Diseases of the Immune System

Robbins Basic Pathology Chapter 4, Pages 99-120
Robbins Pathologic Basis of Disease Chapter 6, Pages 183-208

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Note: This handout follows Robbins Basic Pathology and covers approximately one half of the chapter. The second half of the chapter on Autoimmune Diseases will be covered in the second semester.

Immunity =

**Innate and Adaptive Immunity**

Innate =

Epithelial barriers of skin, GI tract, respiratory tract
Phagocytic leukocytes (neutrophils and macrophages)
Natural killer cells (NK cells)
Complement

(Fig 5-1)

Adaptive

Humoral: B lymphocytes produce antibodies

Cell mediated: T lymphocytes

Direct killing of infected cells by cytotoxic T lymphocytes (CD8+ T cells)

Production of cytokines by helper T cells to activate phagocytes (CD4+ T cells)

“Immune system” and “immune response” refer to adaptive immunity. Excessive or inappropriate immune responses, rejection of organ transplants, immune deficiencies.
Cells and Tissues of the Immune System

Lymphocytes

Total # lymphocytes $\sim 10^{12}$ in humans (1 trillion)
Recognize tens or hundreds of millions of antigens

Somatic rearrangement of antigen receptor genes during lymphocyte maturation
(Figure not in text)

Lymphocytes have a unique DNA rearrangement for each antigen receptor
(Figure not in text)

Antigen receptor gene rearrangement identifies a cell as a lymphocyte

Polyclonal vis-à-vis monoclonal lymphocytes

T lymphocytes

Thymus-derived

Comprise 60-70% of peripheral blood lymphocytes

Recognize MHC-bound peptide fragments presented by antigen presenting cells

T Cell Receptor (TCR): $\alpha\beta$ (alpha beta) or $\gamma\delta$ (gamma delta) (Fig 4-2)

CD3 proteins: on all T cells, deliver intracellular signals
CD4 T cells
60% of T cells
“helper T cells”
secrete cytokines to B cells and macrophages
recognize MHC class II
HIV impairment

CD8 T cells
40% of T cells
“cytotoxic T cells” directly kill virus-infected or cancer cells
recognize MHC class I

NKT cells
Natural Killer cells

Major Histocompatibility Complex Molecules: The Peptide Display System of Adaptive Immunity

MHC = Human Leukocyte Antigen (HLA) complex (Figure 4-3)

Highly polymorphic: diversity whereby a vast range of peptides can be displayed by MHC molecules for recognition by T cells

Class I MHC
-coding by three linked loci HLA-A, HLA-B, and HLA-C
-recognition by CD8 T cells
-display peptides synthesized in the cytoplasm of the cell (e.g. viral antigens)
-present on all nucleated cells
Class II MHC
- coded by HLD-D region with at least three subregions (DP, DQ, DR)
- recognition by CD4 T cells
- display peptides synthesized outside of the cell (e.g. bacterial antigens)
- present only on a few cell types, mainly antigen presenting cells (e.g. dendritic cells), macrophages, and B cells

Each person has a unique MHC antigenic profile (the HLA haplotype)

Rejection of tissue transplants: HLA molecules of the graft evoke both humoral and cell-mediated response, leading to graft rejection

B Lymphocytes

Bone marrow-derived

The effector cells of humoral immunity, producing antibodies

Comprise 20% of peripheral blood lymphocytes

Recognize antigens by membrane-bound IgM antibody on lymphocyte surface

Each antibody has a unique antigen specificity generated from somatic gene Rearrangements

Stimulated B cells differentiate into plasma cells, producing IgG, IgM, IgA, IgE, IgD

Natural Killer Cells

Innate immunity, killing infected or stressed cells
Antigen-Presenting Cells

Dendritic cells (interdigitating DCs) (Figures not in book)

Follicular dendritic cells (FDCs)

Macrophages

Overview of Normal Immune Response

The Early Innate Immune Response to Microbes
The Capture and Display of Microbial Antigens
Skim these sections.

Cell-Mediated Immunity: Activation of T Lymphocytes and Elimination of Cell-Associated Microbes (Figure 4-4)

Cytokines: mediators of inflammation (Chapter 2) and immunity

CD4+ subsets: T_{h}1, T_{h}2, and T_{h}17 (Figure 4-5)
CD8+: Cytotoxic T Lymphocytes

Humoral Immunity: Activation of B Lymphocytes and Elimination of Extracellular Microbes (Figure 4-6)

Isotype (class)switching:

- IgG
- IgM
- IgA
- IgE

Affinity maturation:
Hypersensitivity Reactions: Mechanisms of Immune-Mediated Injury

Hypersensitivity:

Causes of Hypersensitivity Reactions

Autoimmunity: failure of self-tolerance

Reactions against microbes

Environmental antigens

4 Types of Hypersensitivity Reactions

I

II

A.

B.

C.

III

IV
**Type I: Immediate Hypersensitivity**

Interaction of antigen (allergen) with IgE antibody bound to surface of mast cells in a sensitized host (Fig 4-7)

Mediators of response (Fig 4-8)

Phases of response (Fig 4-9)

Clinical manifestations

Atopy

Anaphylaxis
Type II: Antibody–Mediated Diseases

Antibodies targeting antigens on cells or other tissue components

Mechanisms of Antibody-Mediated Responses

A. Opsonization and phagocytosis (Fig 4-10)
   
   e.g. autoimmune hemolytic anemia (figure not in book)

B. Antibodies bound to tissues activate complement (Figure 4-10)

   e.g. pemphigus vulgaris (Figures 23-9 and 23-10)
C. Antibody-mediated cellular dysfunction (Figure 4-10)

Graves Disease

myasthenia gravis

Type III: Immune Complex Disease

Antigen-antibody (immune complexes) formed in the circulation deposit in tissues leading to complement activation and acute inflammation (Figure 4-11 and Figure 1-13)

e.g. polyarteritis nodosa

necrotizing vasculitis:

e.g. lupus nephritis (Figure 4-18)
Type IV: T-Cell-Mediated

CD4+ T Cells (Figure 4-12)

e.g. Rheumatoid arthritis (Figures not in book)

Delayed-Type Hypersensitivity

e.g. Contact dermatitis (poison ivy) (Figure not in book)

  e.g. M. tuberculosis skin test

  granulomatous inflammation (Figure 4-14)

CD8+ T Cells

  Cytotoxic T Lymphocytes

  e.g. organ transplant rejection

******* Table 4-1 for summary of Mechanisms of Hypersensitivity Reactions *******