



PRINCIPLES OF VETERINARY IMMUNOLOGY

VERSION 3

OUTLINES

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VETERINARY
BIOLOGICS
TRAINING
PROGRAM



IICAB



the Center for
Food Security
& Public Health

IOWA STATE UNIVERSITY*
College of Veterinary Medicine

Principles of Veterinary Immunology

Long Course

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Overview of Immunology

Learning Objectives

1. Describe the basic differences between innate and adaptive immunity
2. List the major components of the innate defense system and examples of each.
3. Describe the two major components of the adaptive immune system
4. Explain where antibody comes from, list the different classes of antibody and identify those that are secreted and those that are not
5. List the different types of T cells and give a basic description of how they contribute to a cell-mediated immune response
6. Define antigen, immunogen, antibody, antibiotic, cytokine, and complement
7. Briefly explain the major aspects of memory and tolerance as related to the adaptive immune system

Two Major Components of the Immune System

- Innate Immunity (sometimes called natural immunity/native immunity)
 - Protects a naïve animal; an animal that has not been previously exposed to the pathogen
 - Protects immediately
 - Not antigen specific
 - Respond to danger signals from microbes or damaged tissues, which are generally referred to as:
 - ◆ PAMPS = pathogen associated molecular patterns: molecules produced by microorganisms but not mammalian cells
 - ◆ DAMPS = damage associated molecular patterns: molecules found within mammalian cells and released when the cell is damaged or dies
 - Provide important signals to the adaptive immune response (e.g. costimulatory molecules and cytokines)
 - Components include barriers, phagocytic and sentinel cells, complement, cytokines and NK lymphocyte cells
- Adaptive Immunity (acquired immunity)
 - Develops after exposure to an antigen, e.g. bacteria, virus, or vaccine agent
 - Requires days to weeks to develop
 - Is antigen specific and expandable
 - Has memory (anamnestic response); on subsequent exposures to an antigen it responds more rapidly
 - Has tolerance (does not target self-antigens)
 - Enhances the innate response through cytokines
 - Components include humoral immunity (B cells/antibody) and cell-mediated immunity (T cell mediated)
- Communication between adaptive and innate response is important for a successful response

Five Major Components of Innate immunity

- Barriers to Infection
 - Intact skin and mucous membranes = epithelial barriers
 - Examples of types of protection at these surfaces:
 - ◆ Acid in the stomach
 - ◆ Mucus on the surface provides protection
 - ◆ Antimicrobial peptides, e.g. defensins, secreted at epithelial surfaces
 - ◊ Small molecular weight proteins found along epithelial surfaces like skin and mucosal surfaces and in phagocytic cells
 - ◊ These proteins can poke holes in some bacteria and kill them
- Soluble Factors of the Innate Immune System
 - Complement System (C') - series of 20-30 proteins in blood plasma
 - ◆ An enzyme cascade system that has antimicrobial activity
 - ◆ Very rapidly induced

- ◆ Multiple mechanisms for controlling microbial infection
- ◆ Potent; if it is induced and not regulated (turned off) the result is death; one of the components of cobra venom can initiate the alternative pathway of complement and is resistant to the normal regulatory mechanisms
- Innate Defense Cytokines - (cytokines = protein messenger molecules produced by stimulated cells; the cytokines can act on the cell that produced it or nearby cells or cells at a distant site)
 - ◆ Pro-inflammatory cytokines (key ones = Interleukin (IL)1, IL6, tumor necrosis factor (TNF))
 - ◇ Secreted by sentinel cells (macrophages, dendritic cells, mast cells) in response to DAMPs and PAMPs
 - ◇ Cause fever, lethargy, loss of appetite
 - ◆ Chemokines – molecules that cause cells to migrate to sites of infection, some produced by sentinel cells
 - ◆ Interferons – interfere with replication of some viruses
 - ◇ Produced by virally infected cells within 24 hours of some viral infections
 - ◇ Production of interferon by one cell protects nearby cells by in various ways including activating proteins that inhibit viral replication
 - ◆ Cytokines are produced by many different cell types; the types of cytokines produced depend on the cell, the stimulating cause, and the environment; different cell types can produce the same cytokines, different cytokines have similar actions; one cytokine can have many actions. The network of cytokines is complex.
- Defensins – antimicrobial molecules (peptides) associated with epithelium and phagocytic cells
- Cellular Components of the Innate Defense System
 - Phagocytic and Sentinel Cells
 - ◆ Important for ingesting and killing pathogens
 - ◇ Neutrophil
 - ◇ Macrophage
 - ◆ Sentinel cells: resident tissue cells that detect invasion by recognizing DAMPs and PAMPs and sending signals to initiate a response
 - ◇ Dendritic cells
 - ◇ Macrophage
 - ◇ Mast cells
 - Innate Lymphoid Cells (ILC)
 - ◆ Cytokine secreting ILCs, and
 - ◆ Cytotoxic ILC-NK cells (natural killer)

Summary of Innate Immunity

- Is fairly efficient and works most of the time
- No memory, not antigen specific
- Extremely important as a first line of defense
- Can be suppressed by crowding, stress, cold, etc.
- Can work independently of adaptive immunity but function can be enhanced by adaptive immunity making the components of innate defense even more powerful and efficient

Two Major Components of the Adaptive Immune System

- Humoral - Antibodies
 - Named because it was discovered that transfer of body "humors" (fluids) from a protected animal to a naïve (susceptible) animal could provide protection from certain diseases.
 - B (B= Bursa of Fabricius) cells produce antibodies and antibodies provide humoral immunity
 - Immunoglobulin = antibody = Ig = Ab; often drawn as a Y
 - Classes (Isotypes) of antibody – IgM, IgG, IgA, and IgE can be secreted; each has some unique characteristics that influence where and how they provide protection. Very small amounts of IgD are secreted; function of IgD is not as well defined as the other isotypes.

- ♦ IgM - the first antibody produced in every antibody response and the largest antibody molecule, functions primarily in the bloodstream and has a short half-life.
- ♦ IgG - high in serum, important in systemic diseases in general
- ♦ IgA - important on mucosal surfaces as a dimer
- ♦ IgE - important in allergy and parasitic infection; found on mast cells; very little in serum
- ♦ IgD – major role as a B cell surface receptor not as a secreted antibody; co-expressed with IgM on the surface of mature, naïve B cells, a marker of maturation in B cell development.
- **Cell Mediated Immunity (CMI)**
 - o Named because transfer of immunity from a protected animal to a susceptible animal required transfer of cells
 - o $\alpha\beta$ T lymphocytes are important in CMI ($T = \text{Thymus}$)
 - ♦ CD4+ cells = T helper cells, T_H cells (functional designation) or CD4 (surface molecule designation)
 - ◊ Types: T_H1 , T_H2 , T_H17 , T_{fh} , T_{reg}
 - ◊ Function: Produce cytokines that regulate innate and adaptive immune mechanisms
 - ◊ Important for directing which antibody class is produced, i.e. a B cell produces IgM and then based on cytokines from T_H cells will switch and make IgG or IgA or IgE
 - ◊ Important for activating cellular responses
 - ♦ CD8+ cells - T_C cell, cytotoxic T lymphocyte (CTL), CD8+ -
 - ◊ Function: Attack and kill cells that make foreign proteins, e.g. viral infected cell or tumor cell
 - o $\gamma\delta$ T cell (gamma delta T cell or $T\gamma\delta$) - named for the type of T cell receptor it has (T_H and T_C are alpha beta ($\alpha\beta$) T cell receptors)
 - ♦ Function: protection at mucosal surfaces; still seems there is a lot more to be discovered about this cell type

Antigen Recognition by the Adaptive Immune System

- Antibodies recognize a small portion of a molecule (epitope)
 - o Example: proteins - about 6-8 amino acids
 - o Very specific - 10^9 different antigen specificities or epitopes recognized by B cells
- T and B cells recognize antigen differently
 - o B cells recognize intact antigen (not processed); 3D structure of antigen (epitope) is important. They recognize a wide variety of chemical types: protein, carbohydrate, lipids, etc...
 - o T cells (T_H and $T_C = \alpha\beta T$ cells) – recognize only peptides (processed proteins) presented on major histocompatibility complex molecules (MHC); 3D structure is not important.

MHC – there are two important MHC molecules for presenting peptide (antigen) to T cells:

- **MHCI** - a surface molecule on all nucleated cells and presents antigen to CD8+ T cells
- **MHCII** – found on the surface of professional antigen presenting cells (APCs) such as dendritic cells, macrophages, and B cells.

- ♦ Gamma delta ($\gamma\delta$) T cells recognize cell surface molecules –Most don't require antigen presentation on MHC molecules

Fundamentals of the Adaptive Immune System

- Clonal Selection of Lymphocytes
 - o Lymphocytes develop in the primary lymphoid tissue and acquire an antigen receptor. They then exit the primary lymphoid tissue and go to secondary lymphoid tissues. A lymphocyte clone that binds to its specific antigen gets activated and will undergo mitosis and make many copies of the clone for that antigen. The clones then differentiate into effector cells or memory cells.

- Memory response, also called an anamnestic response, occurs on re-exposure to antigen. This memory response is:
 - Faster than a primary response
 - Antigen specific clones of B lymphocytes have expanded and matured. The antibody produced in a secondary (anamnestic response) is:
 - ◆ Higher in titer than a primary response
 - ◆ The antibody can bind more tightly – higher affinity
 - ◆ Antibody class switching has already occurred (from IgM, the first type of antibody produced in a primary response, to a different class depending on the nature of the infectious agent)
 - T helper and CTL clones have expanded, matured, and are circulating so there are many more cells that can recognize the antigen
- Tolerance - the adaptive immune system "tolerates" self-molecules (does not attack)
 - Antigens presented during lymphocyte development are recognized as self and tolerated
 - Antigens presented after lymphocyte development are recognized as foreign and attacked
 - Tolerance can break down resulting in autoimmune diseases

Immune System Dysfunction

- When the immune system causes damage and is responsible for the disease process
- An inappropriate response of the immune system
- Examples: hypersensitivities, allergies, autoimmune disease, and immunodeficiencies/suppression
- Hypersensitivity reactions (immune mediated diseases)
 - Allergies
 - ◆ Adaptive immune system attacks molecules that are not dangerous
 - Autoimmune disease
 - ◆ Adaptive immune system attacks self-molecules/cells
- Immunodeficiency/suppression
 - Failure to protect from infections or cancer