reactions involve the activation of mast cells or basophils through the binding of antigen to IgE on the cell surface:

- mast cells & basophils have IgE receptors that bind the constant region of any IgE antibody
- "cross-linking" of IgE molecules on the cell surface by binding to antigen triggers the release of "mediators"
  - mediators = histamine, prostaglandins & leukotrienes

...more on Allergic Reactions

The release of these mediators causes the redness, swelling, itching, mucus, etc, that characterize allergic reactions:

Most allergic reactions are local:
  - itching, redness, hives in the skin, mucus, sneezing
  - usually due to inhaled or ingested antigens

Systemic allergic reactions can be lethal:
  - severe loss of blood pressure, breathing difficulty (anaphylactic shock)
  - usu. due to animal venoms or certain foods
  - epinephrine can "shut down" the allergic reaction
Some common Allergens

- Grains of pollen
- Foods: e.g., corn, eggs, nuts, peanuts, onions
- Dust mites: the allergen is actually dust mite feces (yuck!)

Managing Allergic Reactions

Avoidance
- avoiding contact with allergen is by far the safest and most effective way of managing allergies

Medications
- antihistamines: drugs that block histamine receptors on target cells, histamine is still released but has little effect
- epinephrine (aka – adrenalin): necessary to halt systemic anaphylaxis

Desensitization
- antigen injection protocol to induce tolerance

Type II: Cytotoxic Reactions

Type II cytotoxic reactions involve destruction of cells bound by IgG or IgM antibodies via the activation of complement:
- symptoms take several hours to appear
- most commonly observed with blood transfusions: reaction to ABO blood antigens, reaction to Rh antigen
- can occur via the Rh antigen in newborns: requires Rh- mother and Rh+ child, Rh- mother produces anti-Rh+ IgG following birth, subsequent Rh+ children are vulnerable
The ABO Blood Antigens

- A or B type polysaccharide antigens on surface of RBCs
- Individuals lacking enzymes producing A or B are type O

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Enzyme or Red Blood Cell Antigens</th>
<th>Plasma Antigens</th>
<th>Blood Type Can Be Housed</th>
<th>Frequency (%) US Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A and B</td>
<td>Anti-A</td>
<td>A, B, AB, O</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
<td>B, O</td>
<td>9, 23, 37</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
<td>A, O</td>
<td>41, 27, 28</td>
</tr>
<tr>
<td>O</td>
<td>Neither A nor B</td>
<td>Anti-A and Anti-B</td>
<td>O</td>
<td>47, 49, 43</td>
</tr>
</tbody>
</table>

ABO mediated Cytotoxicity

Blood type “O” individuals (tolerate type O blood only)
- Do not produce type A or type B antigens
- Produce antibodies to type A and B antigens and thus will lyse type A, B or AB RBCs via complement

Blood type “A” individuals (tolerate blood types A & O)
- Produce only type A antigens
- I.e., tolerant to type A antigen, antibodies to B antigen

Blood type “B” individuals (tolerate blood types B & O)
- Tolerant to type B antigen, antibodies to A antigen

Blood type “AB” individuals (tolerate all blood types)
- Tolerant to both A & B antigens

The Rh Blood Cell Antigen

- Rh antigen is also a polysaccharide on red blood cells
- Rh+ mother produces antibodies during birth of 1st Rh+ child, which can harm later Rh+ children
Drug-induced Type II Hypersensitivity

- Involves drugs that bind to the surface of cells or platelets.
- Drug functions as a hapten which in conjunction with cell can stimulate humoral immunity.
- Antibody binding triggers complement activation, lysis of cells binding the drug.

Type III: Immune Complex Reactions

Caused by high levels of antigen-antibody complexes (due to foreign or self Ag) that are not cleared efficiently by phagocytes and tend to deposit in certain tissues:

- Blood vessel endothelium in kidneys, lungs, joints.

This can result in local cell damage via:

- Complement activation.
- Attraction of phagocytes, other cells involved in inflammation (e.g., neutrophils).

Type III: Immune Complex Reactions

- Antigen:antibody complexes trapped in endothelium.
- Inflammatory response damages blood vessel walls.
**Type IV: Delayed Hypersensitivity**

Delayed cell-mediated hypersensitivity takes 1 or 2 days to appear and involves the action of T cells & macrophages, NOT antibodies:

- proteins from foreign antigen induce TH1 response
- secondary exposure results in the activation of memory TH1 cells which attract monocytes to area
- monocytes activated to become macrophages
- macrophages release toxic factors to destroy ALL cells in the immediate area

**general response to intracellular bacteria but can also occur with other antigens (latex, poison ivy)**

**Infection Allergy**

A type of delayed cell-mediated hypersensitivity resulting from infection with an intracellular bacterial pathogen:

- a Tc cell-mediated reaction, NOT IgE based allergy
- basis of the tuberculin test
- previous exposure to *Mycobacterium tuberculosis* gives a positive test result

**Contact Dermatitis**

- certain substances act as haptens in combination with skin proteins
- activates a potent T cell mediated response upon secondary exposure (e.g., poison ivy)
2. Autoimmunity

What is Autoimmunity?

Autoimmunity refers to the generation of an immune response to self antigens:

- normally the body prevents such reactions
  - T cells with receptors that bind self antigens are eliminated (or rendered anergic*) in the thymus
  - B cells with antibodies that bind self antigens are eliminated or rendered anergic in the bone marrow or even in the periphery (i.e., outside the bone marrow)
- however in rare cases T and/or B cells that recognize self antigens survive & are activated

*anergic = non-reactive or non-responsive
How is Autoimmunity Generated?

It’s not entirely clear, however some factors thought to trigger autoimmunity are:

• genetic factors  
  • e.g., certain HLA (human MHC class I) alleles are associated with particular autoimmune diseases

• foreign antigens that mimic self antigens  
  • peptide antigens from certain viral and bacterial pathogens are very similar to specific self peptides  
  • once an immune response is generated to pathogen, these T and B cells continue to respond to tissues expressing the similar self peptide

Common Autoimmune Diseases

Lupus  
• antibodies to self including DNA and histone proteins

Rheumatoid Arthritis  
• immune response to self antigens in synovial membranes of joints

Type I Diabetes  
• immune response to self antigens in pancreatic β cells (insulin-producing cells)

Multiple Sclerosis  
• immune response to myelin basic protein in Schwann cells (form myelin sheath of neurons)

3. Transplant Rejection
Transplants & MHC molecules

Transplanted organs and tissues are rejected as foreign by the immune system due to the presence of non-self MHC class I molecules:

• human MHC class I molecules are referred to as the HLA (human leukocyte antigen) complex
• there are 3 HLA genes resulting in up to 6 different HLA proteins per individual
• there are many different HLA alleles in the human population, so each person’s HLA make up is unique
• close relatives are much more likely to have similar HLA antigens to recipient than non-relatives

How are Transplant Cells Killed?

The recipient has no tolerance to donor MHC:

1) recipient T cells that bind strongly to donor MHC molecules with peptide will be activated
   • donor cells with foreign MHC class I
   • donor APCs with foreign MHC class II

2) MHC presentation of foreign donor MHC peptides

This leads to:

• activated CTLs that attack & kill donor cells
• activated B cells producing donor MHC-specific Ab
  • antibody mediated cytotoxicity toward donor cells

Identifying Donor by Tissue Typing

• antibodies specific for particular MHC class I molecules are added to donor test cells in vitro
• complement lysis occurs if test cells express that MHC class I molecule
• identifying class I types facilitates finding the best matched donor
How can a Transplant be Protected?

By immunosuppression:

• drugs such as cyclosporine are given to the recipient to suppress the adaptive IR
  • humoral immunity is not suppressed so antibodies to donor MHC molecules are still produced
  • some newer drugs are capable of repressing both the cellular and humoral immune responses
• normal, healthy immune surveillance is impaired, so there is greater risk of infection

Key Terms for Chapter 19

• sensitization, types I, II, III & IV hypersensitivity
• anaphylaxis, anaphylactic shock
• histamine, prostaglandins, leukotrienes
• ABO & Rh blood antigens
• autoimmunity, anergic
• infection allergy, contact dermatitis
• HLA, tissue typing

Relevant Chapter Questions
rvw: 1-9   MC: 1-3, 6-10