SACRAMENTO STATE
Leadership begins here.

Chapter 17: Adaptive (specific) Immunity

Bio 139

Dr. Amy Rogers

Adaptive Immunity

★ Host defenses that are ***specific*** to a particular infectious agent
- Can be "innate" or "genetic" for humans as a group: most microbes can only infect certain species

★ Most specific immune responses *improve with repeated exposures* to the infectious agent or antigen

Adaptive Immunity: 2 kinds Humoral & Cell-mediated

★ **Humoral immunity**: mediated by **antibodies** circulating in the blood.
- **B cells**

★ **Cell-mediated immunity:**
- **T cells**

Humoral Immunity

B cells

- are **lymphocytes** (leukocytes of the lymphoid lineage)
- are produced & differentiate in (human) **bone marrow**
  - Subsequently, they circulate/reside in blood & various lymphoid tissues

★ produce **antibodies**

Antibodies

★ are **proteins**

★ have **highly specific binding sites for antigen**
- Each individual antibody is specific for ONE antigen
- Each B cell produces ONLY antibodies with that one specificity

Antigens

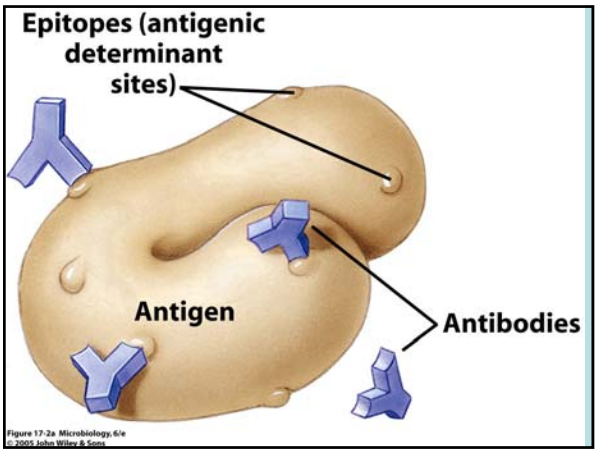
★ Are substances that trigger an immune response, including (but not only) antibody production by B cells

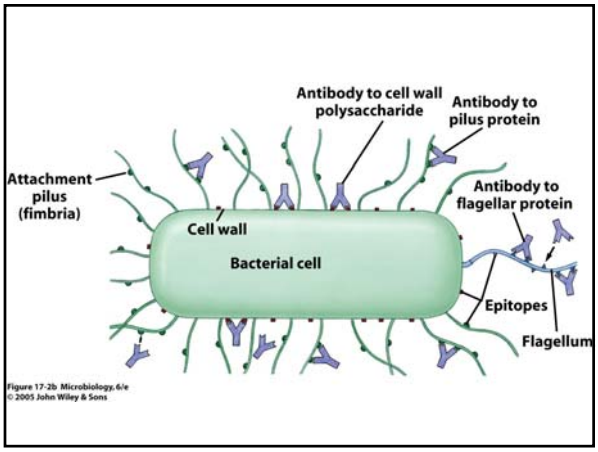
- The **best antigens** (that provoke the strongest, most specific immune responses) are **large proteins**
  - Other molecules *can* also be antigens (polysaccharides, peptides)

- **Antibodies bind to antigens**

Antigens

- Chemically complex antigens may have more than one specific target / binding site for antibodies / antigenic determinant
  - called **epitopes**
- In the case of invading microorganisms, each one may present **many antigens** to the immune system, prompting B cells to make many kinds of antibodies

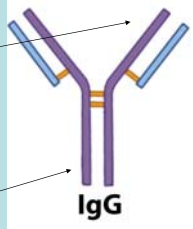




What do antibodies look like?

★**Immunoglobulin** (Ig)
- proper name for the antibody protein

Ig structure:
- Y-shaped
- **Variable** region with **two antigen binding sites** at tips of Y
- **Constant** region "stem"



★ Immunoglobulin classes: IgG

- Ig classes differ in structure of constant region
  - Each Ig class has a different function
    - **All** Ig's bind specific antigens

IgG:

- Prominent in **blood**
- Main antibody of **memory** (secondary) immune responses
- Acts as an **opsonin**
- Activates **complement** (classical pathway)
- Crosses the **placenta** from mother to fetus
- Is found in **milk**

★ Immunoglobulin classes: IgM

IgM:

- Secreted as a **pentamer** (5 "Y" units connected together; **ten** antigen binding sites)
- **First** class of antibody secreted, especially during **primary** immune responses; high levels indicate recent exposure to antigen
- Activates **complement**
- Causes very strong **agglutination** reactions (clumping microbes helps to eliminate them)

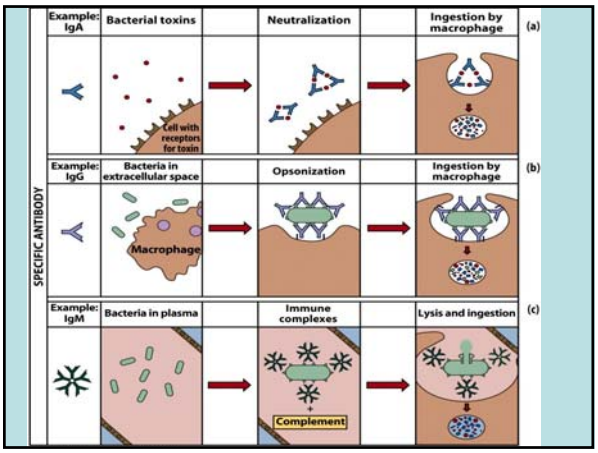
Others: IgE, IgA, IgD

What do antibodies do?

★ **Neutralize**: antibody binding to antigen can render it harmless
- Toxins: antibodies can block toxin's active site, or agglutinate toxin molecules
- Bacteria & viruses: antibodies can agglutinate them, prevent them from adhering to cell surfaces

★ **Opsonize**: antibody binding enhances phagocytosis of the antigen (including whole bacteria or viruses)

★ **Lyse**: antibodies that activate complement can trigger formation of membrane attack complexes



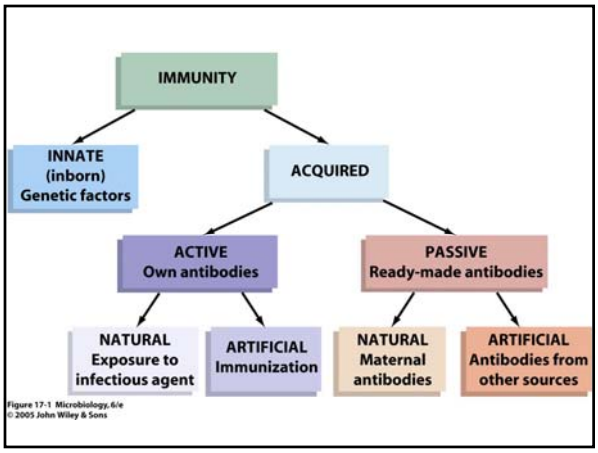
Getting antibodies

- **Active immunization:**
  - Natural exposure to infectious agent stimulates *your own B cells* to produce antigen-specific antibodies
  - Artificial immunization (vaccination) with key antigens or epitopes from an infectious agent does the same thing
  - Active immunization results in immunologic **memory** (more vigorous response next time)
    - Passive immunization (next slide) does NOT

Getting antibodies

Passive immunization:
Antibodies NOT produced by your own B cells

- Maternal antibodies (IgG)
  - can cross the placenta to protect the fetus;
  - **Colostrum**, the milk produced during the first days after birth, contains large quantities of maternal antibodies
- Under certain circumstances, antibodies can be (artificially) injected into a person recently exposed to a toxin or microbe
  - "**antiserum**" produced in animals; monoclonal antibodies made in a lab



Active Immunization, or How B lymphocytes make antibodies

- B cells (B lymphocytes) are "born" in the bone marrow
  - Lymphoid stem cell precursor differentiates into pre-B cell
- Young B cells express membrane-bound antibodies on their surface
  - ★**Each B cell makes a different antibody** (i.e., an antibody with a different variable region that can specifically bind to a different antigen)

Active Immunization, or How B lymphocytes make antibodies

- Antibody on the surface of a B cell encounters the antigen it is specific for
- The antigen binds to the membrane-bound antibody
- The B cell is activated

Active Immunization, or How B lymphocytes make antibodies

Antigen stimulation leads to:

1. **Clonal expansion**:

The one B cell that produces the correct antibody multiplies into many identical B cells, all producing the right antibody

Active Immunization, or How B lymphocytes make antibodies

Expanded B cell clones then will either:

1. Differentiate into **Plasma Cells**

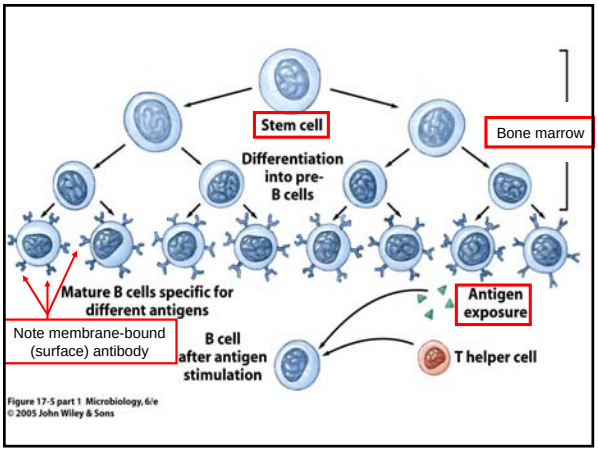
Plasma cells are mature B lymphocytes which synthesize and **secrete** massive quantities of the needed **antibody**

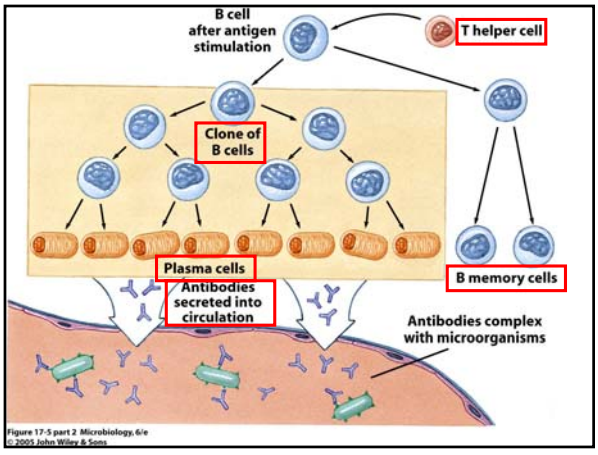
or, with the help of T_H (T helper) lymphocytes,

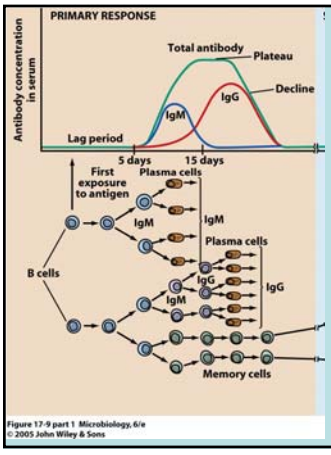
2. Become **B memory cells**

Memory cells are **long-lived**. If these cells encounter the antigen again in the future, the humoral immune response is faster & more vigorous

(secondary or **anamnestic response**)



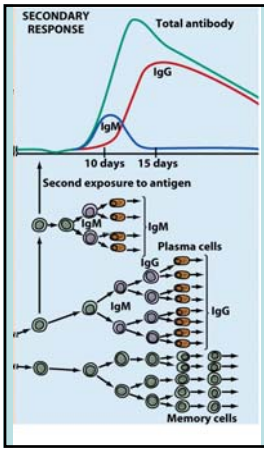




Primary antibody responses

(first time the antigen or infection is encountered)

- Initial B cell clonal expansion
- Response is dominated by IgM
- Memory cells are generated



Secondary (anamnestic) antibody responses

•B Memory cell population is activated

•IgG appears faster and in greater quantity

•More memory cells are generated

Generation of Antibody Diversity

- How does a B cell "know" what antibody to produce?

- Immunoglobulins (antibodies) are proteins. Each Ig must be coded for by a gene.
- The human immune system can recognize more than 10,000,000 different antigens
  - This means if we had one gene for each antibody, we would need 10^7 genes for Ig production alone!
    - (The entire human genome actually codes for only about 30,000 structural genes.)

★Generation of Antibody Diversity

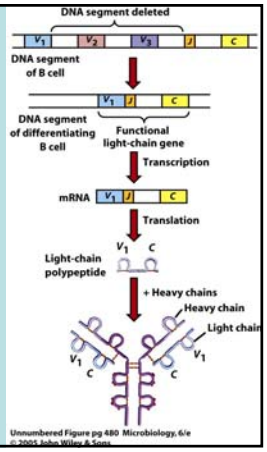
★ Antibody genes are constructed individually in each B cell by **recombination** of gene parts

★ Gene bits for the variable region are randomly mixed and "intentionally" mutated to generate a spectacular number of **genetically unique B cell clones**

Generation of antibody diversity

B lymphocytes *break the rule* that every cell in your body has exactly the same DNA

The antibody-encoding gene in each B cell is ***unique*** to that cell



Generation of Antibody Diversity

★ Antibody diversity is **randomly generated**
- **before antigen exposure**

★When antigen enters the body, appropriate antibodies are **selected from the pool of B cells** with membrane-bound antibody on their surface
  – See fig. 17.5
- Selected B cells proliferate, differentiate

Self-tolerance

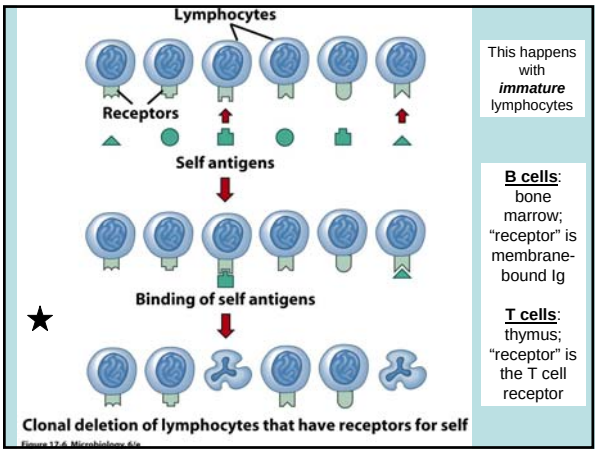
Q: If antibody sequences are generated randomly to include all possible antigens, why don't B cells produce antibodies that react with normal proteins or cells in our bodies (self)?

Self-tolerance

- Anti-self antibody genes are (randomly) generated *all the time*

…but…

★B (and T) lymphocyte clones with anti-self specificity are **deleted** during lymphocyte maturation



This happens with ***immature*** lymphocytes

B cells: bone marrow; "receptor" is membrane-bound Ig

T cells: thymus; "receptor" is the T cell receptor

Clonal deletion & Self-tolerance

- Lymphocytes that could potentially react against self are killed ("deleted") early in their development
- This mechanism sometimes fails, and **autoimmune disease** results
  - Lupus, myasthenia gravis, rheumatoid arthritis, etc.

Cell-mediated Immunity

- Humoral immunity: B lymphocytes & antibodies
  - particularly important for bacteria & extracellular toxins
- Cell-mediated immunity: T lymphocytes & NK (natural killer) cells
  - particularly important for viruses & other intracellular pathogens
  - also acts on tumors & transplants

T cells

- are **lymphocytes** (leukocytes of the lymphoid lineage)
- are produced from stem cells in the bone marrow but mature in the **thymus**
- do NOT produce antibodies
- ★have **clonally unique surface proteins** called **T cell receptors** (TCR)

What do T cells do?

More than you can imagine!

- Multiple types exist including
  - T_H (helper): CD4+, activated by MHC II
  - T_c (cytotoxic or killer): CD8+, activated by MHC I
- T cells secrete a large number of immunologically important molecules called **lymphokines or cytokines**
  - **Interleukins** (especially IL-2)
  - **Interferon gamma**

★ Helper T cells (CD4)

- "CD" molecules are a large group of unrelated cell surface markers
  - CD4 is a marker of T_H cells; CD8 of T_c cells

Main functions of Helper T cells:

- Assist with cellular immunity
  - Activate macrophages to fight intracellular infections
  - Activate cytotoxic T cells
- Assist with humoral immunity
  - activate B cells
  - trigger memory B cell formation

★ Cytotoxic T cells (CD8)

- T_c cells attack **virus-infected cells**
- T_c cells produce **perforin**
  - Like C9 membrane attack complex, perforin bores holes in target cell membranes
    - Occasionally, the action of cytotoxic T cells is more damaging than the actual infection!

- NK cells are murderous lymphocytes which do **NOT** have antigen-specific surface receptors
- NK cells can destroy malignant (cancer) cells

How are T cells activated?

- B cells are activated when antigen binds to their surface Ig molecules

★ T cells also have antigen-specific surface molecules called **T cell receptors** (TCRs)

- TCRs are NOT activated by direct contact with an antigen

★ T cell receptors recognize **antigenic peptides** "presented" by **MHC molecules** on the surface of ***other cells***

Antigen presentation & MHC

MHC: major histocompatibility complex

- Cell-surface proteins

★ **MHC class I (one):** expressed by **all cells**

- **MHC class II (two):** expressed **only** by **professional antigen presenting cells**
  - Macrophages, B cells, other lymph node cells (dendritic cells)

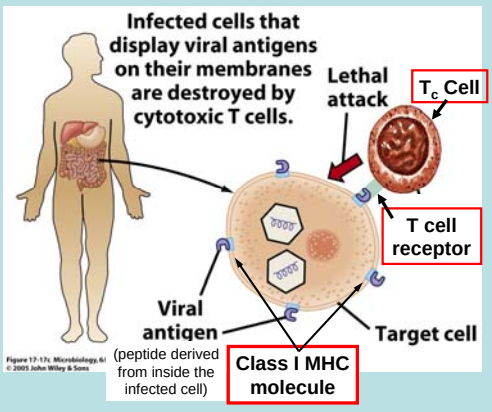
– Think of MHC molecules as tiny hands that randomly pick up peptides (bits of protein) from inside a cell, and then display those peptides to passing T cells

Antigen presentation & MHC I

★ If a cell is infected by a virus (or other intracellular microbe), some of the peptides presented on its class I MHC will be viral peptides.

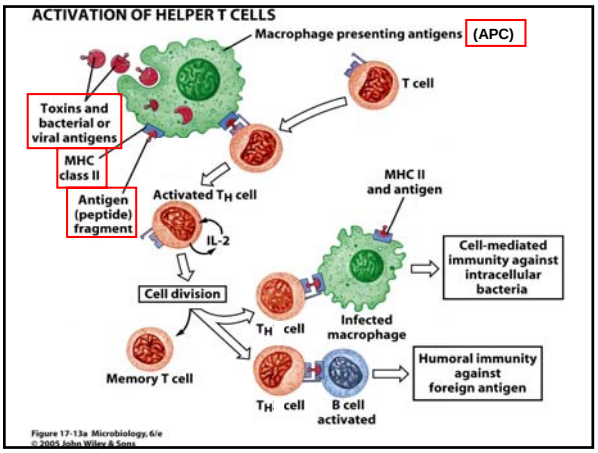
The right T cell receptor will bind to the viral peptide antigen + MHC class I and *activate* the T cell

Cytotoxic T cell will then know that the cell has a virus inside, and will kill it.



Antigen presentation & MHC II

- **MHC class II** molecules are found only on specialized cells of the immune system (**antigen presenting cells** or APCs)
- Such cells include macrophages, B cells, and dendritic cells
- APCs present antigens from stuff they have phagocytosed or acquired some other way
- MHC class II + peptide antigen on APCs activates T cell receptors on **T_H helper cells**



Formation of B memory cells requires T cell help