VETERINARY BIOLOGICS TRAINING PROGRAM

# INTRODUCTION TO VETERINARY IMMUNOLOGY

## LECTURE OUTLINES

JAMES A. ROTH, DVM, PhD, DACVM • GAYLE BROWN, DVM, PhD • KEVAN FLAMING, DVM, PhD

IICAB

the Center for Food Security & Public Health
IOWA STATE UNIVERSITY®
College of Veterinary Medicine

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# Introduction to Veterinary Immunology

An Online Course

James A. Roth, DVM, PhD
Gayle B. Brown, DVM, PhD
Kevan P. Flaming, DVM, PhD

Institute for International Cooperation in Animal Biologics (IICAB)

Center for Food Security and Public Health (CFSPH)

Iowa State University
College of Veterinary Medicine

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| Acronym | Meaning |
|---|---|
| Ab | antibody |
| ADCC | antibody independent cell mediated cytotoxicity |
| Ag | antigen |
| APC | antigen presenting cell |
| APHIS | Animal and Plant Health Inspection Service |
| ARDS | acute respiratory distress syndrome |
| BALT | bronchus associated lymphoid tissue |
| BCR | B cell receptor |
| C' | complement |
| C1, C2… | complement proteins |
| CD | cluster designation; used in naming surface molecules; e.g. CD3, CD4 |
| CMI | cell mediated immunity |
| COBTA | Council on Biologics and Therapeutic Agents |
| CR1 | complement receptor 1, the receptor for C3b |
| CTL | cytotoxic T lymphocyte |
| CVB | Center for Veterinary Biologics |
| DAMPS | damage associated molecular patterns |
| DIC | disseminated intravascular coagulopathy |
| EALT | eye-associated lymphoid tissue |
| ER | endoplasmic reticulum |
| ERAP | endoplasmic reticulum resident aminopeptidase |
| Fab | fragment antigen bonding |
| Fc | fragment crystallizable, a portion of the antibody molecule |
| FcR | Fc receptor- a cell receptor that binds to Fc portion of antibody |
| FeLv | feline leukemia virus |
| FIP | feline infectious peritonitis |
| FIV | feline immunodeficiency virus |
| GALT | gut-associated lymphoid tissue |
| HA | hemagglutinin |
| HMGB-1 | high mobility group box protein-1 |
| IFN | interferon |
| Ig | immunoglobulin |
| IL | interleukin |
| LPS | lipopolysaccharide |
| M1 | macrophage whose function is killing |
| M2 | macrophage whose function is healing and repair |
| MAC | membrane attack complex of complement |
| MALT | mucosal associated lymphoid tissue |
| MBL | mannose-binding lectin |
| MHC | major histocompatibility complex |
| MHC I | major histocompatibility complex 1; found on all nucleated cells |
| MHC II | major histocompatibility complex 2; found on antigen presenting cells |
| MICA | surface molecule expressed by stressed cells |
| MICB | surface molecule expressed by stressed cells |

| Acronym | Meaning |
|---|---|
| MLV | modified live vaccine |
| NK cells | natural killer cells |
| PAM | pulmonary alveolar macrophage |
| PAMPS | pathogen associated molecular patterns |
| PCR | polymerase chain reaction |
| PMN | polymorphonuclear cell; granulocyte |
| RBC | red blood cell |
| RER | rough endoplasmic reticulum |
| TCR | T cell receptor |
| TNF | tumor necrosis factor (a cytokine) |
| USDA | United States Department of Agriculture |
| $V_H$ | variable heavy chain of an antibody molecule |
| $V_L$ | variable light chain of an antibody molecule |
| WBC | white blood cell |
| WNV | West Nile virus |
| αβ | Greek letters alpha and beta |
| γδ | Greek letters gamma and delta |

## Lecture 1
## Overview of the Immune System

**Learning Objectives**

1. Describe the basic differences between innate and adaptive immunity
2. List the major components of the innate defense system and give 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
5. List the different types of T cells and describe how they contribute to a cell mediated immune response
6. Define antigen, antibody, antibiotic, and cytokine

**Two Major Components of the Immune System**

- **Innate Immunity (natural 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**

**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
- **Phagocytic and Sentinel Cells**
  - Phagocytic cells with important killing mechanisms
    - Neutrophil
    - Macrophage
  - Sentinel cells – these are resident tissue cells that detect invasion by recognizing DAMPS and PAMPs and sending signals to initiate a response
    - Macrophage
    - Dendritic cells
    - Mast cells
- **Complement System** - series of 20-30 proteins in blood plasma
  - An antimicrobial enzyme cascade system
  - Very rapidly induced
  - Helps control microbial infection in a variety of ways

- Potent; if it is induced and not regulated (turned off) the result is death
  - An example of its potency: one of the components of cobra venom can initiate the alternative pathway of complement and is resistant to the normal regulatory mechanisms; it kills its victims
- **Innate Defense Cytokines** - (cytokines = protein messenger molecules; secreted by cells; cytokines can act on the cell that secreted them and/or on other cells)
  - Pro-inflammatory cytokines
    - Secreted by sentinel cells (macrophages, dendritic cells, mast cells) in response to DAMPs and PAMPs
    - These cytokines act on other cells and result in the clinical signs of fever, lethargy, loss of appetite
  - Chemokines – molecules that cause cells to migrate to sites of infection
  - Interferons – interfere with replication of some viruses
    - Produced by virally infected cells within 24 hours of some viral infections
    - Production and secretion of interferon by one cell protects nearby cells by in various ways including activating proteins in the neighboring cells that inhibit viral replication
- **NK cells (natural killer)**
  - A type of lymphocyte (a unique lymphocyte because it is part of innate immunity not adaptive immunity)
  - Important for killing virus infected cells and tumor cells
  - Targeted to cells that do not express normal proteins (i.e. MHC1), cells expressing stress proteins, and/or cells with antibody bound to them
- **Antimicrobial Peptides = defensins**
  - Small molecular weight proteins found along epithelial surfaces like skin and mucosal surfaces and in phagocytic cells
  - These proteins can poke holes in some bacterial membranes and kill the bacteria.

**Two Major Components of the Adaptive Immune System**

- **Humoral Immunity = Antibodies**
  - There are four different classes (isotypes) of antibody that are secreted and each has a few unique characteristics that influence where and how they provide protection
    - IgM - the first antibody produced in every primary antibody response and the largest antibody molecule; functions primarily in the blood stream, short half-life
    - IgG - high in serum; in general, important in systemic diseases
    - IgA - important on mucosal surfaces (e.g. gastrointestinal tract, respiratory tract, mammary gland) as a dimer
    - IgE - important in allergy and parasitic infection; found on mast cells
- **Cell Mediated Immunity (CMI)** - adaptive immunity mediated by T cells
  - T helper cells = CD4+
    - Function: produce and secrete cytokines (messenger molecules) to "help" or direct the immune response
    - Different cytokines in different combination result in different effects; for example, IL4, from $T_H2$ cells, influences B cells to make IgE and IFNγ, from $T_H1$ cells, influences B cells to make IgG
  - Cytotoxic T lymphocyte (CTL) = CD8+ -
    - Function: attack and kill cells that make foreign proteins, e.g. viral infected cell or tumor cell
  - Gamma delta (γδ T cell **)**
    - Function : protection at mucosal surfaces; still not well defined

**Types of Blood Cells - originate in the bone marrow**

- Platelets - important in blood clotting – no major role in immune response
- Red blood cells (RBCs) – do not play a role in immune response
- **Five types of white blood cells (WBCs) or leukocytes** – play a major role in the immune system
  - **Basophil** - 0.5% of WBCs in circulation
    - Contain granules (which stain basophilic) that are filled with inflammatory mediators, very similar to the mediators in mast cell granules, e.g. histamine, serotonin, other vasoactive substances.
      - ✧ It is unclear whether these cells become tissue mast cells or not
      - ✧ Important in allergy and parasites

- **Eosinophil** - 1-3% of WBCs in the circulation, half-life of 30 minutes
  - Contain granules (which stain eosinophilic) filled with potent mediators capable of killing parasites, e.g. major basic protein and eosinophil cationic protein
  - They are in the blood stream about 30 min. and then go to tissues and are mostly found under epithelial surfaces - live a couple of weeks in the tissues and are then replaced by new ones
  - Eosinophilia (elevated eosinophil counts in peripheral blood) can occur in some types of parasite infections or sometimes with allergies
- **Monocyte** - 3-7% of WBCs in circulation
  - Circulate 1-2 days then migrate to tissue and differentiate into a macrophage
  - Macrophages are found in most tissues and have different and special functions depending on the tissue where they reside; for example, in the liver a tissue macrophage is called a Kupffer cell, in the alveolus of the lung they are called alveolar macrophages. These different tissue macrophages are discussed in a later lecture.
  - The macrophage is extremely important in the immune response and has a variety of roles. For example the macrophage can phagocytose and kill bacteria, it is also an important antigen presenting cell, and it secrete cytokines that play a major role in inflammation and the immune response.
  - The accumulation of macrophages at a site of inflammation is a sign of chronic infection
- **Neutrophil** - 55-90% of WBCs in circulation (the highest)
  - Short lived cell, survive about 1-2 days at most
  - Half-life in the blood is about 8-12 hours; about 2.5 times a day all the neutrophils are replaced by new ones
  - Bone marrow spends a lot of energy making neutrophils
  - Important in protection against bacterial infections
    - Called "first responders;" they arrive within 4 hours at sites of infection, especially bacterial and fungal infections
    - Bone marrow increases production of neutrophils in response to bacterial infections resulting in neutrophilia (left shift)
    - Neutrophils exit the blood stream at sites of infection and accumulate in high numbers to ingest and kill the invading pathogens
    - Neutrophils die in the process of killing microbes and the result is in the formation of pus, which is an accumulation of dead and dying neutrophils and cellular debris.
- **Lymphocyte** - about 30% of WBCs in circulation in most animals
  - The lymphocytes are B cells, T cells and NK cells
  - Circulate about 4 months (120 days) between the blood stream and lymphoid tissues searching for antigen (the other WBCs stay in tissues once they leave the bloodstream; the circulation between the blood stream and lymphoid tissues is unique to lymphocytes)
  - Naive B and T cells are morphologically the same (cannot be distinguished with a light microscope)
    - Both are part of adaptive immunity
    - Circulate about 4 months (120 days) looking for the one antigen they recognize; if they do not come in contact with their antigen they die
    - If they meet their antigen, they are activated, undergo mitosis, some differentiate into memory cells and some differentiate into effector cells
  - Memory T and B lymphocytes are longer lived cells than naïve lymphocytes (exactly how long they live is unknown)

**Important Definitions to Know**

- **Antigen**: Any foreign substance that can bind to specific lymphocyte receptors and induce an immune response. For example bacteria, viruses, fungi, and parasites
- **Antibody**: An immunoglobulin (Ig) molecule is synthesized by B cells after exposure to antigen. The antibody produced binds specifically to the antigen that activated the B cell. The antibody binds to "the body" of the bacteria, etc.
- **Antibiotic:** A chemical compound, usually obtained from microorganisms, that can prevent growth of or kill bacteria
- **Cytokine:** Protein messenger (communicator) molecules made by cells that influence the immune response by their effects on cells; they can act on the cell that made them, a neighboring cell or at a distant site. Types of cytokines include interleukins, interferons, chemokines, colony stimulating factors, and growth factors.