The Immune System of Ruminants
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Stress and Immunity in Dairy Cows

Immunity is defined by Dorland’s Illustrated Medical Dictionary, as security against a particular disease or nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or the toxic effect of antigenic substances. The immune system in the cow consists of two distinct but interactive systems; the innate and the adaptive or antibody mediated. Each of these has specific functions and response times but work in concert to protect the cow from infectious pathogens.

The innate system is composed of natural barriers (skin, stomach acids, enzymes, etc.) and white blood cells (neutrophils, macrophages) which continually monitor for sites of infection and pathogens and are the “first responders”. The adaptive or antibody system consists of other types of white blood cells whose function is to provide “long-term” protection against disease through the production of pathogen specific antibodies.

Stress has been defined as the sum of the biological reactions to any adverse stimulus; physical, mental, or emotional, internal or external, that tend to disturb or disrupt homeostatis, and should these compensating reactions be inadequate or inappropriate, they may lead to disorders or disease (Dorland’s Illustrated Medical Dictionary). Dairy cows can experience stress in a variety of ways, during dry off and calving, in extreme heat or cold conditions, sudden feed changes, etc. and the results of these ‘stressors’ may present itself as a case of mastitis, a retained placenta, an abrupt decline in milk production or an elevated somatic cell count.

Immune status 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 titre against all antigens to which a cow is exposed. Another common measure is titre, which assesses T- and B-cell proliferation and is an index of the adaptive immune systems ability to ‘ramp up’ to a specific chemical or mitogen challenge. More recently, scientists are using several more highly specific methods to assess immune system activity or ‘health’. These have focused on assays and procedures designed to assess the ability of certain white blood cells to kill pathogens via phagocytosis and the production of reactive oxygen species, or communicate with other immune cells through cytokine production, or maintain normal cell functions through the production of key proteins (L-selectin and interleukins) and cell surface receptors.

Research in the area of stress and immunity has shown that many components of the innate and adaptive immune systems are compromised during periods of stress. In particular, hormonal changes around the time of calving (figure 1.) can alter the 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 2.). The detrimental effects of stress on immune function is not limited to those associated with parturition but can occur at any time and because of this it is important to initiate management and nutritional programs to reduce these events so cows are better to withstand pathogen challenges and maintain productivity.

Sources of Stress
- Dry Off and Calving
- Transition
- High Milk Production
- Feed Changes
- Weather (Heat, Cold, Humidity)
- Overcrowding
- Poor Cow Comfort
- Molds and Mycotoxins
- Pathogens

Dairy nutritionists and veterinarians can help producers manage the stresses that impact their cows’ immune status by recognizing the sources of stress and working to minimize them.
The innate immune system represents the cow’s first line of defense against a pathogen challenge and provides the adaptive system the time required to develop the appropriate antibody response. Several components comprise the innate system, and they present barriers to pathogen entry and infection. These barriers consist of: 1) physical (skin, tears, gut and mammary cells); 2) chemical (stomach acid); 3) enzymatic (digestive); and 4) blood cellular components.

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**Neutrophils: “First Line of Defense”**

Granulocytes and macrophages are predominantly white blood cells involved in innate immunity. Granulocytes are also called polymorphonuclear leukocytes (PMN), which are a diverse collection of white blood cells, including neutrophils. In the adult cow, there are approximately 200 billion neutrophils, half in circulation and the other half either attached to vessel walls or stored in bone. The life span of a neutrophil is short – 8 to 24 hours – and these white blood cells go through a process of self-destruction called apoptosis.

The main function of neutrophils is to monitor for sites of infection and kill pathogens. Neutrophils identify pathogens by the recognition of distinct pathogen-associated molecular patterns (PAMPs). Specifically, pathogens contain molecules not typically found in mammalian cells and via this recognition of PAMPs neutrophils are able to find foreign cells. Examples of molecules associated with pathogens and recognized by neutrophils include lipotechoic acids, double-stranded RNA, CpG DNA sequences, and unusual sugar residues.

The neutrophil detects PAMPs by using specific receptors, called Toll-like receptors, which are located on their outer surface (Figure 3). Binding of PAMPs to Toll-like receptors initiates the killing mechanisms of neutrophils of which there are several. These include engulfing pathogens (phagocytosis), or entrapping them using projected strands of DNA called neutrophil extracellular traps or NETS and by respiratory bursts that involve the generation of several reactive oxygen species (ROS) which are bactericidal.
Adaptive or Antibody-Mediated Immunity
The primary function of the adaptive immune system is to develop antibodies against specific antigens. The time required for this response can be variable, ranging from a few days to several months, depending upon the antigen and the health of the cow. The antibodies produced in response to a foreign protein or antigen can be derived from a variety of cell types: T- and B-lymphocytes, antigen-presenting cells and Natural Killer (NK) cells.

Antibody Expressing Cells
B-cells mature in bone marrow (hence the name “B”) and are released into blood where they circulate and are captured by lymphoid tissue. These cells live less than 48 hours, unless they interact with their antigen (trigger activation), resulting in their proliferation and differentiation, a process termed "clonal selection." The type of B-cell that can mature is driven by a process of "random gene rearrangement," which can result in approximately 10^8 different types of B-cells, each with a specific target antigen.

Proliferation of a B-cell antigen-specific lineage is initiated following interaction with the antigen and requires input of interleukins-2, -4, -5, -6 and IFNγ from T-helper cells. These cytokines cause formation of B memory cells from the activated B-cell population. Memory B cells can secrete as many as 2,000 antibody molecules/second into plasma. Antibodies may be of a variety of forms [e.g., IgG, IgM], which are targeted for specific purposes in the fight against pathogens. T-cells are manufactured in bone marrow and mature in the Thymus [hence the name “T”-cell]. T-cells are responsible for “cell-mediated immunity” because the antibodies they manufacture remain attached [tethered] to the surfaces of the T-cell population. As in B-cells, interaction of a T-cell with a specific antigen causes clonal selection and expansion of a specific T-cell population that express as many as 100,000 antibody molecules on the surface of each cell. Clonal selection of T-cells, as with B-cells, leads to the development of “memory T-cells” (figure 5).

Antibodies
Antibodies consist of a Y-shaped molecule, containing a constant (C) region and a variable (V) region. If antibodies are destined to become tethered to the surface of a T-cell membrane (see Figure 6), they are expressed with a transmembrane domain which allows for interaction with membranes. If antibodies are destined to be secreted, the C-terminus of the antibody molecule is assembled lacking a transmembrane domain structure. For both the tethered and secreted forms of antibodies, the variable region [i.e., the fork of the “Y” domain] represents the strategy which animals use to specifically target a unique antigen.

Whether antibodies are tethered or secreted, the constant region may be assembled from distinct genes that in turn yield different antibody isotypes, such as IgG, IgM, IgD, IgA and IgE. Each of these isotypes has different physical properties and different functions in the animal’s body. IgM is the first immunoglobulin isotope to be expressed during B-cell development, and although IgM is an early responder, it has a low affinity against antigen compared to the IgG isotypes. IgG antibodies consist of four subclasses – IgG1, IgG2, IgG3 and IgG4 – and are named in order of abundance in serum.

Relationship of the Innate and Acquired Immune Systems
Initially it was thought that the innate and acquired immune systems functioned independently. However, it is now known that these two arms communicate with one another, and to some extent, rely on similar communication molecules such as interleukin 1B. This molecule, for example, is released by neutrophils when activated by invading pathogens. This stimulates the acquired immune system as a feedback system to start the process for antibody production.
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 can help to:

- Reduce somatic cell count
- Reduce cases of mastitis
- Reduce cases of metritis
- Reduce death loss and culls
- Reduce cows in hospital pen
- Increase milk production
- Improve reproduction

A Cow’s Healthy Immune System Starts with Good Nutrition

Good herd health starts with good nutrition, and good nutrition is required to help maintain a healthy immune system in dairy cows.

When cows are under stress from the strains of production and reproduction, or molds and mycotoxins in feed and pathogens in the environment, their natural immune system goes to work fighting off those challenges. In an ongoing fight, the cow’s immune system itself can begin to weaken.

That’s why good nutrition is so important, including sufficient energy, fiber, vitamins, trace minerals and the special nutritional supplements your nutritionist or veterinarian may recommend.

Summary

The immune system provides protection from infections and disease-causing organisms. First and immediate response to pathogens is the responsibility of a specific group of white blood cells (macrophages and neutrophils) that comprise a portion of the innate immune system. These leucocytes continually monitor for sites of infection and provide protection until the cow can mount an antibody response.

The adaptive or antibody mediated immune system, which is a pathogen-specific immune response, involves the formation of antibodies. T- and B-cells are cells of the adaptive immune system responsible for the production of antibodies that provide long-term protection against numerous types of pathogens and other disease-causing agents.

Transition Cow Diseases and Their Causes

- Mastitis – infectious
- Metritis – infectious
- Retained placenta – metabolic, immunity
- Ketosis – metabolic
- Fatty liver – metabolic
- Milk fever – metabolic
- Acidosis – metabolic
- Laminitis – metabolic with microbial origin

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Prince Agri Products has earned the American Feed Industry Association Safe Feed/Safe Food certification for the production and delivery of a safe and quality feed supply for the growth and care of food producing animals. Company facilities at Marion-IA and Quincy-IL hold valid certification under this program.