Lecture 21 & 22 - Chapter 15

Third line of Defense

Specific immunity is
a complex system of immune cells
interacting against antigens

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Adaptive immunity
Immune Response (IR)

(mediated by B- & T-lymphocytes)

- Specificity
- Tolerance
- Memory

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Lymphocyte Receptors

- Present on B and T cells
  - Have Variable & Constant regions
  - Functional as dimers
- **B cell receptors:** Immunoglobulins
  - Light chain & Heavy chain form hetero-dimers
  - Secreted immunoglobulins (Igs) are called antibodies
- **T cell receptors:** only homo-dimers of one chain

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The structure of a receptor on B cells.

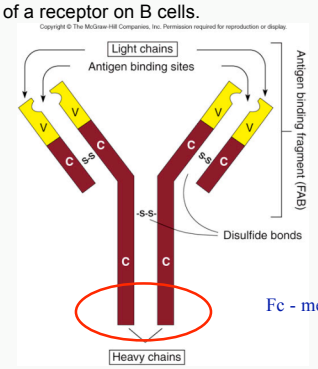

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Fig. 15.5 Simplified structure of an immunoglobulin molecule on the surface of B cells.

The structure of the receptor on T cells.

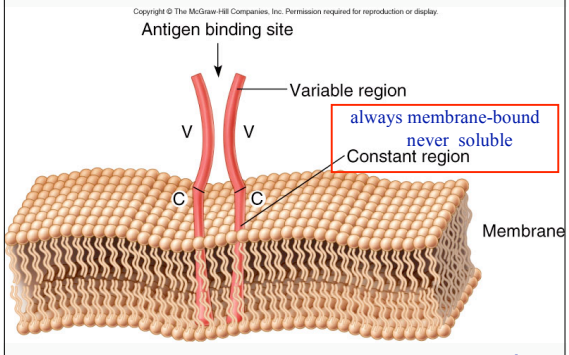

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Fig. 15.6 Proposed structure of the T cell receptor for antigen.

Major Histocompatibility Complex
(MHC)

- Host cell surface proteins (Glycoproteins)
- "Human leukocyte antigen" (HLA) is an old term for the MHC
- 3 Classes of MHC (I, II, III)

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Classes of MHC

- Each individual has a unique MHC profile
  - because of the expression of a particular combination of MHC genes
- **Class I** – all nucleated host cells
- **Class II** – only antigen-presenting cells (*macrophages, dendritic cells*, B-cells)

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Antigen presenting cells (APC)

- *Macrophages, dendritic cells* and B-cells
  - process and present antigen in association with MHC (class) II
  - Interact with T-cell receptor (TCR)/CD4 co-receptor complex, which recognizes MHC II and antigen/MHC II complex

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Antigens

- Foreign material
- Alloantigens
- Superantigens

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Antibody

(soluble B-cell receptor, Immunoglobulin)

- Activated B cells (plasma cell) produce Immunoglobulin (Ig) or antibody
- Structure
  - Four polypeptides
  - Connected by disulfide bonds
  - Antigen binding Fragment (Fab)
  - Crystallizable Fragment (Fc)
- Classes

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Fab (function: antigen-binding)

- Variable (N-terminus of the heavy & light chains)
- Binds to the antigenic determinant (epitope)
- Swiveling enables more efficiency
- Held together by disulfide bonds

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Fc (function: constant)

- Constant (C-terminal of heavy chain)
- Recognized by macrophage receptors
- Anchors membrane-bound Ig to lymphocyte
- Held together by disulfide bonds
- Responsible for **class** identification

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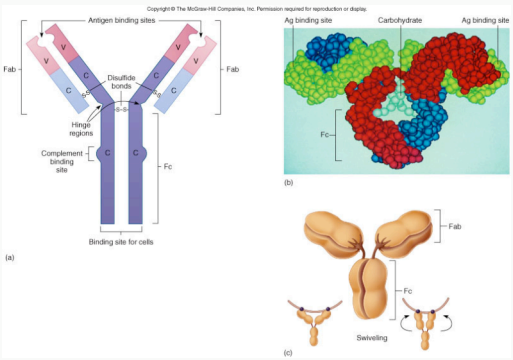

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Fig. 15.11 Working models of antibody structure.

5 Classes of Igs

- based on the Fc fragment of Ig
  - IgM
  - IgG
  - IgD
  - IgA
  - IgE

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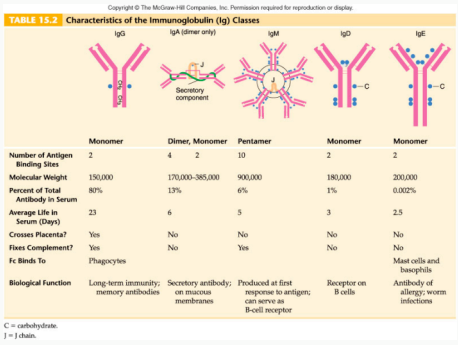

TABLE 15.2 Characteristics of the Immunoglobulin (Ig) Classes

	IgG	IgA (dimer only)	IgM	IgD	IgE
	Monomer	Dimer, Monomer	Pentamer	Monomer	Monomer
Number of Antigen Binding Sites	2	4 2	10	2	2
Molecular Weight	150,000	170,000–385,000	900,000	180,000	200,000
Percent of Total Antibody in Serum	80%	13%	6%	1%	0.002%
Average Life in Serum (Days)	23	6	5	3	2.5
Crosses Placenta?	Yes	No	No	No	No
Fixes Complement?	Yes	No	Yes	No	No
Fc Binds To	Phagocytes				Mast cells and basophils
Biological Function	Long-term immunity; memory antibodies	Secretory antibody; on mucous membranes	Produced at first response to antigen; can serve as B-cell receptor	Receptor on B cells	Antibody of allergy; worm infections

C = carbohydrate.
J = J chain.

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Table 15.2 Characteristics of the immunoglobulin classes.

IgM - first circulatory Ig

- Receptor for antigens on B cells
- **First to be synthesized** during primary immune response
- Circulates in the blood
- **Five monomers**, held together by a J- chain
- Associated with complement fixation and opsonization

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IgG - major circulatory Ig

- **Monomer**
- **Primary response** antibody
- **Memory cell response**
- **Most prevalent** in tissue fluid and blood

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IgD - minor circulatory Ig

- **Receptor** for antigens on B cells
- Monomer
- **Small amounts** in the serum

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IgA - secreted Ig

- Monomer or dimer (secretory IgA)
- Dimer – held together by a J chain
- Secretory IgA (mucous and serous secretions)
  - Local immunity
  - Salivary glands, intestine, nasal membrane, breast, lung, genitourinary tract
- Protection for newborns

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IgE - "allergic" Ig

- Allergies
- Parasite infections
- Fc portion binds to basophils and mast cells
  - release of chemical mediators that aid in inflammation

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Antibody-antigen interactions

- Opsonization
- Agglutination
- Neutralization
- Complement fixation

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A complementary fit between an antibody and antigen involves hydrogen bonds and electrostatic attractions.

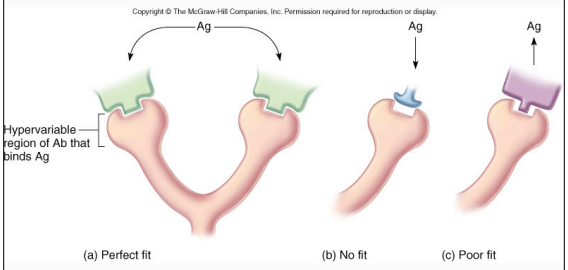

Fig. 15.12 Antigen-antibody binding

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Opsonization

- Microbes or particles coated with antibodies
- Enables macrophages to recognize and phagocytoze microbe or particle

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Agglutination

- Antibodies cross-link cells or particles into clumps
- Renders microbes immobile
- Enhances phagocytosis
- Principle for certain immune tests (RBC typing)
- Reason for some symptoms of disease

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Neutralization

- Antibody binds to
  - The microbe or virus receptor
  - Antigenic site of a molecule (Eg. Exotoxin)
- Prevents further binding of microbe or toxin

Complement fixation

- interaction of antibodies with complement proteins (-> classical pathway) thereby delivering the compliment to antigen.
- Usually followed by lysis of microbial cell facilitated by MAC

The different functions of antibodies.

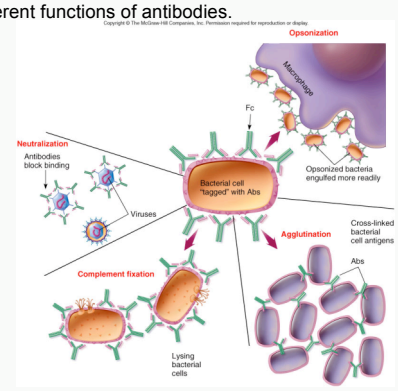

Fig. 15.13 Summary of antibody functions

Clonal selection

- The synthesis of varied receptor types
  - approximately 500 genes can undergo rearrangement
  - Not all individuals have all possible antigen-specificities (~10^{14}) **at any given time** (but throughout life span)
  - eventually one clone recognizes an antigen and expands (proliferates) or it dies
- Clone
  - each mature lymphocyte possesses a single combination or receptor specificity
- Expansion
  - a single cell is stimulated by antigen recognition
- Clonal deletion
  - cells that recognize "self" are removed

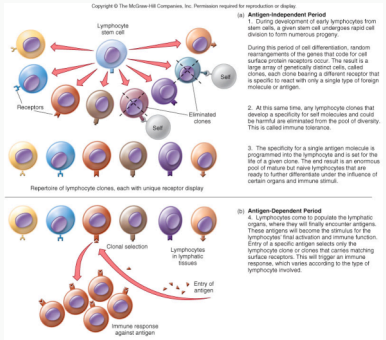

Fig. 15.3 Overview of the clonal selection theory of lymphocyte development and diversity.

T-cell development

- Occurs in Thymus gland (later in bone marrow)
- 2 steps of selection:
  - Positive selection: Specificity (TCR-CD4/8 and MHC I/II;)
  - Negative selection: Tolerance (TCR - self-MHC)
- Mature tolerant T-cells released into blood and lymph systems

B-cell development

- Have Igs as B-cell receptors (IgM, IgD)
  - **Specificity**
- Need to be activated by receptor-antigen interaction (equal to antibody-antigen interaction) to:
  - produce soluble Igs
  - establish **Memory**

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B-cell clones

- Process of **activation** is selection and propagation of a single B-cell (then called a **clone**) to develop into a mature Plasma Cell for the synthesis of antibodies. If only one B-cell is selected, monoclonal antibodies are produced.
- A monoclonal antibody possess only one single specificity for a given antigen

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B-cell Activation

- B-cell encounters and binds antigen
- B-cell processes antigen, presents it with MHC I & II
- MHC II interacts with TCR + CD4, followed by instruction by chemical mediators (interleukins)
- Transmission of signal to the nucleus
- B cell changes into an active cell called plasma cell (lots of ribosomes, enhanced cell division)
- Clonal expansion and memory cell formation
- Antibody production and secretion

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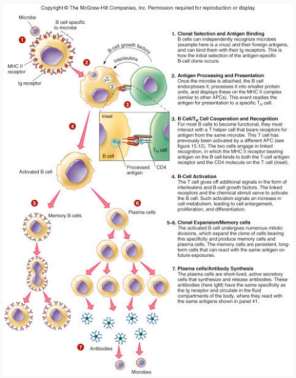

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Fig. 15.10 Events in B-cell activation and antibody synthesis.

Responses to antigens

We distinguish 2 responses to antigens

- Primary
- Secondary

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Primary Response

- First exposure to antigen
  - Latent period
    - Lack of antibody synthesis
  - Synthesis of antibodies
    - Level of antibodies (titer)
    - IgM first
    - Followed by IgG, and some IgA and IgM, very little IgD

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Secondary Response

- Re-exposure to the same antigen (Anamnestic response)
- Antibody synthesis, titer, and length of antibody persistence is rapid and amplified
  - Primarily due to memory cells

If used for medical purposes, what is this called?

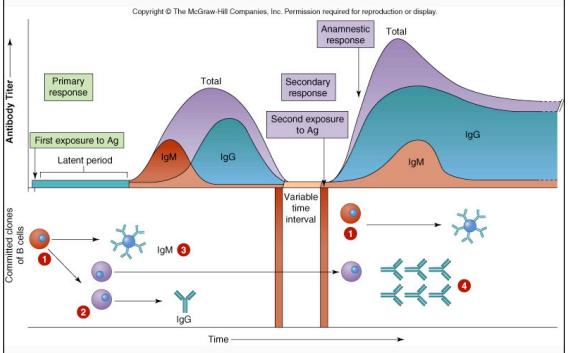

Fig. 15.15 Primary and secondary responses to antigens.

T cell clones

- Activation
- Types

Cell-mediated immunity

- Subset of T cells have unique CD receptors (CD4, CD8)
- Direct involvement of T cells
- Produce and react to cytokines
- Activated simultaneously with B cell activation

Activation

- Activated T cells prepare for mitosis
- Effector cells or types (T_H; T_C) are being produced
- Memory cells are produced
- After interaction with other cells, armed effector cells are produced

Types

- Helper T cells (T_H)
- Cytotoxic T cells (T_C)

T_H

- Regulate immune reactions to antigens by releasing cytokines
- TCR-CD4 co-receptor complex binds to MHC II
- Type of cytokine will determine subset of T_H
  - T_{H1} (inflammatory T cells, delayed type hypersensitivity)
  - T_{H2} (Helper cells involved in B cell differentiation)
- Cytokines also activate macrophages
- T_H is most prevalent in the blood

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T_C

- Binds and lyses cells
  - virus or microbe-infected cells, foreign cells, cancer cells
- TCR-CD8 co-receptor complex will bind to MHC I
- "Perforins" – punch holes in the membrane
- "Granzymes" – degrade proteins
- Natural killer (NK) cells
  - related to T_C
  - attack only virus infected cells and cancer cells

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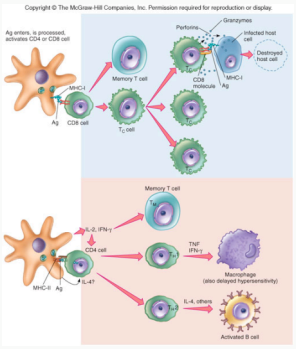

Fig. 15.16 Overall scheme of T-cell activation and differentiation into different types of T cells.

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TABLE 15.3 Characteristics of Subsets of T Cells

Types	Primary Receptors on T Cell	Functions/Important Features
T helper cell 1 (T_H1)	CD4	Activates the cell-mediated immunity pathway, secrete tumor necrosis factor and interferon gamma, also responsible for delayed hypersensitivity (allergy occurring several hours or days after contact)
T helper cell 2 (T_H2)	CD4	Drives B-cell proliferation, secrete IL-4, IL-5, IL-6, IL-10; can dampen T_H1 activity
T cytotoxic cell (T_C)	CD8	Destroys a target foreign cell by lysis; important in destruction of complex microbes, cancer cells, virus-infected cells; graft rejection; requires MHC I for function

Table 15.3 Characteristic of subsets of T cells.

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Specific Acquired Immunities

- Active
- Passive
- Natural
- Artificial
- Vaccines

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Active

- Can be natural or artificial
- Adaptive Immunity
  - Specificity, Tolerance, Memory
- Long-term protection

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Passive

- Can be natural or artificial
- Receive antibodies from another individual or animal
- No memory cells
- No antibody production
- Short-term protection (extended 2nd line of defense)

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Natural

- Immunity produced by normal biological experiences, no medical intervention
  - Natural active
    - Example: Infection
  - Natural passive
    - Example: Mother to child

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Artificial

- Immune protection through medical procedures or intervention
  - Artificial active
    - Example: vaccination
  - Artificial passive
    - Example: immunotherapy

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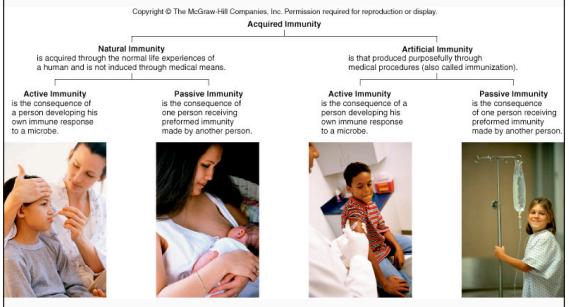

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Fig. 15.18 Categories of acquired immunities

Vaccines

- Types
  - Killed whole cell or inactivated viruses
  - Live, attenuated cells or viruses
  - Antigenic molecules from bacteria or viruses (large enough to elicit and IR)
  - Genetically engineered microbes or microbial antigens

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Benefits of vaccinations

- Long-lasting immunity
- Herd immunity
  - Indirect protection of non-immune
  - Prevents epidemics

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