Acquired Immunity & Parasite Infection

Specific (Adaptive) Immunity: the three R’s

**RECOGNIZE** non-self, **RESPOND** to non-self, **REMEMBER** non-self

How is adaptive immunity different from innate resistance?

- **Specificity**: immunity directed against particular pathogen
- **Memory**: response to second exposure is so fast that there is no noticeable pathogenesis
- **Diversity**: system generates enormous numbers of different molecules that recognize billions of different antigens
- **Discrimination**: between self & non-self (response almost always made only to non-self)

Antigen - *something that elicits an immune response*
- protein, polysaccharides, nucleic acids or glycolipids
- self (autoimmunity) or non-self (foreign organism).
Innate Immunity

Physical & chemical barriers (lysozyme, skin, mucus)

Innate cellular defenses: macrophages, neutrophils, eosinophils, basophils & mast cells

Acquired Immunity

Humoral Immunity: B cells (plasma cells & memory cells)

Cell Mediated Immunity: T cells (helper & cytotoxic cells)

Intracellular Digestion

- microbes are internalized into a **phagosome**
  - respiratory burst reactions occur as soon as phagosome is formed
  - toxic oxygen products are produced which can kill invading microbes

- Phagolysosome: fusion of phagosome with lysosome
  - presence of toxic chemicals
  - e.g., digestive enzymes
  - e.g., toxic reactive oxygen intermediates (ROIs)
  - e.g., reactive nitrogen intermediates (RNIs)
Antigen Presentation

• macrophages & dendritic cells undergo a process called **antigen presentation**
  - important process because it allows wandering lymphocytes to become activated
  - *links nonspecific & specific immune responses*

• pass protein fragments (peptides) from phagolysosome to endoplasmic reticulum
  - peptide components of fragments combine with glycoproteins receptors (MHC II) which become part of cell surface
  - peptides bound so they are ultimately **presented** on the outside of the cell

• *Stimulates development of the adaptive immune response*

Cells of the Immune System

• Innate Immune Response
  - *Immediate response: recognizes distinctive properties of pathogens*
  - Effector cells
    • Granulocytes
    • Mast cells
    • Monocytes, macrophages & dendritic cells

• Acquired Immune Response
  - *Delayed response: recognizes specific properties of individual pathogens*
  - Has memory
  - Effector cells
    • B lymphocytes
    • T lymphocytes
    • Interacts with innate immune cells
Specific (Adaptive) Immunity

- three major functions
  - **recognize** nonself
  - **respond** to nonself → effector response: eliminates or inactivates pathogens
  - **remember** nonself → anamnestic response: upon second encounter with same pathogen immune system mounts a faster & more intense response

**Humoral Immunity**
- B cells (plasma cells & memory cells)
- **B lymphocytes produce antibody & antibody circulates, binds bacteria, toxins, etc.**

**Cell Mediated Immunity**
- **T cells (helper & cytotoxic cells)**
- **T lymphocytes directly kill infected host cells. AKA Cell-Mediated Immunity.**

**Acquired Immunity**
Humoral Immunity: B cells (plasma cells & memory cells)

- humoral immunity
  - also called antibody-mediated immunity
  - based on antibody activity
  - mediated by B cells

Cell Mediated Immunity: T cells (helper cells & cytotoxic cells)

- cellular immunity
  - also called cell-mediated immunity
  - based on action of specific kinds of T cells

Major Histocompatibility Complex (MHC)

- distinguishing between self & non-self is essential for the proper functioning of the immune system
  - this allows for selective destruction of invading pathogens without destruction of host tissues
  - involves major histocompatibility complex
- collection of genes that code for self/nonself recognition potential of a vertebrate
- human leukocyte antigen (HLA) complex in humans
- class I: found on almost all types of nucleated cells
- class II: found only on antigen presenting cells
MHC - Major Histocompatibility Molecules

- "Self" marker molecules on the surface of cells
- Foreign antigens are "presented" in the context of MHC

Class I MHC:
- on nearly all body cells
- identify endogenous (inside) antigens (on intracellular pathogens such as viruses)

"The zombie" - I look like one of your cells, but my MHC I bound to foreign antigen indicates that I’m infected by an intracellular pathogen…

Class II MHC:
- on B cells, macrophages, dendritic cells & some T cells
- identify exogenous (outside) antigens on extracellular pathogens

"The policeman" - I am part of your immune system & my MHC II bound to foreign antigen is a badge that indicates that I have identified a bad guy …

MHC & Antigen Processing

- class I & Class II bind to antigens in the cell
  - **endogenous** antigen processing
    - class I binds to antigen peptides that originate in the cytoplasm & present antigen to CD8+ T cells
    - intracellular viruses, bacteria & parasites
  - **exogenous** antigen processing
    - class II binds to antigen fragments that come from outside the cell & present to CD4+ T helper cells
    - extracellular bacteria, protozoa & fungi

Red blood cells lack MHC I, therefore are a good choice for hiding from the immune system. The malaria parasite uses RBCs as host cells.
B & T Lymphocytes

• major cells of the immune system
• differentiate in bone marrow from stem cells
  – only activated by binding of *specific antigen* onto lymphocyte surface receptors
  – after activation replication continues as lymphocytes circulate & enter lymphoid tissue
  – memory cells have ability to respond rapidly to re-exposure to pathogen (*adaptive response*)

B Cells

• B cells (*B lymphocytes*)
  – mature in **bone marrow**
  – circulate in blood
  – can settle in lymphoid organs
  – after maturation & activation are called plasma cells & **produce antibodies**
  – memory cells have ability to respond rapidly to re-exposure to pathogen (*adaptive response*)
T Cells

- mature in **thymus**
- can remain in thymus, circulate in blood, or reside in lymphoid tissue
- like B cells, require antigen binding to surface receptors for activation & continuation of replication
- activated T cells differentiate into helper T cells (TH) & cytotoxic lymphocytes (CTLs)
- secrete cytokines, chemicals that have effects on other cells, are produced & secreted by activated T cells
Organs & Tissues of the Immune System

- primary organs & tissues: sites where lymphocytes mature & differentiate into antigen-sensitive mature B & T cells
- secondary organs & tissues: areas where lymphocytes may encounter & bind antigen, followed by proliferation & differentiation into fully mature effector cells

Primary Lymphoid Organs & Tissues

- **thymus**
  - *bone marrow precursors* migrate here & proliferate
  - *thymic deletion* removes T cells that recognize self antigens
  - remaining cells become mature T cells
  - enter bloodstream & recognize non-self antigens
- **bone marrow**
  - *site of B cell maturation in mammals*
  - maturation involves removal of nonfunctioning & self-reactive cells
Secondary Lymphoid Organs & Tissues

• **spleen**
  – filters blood
  – macrophages & DCs trap microbes & antigens
  • present antigens to B & T cells
    – *most common way that lymphocytes become activated to carry out their immune functions*

• **lymph nodes**
  – filter lymph (microbes & antigens trapped & phagocytosed by macrophages & dendritic cells)
  – B cells differentiate into memory & plasma cells within lymph nodes

Lymphoid Tissues

*located throughout the body*

*interface between innate & acquired host immunity*

*areas of antigen sampling & processing*

some lymphoid cells are found closely associated with specific tissues
  
e.g., skin-associated lymphoid tissue (SALT)
  
e.g., mucous-associated lymphoid tissue (MALT)
  
e.g., gut-associated lymphoid tissue (GALT)
Antigens

- name comes from *antibody* generators
- large, complex molecules recognized as **foreign**
  - usually proteins
  - invoke immune responses
- antigen presence in body $\rightarrow$ B cell activation $\rightarrow$ production of antibodies
- **epitopes**: site on antigen that reacts with specific antibody or T cell receptor
- protein epitopes are 9-11 amino acids long
- antibodies bind to specific antigens, inactivating or eliminating them

B-Cell Biology

- B cells must be activated by a **specific antigen** to continue to replicate & differentiate into plasma cells to secrete antibodies
- B cells have immunoglobulin (Ig) receptors for a specific antigen that will activate that specific B cell.
- interaction with that antigen is communicated to the nucleus via a signal transduction pathway
B-Cells & Antibodies

• can act as antigen-presenting cells
• activation by antigen binding to Ig receptor
  – proliferation
  – antigen-specific activation
  – triggers differentiation
• B cell differentiates into plasma cell & memory cell
• antibodies
  – immunoglobulin (Ig) glycoprotein
  – antigen receptor (BCR) on cell surface
  – secreted by activated B cells (plasma cells)
  – found in blood, tissue fluids, & mucosal surfaces
  – an antibody recognizes & binds to the antigen that caused its production

Immunoglobulin Structure

all antibody types have the same basic structure

• four polypeptide chains
  – two identical heavy chains
  – two identical light chains
  – heavy & light chains connected to each other by disulfide bonds
• both chains contain two different regions
  – constant (C) regions (CL & CH)
  – variable (V) regions (VL & VH)
Immunoglobulin Structure

Four chains are arranged in form of a flexible Y with a hinge region
- stalk is Fc region: composed of constant region & recognized by receptors
- top of Y is 2 antigen binding fragments (Fab): composed of both constant & variable regions

Immunoglobulin Function

- Fab binds antigen specifically
  - marks antigen for immunological attack
  - activates nonspecific defense mechanisms that can destroy antigen
    - e.g., opsonization for enhanced phagocytosis
- Fc mediates binding to:
  - various cells of immune system
  - first component of complement system
Immunoglobulin Classes

- **IgG** (monomer)
  - 80% of serum immunoglobulin
  - opsonization, neutralization, activates complement
  - can cross the placenta for natural passive immunity to fetus
- **IgD** (monomer)
  - part of the B cell receptor complex
  - signals B cells to start antibody production

- **IgM** (pentamer, pinwheel)
  - first in all immune responses
  - agglutination, activates complement
- **IgA, secretory IgA** (sIgA; monomers & dimers)
  - secreted across mucosal surfaces
  - tears, saliva, breast milk, MALT
- **IgE** (monomer)
  - elevated in parasite infection & allergic reactions
  - mast cells bind Fc portion & are activated to degranulate when Fab portion binds antigen
ADCC - Antibody-dependant cellular cytotoxicity

Antibody Kinetics

- Antibody synthesis & secretion change over time
  - monomeric IgM is the B cell receptor for antigen
  - after B cell activation, pentameric IgM is secreted
- **class switching**
  - change in antibody class secreted by plasma cells under the influence of T helper cells
Primary Antibody Response

- days to weeks after initial exposure to antigen before antibody detectable in blood
- B cell differentiation into plasma cells $\rightarrow$ antibody secreted
- IgM appears first, followed by IgG

Secondary Antibody Response

- secondary exposure to same antigen $\rightarrow$ B cells have a memory response
  - shorter lag
  - higher IgG concentration (titer)
  - IgG increases before IgM
  - antibodies have a higher affinity for the antigen
Diversity of Antibodies

_three mechanisms contribute to antibody diversity_

1. **rearrangement** of antibody gene segments (combinatorial joining): genes are split or interrupted into many gene segments

2. **generation of different codons** during antibody gene splicing

3. **somatic mutation**: antibody genes have a high rate of mutation during an antigen challenge: this increases the affinity of the antibody for antigen over time.
Clonal Selection Theory

• body forms large & diverse B cell pool that can bind to large range of antigenic epitopes
• *self-reactive cells* are eliminated at an early stage of development (clonal deletion)
• antigen stimulates B cells that recognize & bind antigen to proliferate
• stimulated B cells proliferate to produce B cell clone (all have same antigen specificity)
• B cell clone differentiates to form 2 cell populations
  – plasma cells
  – memory B cells

![Diagram of clonal selection theory](image-url)
Action of Antibodies

- bind antigens with great **specificity**
  - essential for the protection of animal from viruses, microbes, & cancer cells
- antibody coats foreign invading material
  - marks it for recognition by components of the innate & adaptive immune systems
  - neutralization, opsonization, & immune complex formation
Opsonization

- process in which microbes are coated by complement components or antibody prior to ingestion by phagocytic cells
- coating molecules are called opsonins
- opsonizing antibodies bind Fc receptors on macrophages & neutrophils
- opsonization increases efficiency of phagocytosis

Antigenic Variation

- A successful immune response destroys the pathogen
- Trypanosomes change surface proteins that to hide from the immune system → antibodies against the variable surface glycoprotein (VSG)
- before all parasites killed, some express different VSG
- new group grows until host makes new antibodies
- expression of 3rd VSG gene, etc.

Although African trypanosomes represent the most extreme version of antigenic variation, other parasites such as Giardia & Plasmodium also use this strategy.
**T-Cells**

- major players in cell-mediated immune response
- originate from stem cells in the bone marrow but mature in thymus
- have major role in B cell activation
- immunologically specific & function in a variety of regulatory & effector ways
- T cell receptors (TCRs)
  - at the plasma membrane surface
  - recognize & bind antigen
  - *antigen must be presented by antigen-presenting cells (APCs)*

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**Types of T Cells**

- mature T cells are **naïve** until they are *activated by antigen presentation*
- activated T cells proliferate & differentiate:
  - effector cells
  - memory cells
- effector cells carry out specific immune functions
- three types
  - T helper (T<style>.superscript{font-size:75%;vertical-align:-25%;text-decoration:overline;}H</style>)
  - cytotoxic T lymphocytes (CTLs or T<style>.superscript{font-size:75%;vertical-align:-25%;text-decoration:overline;}CS</style>)
  - regulatory T cells (T<style>.superscript{font-size:75%;vertical-align:-25%;text-decoration:overline;}regs</style>)
T Helper Cells

• CD4+ T cells
• activated by antigen presentation with class II MHC
• subdivisions of T helper cells
  – T\(_{H0}\) – undifferentiated T cells
  – T\(_{H1}\), T\(_{H2}\), T\(_{H17}\), Treg
• T\(_{H1}\) cells (inflammatory response “for germs”)
  – promote CTL activity & activate macrophages
  – mediate inflammation & delayed hypersensitivity by producing a specific set of cytokines
• T\(_{H2}\) cells (allergic response “for worms”)
  – stimulate antibody responses & defend against helminths
  – involved in promoting allergic reactions
  – produce a specific set of cytokines

Cytokines

• soluble proteins or glycoproteins that are released by one cell population that act as intercellular mediators or signaling molecules
• four families
  – chemokines, hematopoietins, interleukins, tumor necrosis factor (TNF) family

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<td>Hematopoietins</td>
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<td>Tumor necrosis factor (TNF) family</td>
<td>TNF-α, TNF-β, Fas ligand</td>
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Cytokine Biological Effects

- must bind to specific receptors on target cells
- many activities
  - e.g., differentiation, proliferation, apoptosis
  - chemokines
    - stimulate chemotaxis & chemokinesis
      (direct cell movement)

Cytotoxic T Cells

- CD8$^+$ T cells, aka cytotoxic lymphocytes (CTLs)
- activated by antigen presented on MHC-1
- activated CTLs can kill target cells that have the same antigen-MHC-1 combination that activated the CTL
  - CTL binds target cell,
  - kills target cell via the perforin pathway
Vaccines & Immunization

• **vaccine**
  - preparation of microbial antigens used to induce protective immunity
  - may consist of killed, living, weakened (**attenuated**) microbes or inactivated bacterial toxins (toxoids), purified cell material, recombinant vectors, or DNA

• **immunization**: *protection when vaccine stimulates immunity*

• vaccines may induce antibodies & activated T cells to protect host from future infection
The Immune System & Parasites: Premunition

Premunition: resistance to infection by a pathogen established after an acute infection has become chronic & *lasting as long as the infecting organisms are in the body.*

This is in contrast to **sterilizing immunity** where all viable pathogens are cleared from the body by the immune response.

Immunity to many parasites including *Toxoplasma, Leishmania & T. cruzi* is by premunition. This may explain why we have not been able to develop effective vaccines for any parasitic diseases – the immune system needs to be “*reminded*” at frequent intervals by the slow release of parasite antigens during chronic infection.

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**Kill or Cure:**
*Kill or Cure: Malaria Vaccine*
Season 5 Episode 8

There has never been a vaccine developed against a complex multi-stage parasite. The organism that causes malaria is one such parasite. Advances in biotechnology however, such as new cell culture techniques, DNA modification, and the mapping of the malaria genome, all make a vaccine more feasible now than ever. *Kill or Cure* looks at the progress being made in this regard in Tanzania and the USA.

http://www.rockhopper.tv/programmes/110/
Terms from the documentary-Malaria Vaccine

“traveler’s market” - in order to a commercial vaccine, it needs to be sold to some people for a profit: not disease endemic populations (no money), but tourists going to disease endemic countries. For this to be marketable, the vaccine needs to be 100% effective.

RTS,S Vaccine: GlaxoSmithKline, 1st vaccine candidate that has reached Phase III clinical trials: efficacious for at least 18 months in reducing clinical malaria by 35 %, and severe malaria by 49 %.

Attenuated vaccine: in the case of bacterial or viral vaccines, the altered vaccine strain can be propagated in the laboratory, but has one or more mutations that eliminate virulence. The sporozoite vaccine uses irradiated parasites that must be purified from mosquitos and irradiated for every dose. This is much more difficult. Attenuated vaccines usually produce a more robust immune response with B and T cells.

Immunologically Privileged Sites

Some areas of the body suppress the full activation of inflammation in order to prevent collateral damage to sensitive organs or tissues:

• central nervous system (CNS)
• eyes
• placenta & fetus
• testicles

parasites often exploit or damage these
• Toxoplasma: brain, eye, fetus
• Trypanosoma brucei: brain
Chronic Inflammation

- formation of new connective tissue
- usually causes permanent tissue damage
- dense infiltration of lymphocytes & macrophages at site of inflammation
- **Granuloma**: walled off area formed when phagocytic cells can’t destroy pathogen

The Immune System & Parasites: Granulomas

Granuloma: a tumor-like mass of inflammatory tissue consisting of macrophages and lymphocytes. This inflammatory reaction develops around a persistent antigen & occurs frequently in parasitic infections.

Helminths trigger the production of granulomas which "wall off" the worm eggs or adults. This is a lung granuloma containing a dog heartworm.
Allergies: the immune system goes on alert when an allergy-causing agent (pollen) wafts through the air, settles on the skin or tickles the tongue. This is $T_{H2}$ biased.

Autoimmune diseases: the immune system cannot distinguish between self & foreign proteins. Mistaking self as foreign, the immune system attacks the bowel in Crohn's disease or insulin-producing cells in Type 1 diabetes. This is $T_{H1}$ biased.

Autoimmunity & allergies result from an imbalanced immune system

The Hygiene Hypothesis: epidemiological data suggests that cleaner conditions have gone hand in hand with increased immune disorders such as asthma. By wiping out the microbes that keep the immune system balanced, people are vulnerable to diseases where the immune system is misdirected at non-threats.