OmniGen®

Report

Information from Phibro Technical Services

The Immune System of Ruminants

The immune system is a multi-layered complex collection of cells and mechanisms essential for maintaining health and for protecting the body from a wide variety of disease-causing organisms or pathogens. Two distinctive and interactive arms of the immune system, the innate and the acquired immune systems, work in concert to provide this protection. These systems communicate with each other through small proteins called cytokines and chemokines secreted by both immune and other body cells to signal other cells or attract cells to sites of inflammation or infection.

Stressor	Impact on Dairy Cows
Molds & Mycotoxins	Impaired immunity; diarrhea; poor breeding; lower milk yield
Feeding Management	Impaired immunity; reduced milk fat and protein; poor hoof health
Sanitation	Higher SCC; more mastitis
Social	Impaired immunity; higher SCC; lower milk fat; lower milk yield
Comfort	Impaired immunity; higher SCC; lower milk yield
High Temperature Humidity Index	Impaired immunity; higher SCC; poor breeding; lower milk yield
Calving	Impaired immunity; retained placentas, metritis and mastitis
Dry-off	Impaired immunity; higher SCC
Transportation	Impaired immunity; decreased embryo survival & pregnancy rates
Handling	Impaired immunity; higher SCC; lower milk yield
Ventilation	Impaired immunity; pneumonia; reduced growth and production

Innate Immunity

The innate immune system represents the cow's first line of defense against pathogens and other infectious agents by providing an immediate response, allowing the time required to develop the appropriate acquired immune response to the specific invader. The innate system is comprised of several layers or barriers of protection to prevent pathogen entry and infection. These barriers consist of: 1) physical (skin, tears, GI mucosal and mammary cells), 2) chemical (stomach acid), 3) enzymatic (digestive) and 4) blood cellular components (white blood cells or leukocytes).

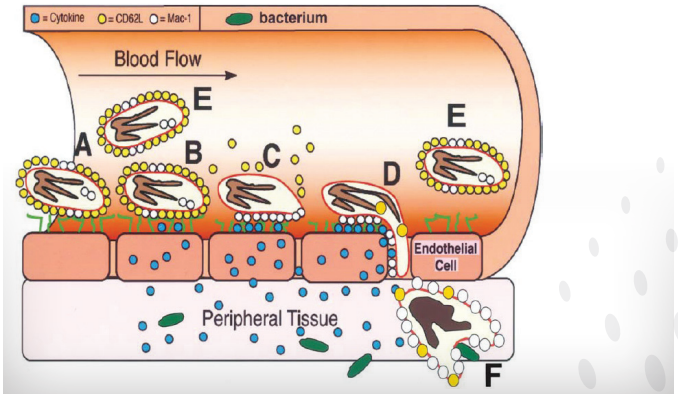
Neutrophils: "First Responders"

Granulocytes and macrophages originate in bone marrow and are the predominant white blood cells involved in innate immunity. Granulocytes, also referred to as polymorphonuclear leukocytes (PMN), are a diverse collection of white blood cells of which the majority is comprised of neutrophils. Approximately 200 billion neutrophils are present in adult dairy cows with half in circulation and the other half either attached to capillary vessel walls or stored in bone. Neutrophils have a short life span of approximately eight to 24 hours and, if not delayed by encountering a pathogen, are removed from circulation by a programed 'self-destructive cell death' process called apoptosis.

The main function of any neutrophil is to monitor for sites of infections and kill pathogens (Figure 1). Each pathogen contains distinctive molecules not typically found in mammalian cells. Neutrophils are able to recognize pathogens by these distinct pathogen-associated molecular patterns (PAMPs) using surface receptors called Pattern Recognition Receptors (PRR). Each PRR is specific to a pathogen's molecular pattern, giving neutrophils the ability to recognize a variety of harmful pathogens such as *Staphylococcus aureus*, *Streptococcus uberis*, *Escherichia coli* and certain fungal species. The binding of PAMPs to the PRR initiates killing mechanisms of neutrophils,

which include engulfing or phagocytosis, degranulation or the release of antimicrobial molecules, or entrapment using projected strands of DNA called neutrophil extracellular traps or NETS.

Figure 1. Neutrophils (A) use an adhesion molecule (L-selectin or CD62L) for vascular margination or rolling motion (B) and migration (D) into sites of infection. L-selectin allows neutrophils to loosely attach to the vessel wall (C) for effective infection surveillance. Biochemical signals emitted from immune cells at infection sites initiate diapedesis, the migration process, by which neutrophil shed the L-selectin and move through the vessel wall and into the infective tissue (D, F).



Adapted from Burton and Erskine, 2003.

Acquired Immunity

The acquired immune system is the arm of the immune system responsible for providing long-term protection against a great diversity of potential invaders as a result of "immunological memory." Harmful invaders can be classified into two broad categories, depending on whether the origin is from outside the body (e.g.; bacteria, fungi, protozoa, helminths) or are organisms that originate or live inside the body's own cells (e.g.; viruses, intracellular bacteria or protozoa). These invader types require different defensive strategies, so the adaptive immune system consists of two major branches: the antibody-mediated and cell-mediated.

The antibody-mediated immune responses are directed against extracellular invaders by developing and releasing soluble proteins called antibodies. B lymphocytes, or B cells, are the cell types associated with this immune response. Intracellular invaders require specialized cells to destroy these infections since antibodies do not work inside cells. This protection is initiated by T lymphocytes, or T cells, and is termed a cell-mediated immune response.

B Cells and Antibodies

B cells mature in the bone marrow and are released into the blood stream and found to reside in lymph nodes, spleen, intestine and Peyer's patches. Few B cells circulate in the blood. B cells have a large number of identical antigen-binding surface receptors generated at random and only bind and respond to a specific single antigen, which can be a toxin, a foreign substance or pathogen. Each B cell is covered with approximately 200,000 to 500,000 identical antigen receptors (B cell receptors or BCRs), which are divided into antigen-binding and signaling components. Antibodies are these soluble BCRs that are secreted into body fluids, all belonging to the family of proteins called immunoglobulins (Table 1).

Table 1: Classes of Immunoglobulins

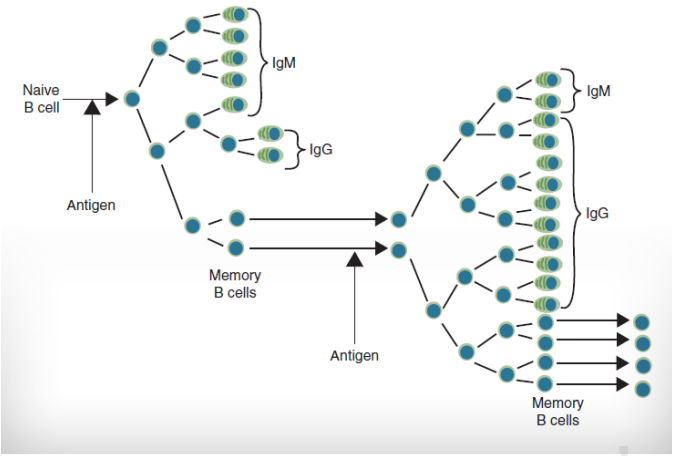
Class	Description and Function
IgG	Predominant immunoglobulin in serum, responsible for systemic defense
IgM	Large immunoglobulin produced during a primary immune response
IgA	Produced on body surfaces, responsible for defense in GI and respiratory tracts
IgE	Small quantities found in serum, responsible for immunity to parasitic worms and allergies
IgD	Found on surface of immature lymphocytes, function is unknown

Antibodies are Y-shaped immunoglobulin molecules synthesized when naïve B cells are activated when exposed to an antigen, which can then combine specifically with that antigen. Antibodies contribute to immunity in one of three ways; 1) by binding to the pathogen and preventing entry into or damage to cells, 2) by stimulating the removal of pathogens as a result of macrophages and other cells coating the pathogen, or 3) by triggering the destruction of pathogens through the stimulation of other immune responses such as the complement pathway.

Activated B cells differentiate (change or develop) into either antibody-producing cells called plasma cells that

secrete soluble antibodies, or memory cells that survive in the body for years afterward in order to allow the immune system to remember an antigen and respond faster upon future exposures (Figure 2).

Figure 2. B cell response and accompanied cellular events to initial and subsequent antigen exposure.



Veterinary Immunology, Ian R. Tizard, 9th Edition, Elsevier Saunders, St. Louis, MO.

T Cells and Cellular Immunity

Cell-mediated immunity does not involve antibodies, instead it involves the activation of groups of specific, differentiated T cells. T cells are formed in bone marrow but mature in the thymus, hence the T cell designation. T cells differ from other lymphocytes by the presence of cell surface receptors allowing protective function by activating phagocytes, antigen-specific cytotoxic T lymphocytes and the release of various cytokines in response to the antigen.

These groups of differentiated T cells provide immune protection from intracellular invaders in one of three ways, 1) by causing cell-mediated cell death, carried out by T cells called 'killer cells' or cytotoxic T cells which destroy infected target cells by apoptosis, or 2) through TH1 cells (helper cells) which function to activate macrophages (phagocytes), or 3) by TH2 cells, which primarily function to stimulate B cells into producing antibodies.

In addition to providing immune protection from intracellular invaders, T cells have an immune regulatory function (Regulatory T cells, or Tregs), allowing the immune system to distinguish between invading cells, or organisms, and the body's own cells, thus preventing immune cells from mounting an inappropriate response against oneself. For this reason, these regulatory immune cells are called suppressor T cells.

Stressors and Immune Competence

Stressors are stimuli that the animal recognizes as a threat. Stressors may be physical, mental, emotional, internal or external. Stress is defined as the animal's response to a stressor. Stress tends to disturb or disrupt the body's homeostasis, and should the compensating reactions be inadequate or inappropriate, it may lead to disorders or disease. Dairy cows can experience stress in response to a variety of stressors including: dry off, calving, high temperature and humidity, feeding management, molds and toxins, poor sanitation, social disruptions, poor cow comfort, air quality, handling and transportation. The results of exposure to these stressors may present as a case of mastitis, an abortion, a retained placenta, an abrupt decline in milk production or an elevated somatic cell count.

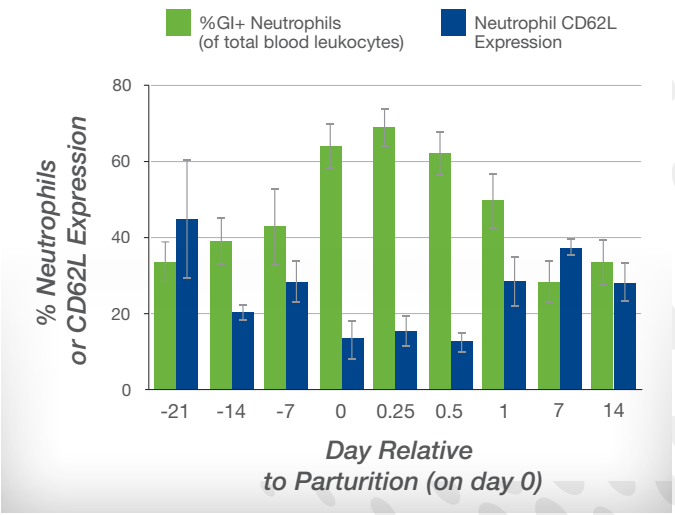
Dairy Cattle Stressors

Immune competency or immune 'health' has been assessed using several immunological methods. One method is to assess total production of immunoglobulins (IgM and IgG's). These are non-specific indicators of the combined antibody responses against all antigens to which the cow may have been exposed. Another common measure is titre which assesses antibody concentration. More recently, several more highly specific methods to assess immune system activity or 'health' are available. These have focused on functional assays designed to assess the ability of specific white blood cells to recognize and 'kill' pathogens either by phagocytosis or by generating oxidative bursts containing reactive oxygen species (ROS). Other assays have been used to evaluate the ability of immune cells to communicate through measuring cytokine production (e.g.: Interleukin 1 Beta (IL-1ß)) or maintaining key functional surface receptors (e.g.: Interleukin 8 receptor (IL-8R)) and proteins (e.g.: L-selectin (CD62L)) necessary to identify and migrate to infection sites.

Research in the area of effects of stress on immunity has shown components of the innate and acquired immune systems can become compromised or temporarily dysfunctional during stressful periods. As an example, the hormones associated with calving can alter the

functional ability of innate immune cells to respond and kill mastitis-causing pathogens, through the inhibition of the production of L-selectin, which is vital for normal neutrophil function (Figure 3). The detrimental effects of stress on immune function are not limited to those associated with parturition but can occur at any time during the lactation cycle and because of this it is important to initiate management and nutritional programs to minimize these events so cows are better able to withstand pathogen challenges and maintain productivity.

Figure 3. Glucocorticoid hormones (cortisol) released around the time of parturition inhibits neutrophil expression of L-selectin (CD62L) increasing susceptibility to periparturient diseases and infections.



Adapted from Burton and Erskine, 2003.

Summary

The immune system provides protection from infections and a wide variety of disease-causing organisms. The first and immediate response to pathogens is from cells of the innate arm of the immune system, specifically macrophages and neutrophils. These cells are phagocytic white blood cells that function to monitor and respond to all types of pathogens (bacteria, fungi, viruses, parasites) providing protection until an acquired immune response can be mounted. The acquired immune system is comprised of B cells, which produce and secrete antibodies and T cells, which attack intracellular pathogens using a variety of specialized 'killer' cells, both of which develop memory to specific pathogens. The innate and acquired immune systems work in concert to provide protection against all types of infections and pathogens allowing cows to maintain health and productivity.

A Healthy Immune System Starts With Good Nutrition

When cows experience stress, their natural defenses go to work to fight off these challenges.

The cow's immune system can be compromised if not supported effectively. Good nutrition, including sufficient energy, fiber, vitamins, trace minerals and OmniGen® nutritional specialty products help the cow maintain a healthy immune system.

It is far more important and cost effective to promote health by maintaining a healthy immune system than it is to treat the disease.

Maintaining a healthy immune system in cows can help to:

- Increase milk production
- Improve reproductive efficiency
- Improve milk quality by lowering somatic cell counts
- Reduce cases of mastitis & metritis
- Reduce time spent in hospital pen
- Extend production longevity of cows in the herd by reducing death loss and culls

References

Burton, Jeanne L. and Ronald J. Erskine. 2003. Immunity and mastitis. Some new ideas for an old disease. Vet Clin Food Anim 19:1-45.

Tizard, Ian R. 2012. Veterinary Immunology. 9th Edition. Elsevier Saunders, St. Louis, MO.

This information has been prepared for industry technical professionals.