

Current concepts in dairy cattle immunology

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Abstract

Protection from disease-causing organisms is critical to the survival of cattle in all production systems. The immune system is composed of organs, tissues, and cells tasked with providing protection from invading pathogens. The first line of protection of pathogens relies on physical, chemical, and mechanical barriers to invasion. Durable tissues, harsh environmental conditions, and targeted chemical defenses provide continuous protection. When these barriers are breached, innate immune cells use molecular patterns common to large groups of pathogens to quickly recognize and respond to invaders. Innate immune cells also serve to alert and activate adaptive immune cells through the process of antigen presentation. As an infection progresses, adaptive immune cells (lymphocytes) produce molecules, including cytokines and antibodies, that direct innate immune cells to clear pathogens from the host. The purpose of these proceedings is to discuss each of these defenses to provide an understanding of immune protection in cattle.

Key words: bovine, dairy, immunology

Résumé

La protection contre les organismes qui causent des maladies est essentielle à la survie du bétail dans tous les systèmes de production. Le système immunitaire se compose d'organes, de tissus et de cellules dont la tâche est de protéger l'animal contre les agents pathogènes envahisseurs. Les barrières physiques, chimiques et mécaniques contre l'invasion sont la première ligne de défense contre les agents pathogènes. Les tissus résistants, les conditions environnementales difficiles et les défenses chimiques ciblées fournissent une protection de tout instant. Lorsque ces barrières sont assiégées, les cellules de l'immunité innée utilisent des structures moléculaires que se partagent de grands groupes de pathogènes pour reconnaître et réagir rapidement aux envahisseurs. Les cellules de l'immunité innée servent aussi à alerter et à activer les cellules du système immunitaire adaptatif via le processus de présentation des antigènes. Durant la progression de l'infection, les cellules du système immunitaire adaptatif (lymphocytes) produisent des molécules comme les cytokines et les anticorps qui dirigent les cellules de l'immunité innée afin d'éliminer les agents pathogènes de l'hôte. Le but de cette présentation est de discuter chaque type de défense pour approfondir les connaissances sur la protection immunitaire chez le bétail.

Introduction

Protection from disease-causing organisms is critical to the survival of cattle in all production systems. The immune system is composed of organs, tissues, and cells tasked with providing protection from invading pathogens. These proceedings will provide an overview of how the structure and function of the immune system work in concert to protect the host from disease.

Anatomy of the Immune System

Generally, the anatomical structures associated with immune defense can be separated into three broad systems. First, a barrier defense systems exists to create inhospitable conditions for invading pathogens. Second, a systemic immune system provides surveillance and defense against invasion into internal organs. Finally, a mucosal immune system provides surveillance and defense against invasion via mucosal surfaces.

The barrier defense system is a series of physical, mechanical, and chemical obstructions to invasion via several common routes of entry into the animal. Physical barriers to infection include tight junctions between epithelial cells that seal pathogens out of sensitive, sterile internal environments. Many layers of relatively dry squamous cells of the skin also provide an inhospitable environment for pathogens that would gain entry via a transdermal route. Mechanical barriers to infection include the flushing action of secretions across sensitive surfaces (e.g. tears, respiratory secretions) as well as the uni-directional flow of ingesta and urine through the GI and urogenital tracts, respectively. Fluid and air flow help displace potential pathogens from the host. Finally, low pH conditions in the stomach and antibacterial systems in the respiratory, mammary, and ocular systems kill pathogens in areas sensitive to infection.

The systemic immune system is composed of organs (thymus, spleen, lymph nodes, bone marrow), transport paths (lymph vessels, blood vessels), and cells (Dendritic cells, macrophages, phagocytes, etc) that survey for and respond to threats in the vasculature and internal tissues. The central area of activity in a mature immune system is the lymph node. Lymph nodes serve as a common area where both T and B lymphocytes and antigen presenting cells (APC) can interact. Tissue fluid containing antigen-bearing APCs flows from all points in the body to regional draining lymph nodes via afferent lymph vessels. T and B lymphocytes interact with the APC in the lymph nodes and circulate out of the lymph node

via efferent lymph vessels. Lymph fluid ultimately returns to the vasculature via the thoracic duct. Lymphocytes then home back to lymph nodes either by specialized venules (naïve lymphocytes) or by extravasating in tissues and returning via the tissue fluid route.

The mucosal immune system is comprised of specialized tissues located on mucosal surfaces known as mucosa-associated lymphoid tissue (MALT). MALT tissue takes two basic forms. First, tonsils are immune organs designed to survey incoming materials, including air and ingesta, for the presence of pathogens. Tonsils have many of the same characteristics as lymph nodes with the notable exception that tonsils are located on mucosal surfaces and have exposure to air and ingesta to allow sampling and surveillance. The second type of MALT takes the form of discrete areas of lymphoid tissue in various locations across all mucosal surfaces. The most well-known form of this type of tissue is the Peyer's patch in the small intestine. Peyer's patches contain specialized cells designed to sample intestinal lumen contents as well as APCs and Lymphocytes. Lymphocytes of activated at one mucosal site travel to mucosal sites distant from the point of activation.

Immune System Function

An immune response is a tightly control sequence of events that is designed to control pathogens quickly while minimizing damage to the host. Successful immune responses proceed through a series of 4 stages. First, pathogens invade the host and are recognized as foreign and potentially dangerous. Second, innate immune functions act quickly to control spread and limit damage associated with the pathogen. Third, innate immune cells communicate with cells from the adaptive immune system to initiate a targeted adaptive immune response to eliminate the pathogen. Fourth and finally, the adaptive immune system eliminates the infection, resolves damage, and generates long-lived memory to prevent future infections by the same pathogen.

The first step, pathogen invasion and recognition, occurs locally in the area of the host where invasion occurs. Sentinel cells, including dendritic cells, macrophages, and mast cells are equipped with pattern recognition receptors (PRRs). PRRs recognize molecular patterns that are common to certain classes of pathogens. An important class of PRRs are the Toll-like receptors (TLRs). TLR binding indicates the presence of a pathogen invader and triggers inflammation in the host. For example, TLR4 recognizes lipopolysaccharide found on gram negative bacteria. TLRs are found either on the surface of sentinel cells to detect the presence of extracellular pathogens or in vesicles inside the cells to detect the presence of intracellular bacteria and viruses. Other systems can also play a role in pathogen recognition. Complement fixation produces molecules that draw phagocytes to the site of infection. Also, physical damage to cells and the resulting leakage of enzymes into the extracellular space can trigger inflammation.

The second step in an immune response is characterized by rapid activation of innate immune defenses to limit the spread of infection and the resulting damage. Once a PRR is activated, the innate immune systems uses localized measures to inactivate pathogens. Less-than-specific responses like phagocytosis, oxidative burst, etc. to capture and remove pathogens. Innate immune cells also produce many cytokines that elicit inflammatory effects. Vasoactive cytokines result in increased vascular permeability to ease delivery of cells and serum components to sites of inflammation. Other cytokines activate tissues to increase fibroblast and phagocyte production. Cytokines also serve as chemotactic agents that draw more immune cells to the site of inflammation.

An important step in the inflammatory process is the communication between innate immune cells and lymphocytes. Antigen presenting cells recruited the site of inflammation collect antigens and carry them back to the draining lymph node for presentation to helper T lymphocytes. APCs process antigens into small peptide chains and present them to the T cells on major histocompatibility complex II (MHCII). APCs and T cells in lymph nodes essentially perform a version of cellular speed dating in which various T cells assess the fit of T cell receptor for the antigen expressed on MHCII by the APC. Once a T cell binds to the antigen displayed by the APC, the T cell becomes activated and begins to replicate itself to form a large population of identical T Cells. During the process of activation, the APC also supplies additional information to the T cell in the form of cytokines that convey the circumstances of the activation. Based on the cytokines it detects, T cells will either differentiate into T helper 1 or T helper 2 lymphocytes (TH1 or TH2, respectively).

Antigen presentation can also occur via presentation on MHC I. MHC 1 molecules are found on nearly all cells in the body and are used to give surveying immune cells a snapshot of the protein profile being made inside a cell. During intracellular infections, pathogen proteins are degraded, loaded onto MHC I, and displayed in the same way that host proteins are in homeostatic conditions. Naïve cytotoxic T lymphocytes patrol the MHC I receptors and destroy any cell that harbors a protein sequence recognized by the cytotoxic T lymphocyte. Cells that are carrying non-self proteins are force to undergo apoptosis by cytotoxic T cells and professional antigen presenting cells collect the debris and display it to T helper cells on MHC II. In this way, T helper cells can provide cytokine stimulation to cytotoxic t cells as well.

B lymphocytes must also be activated to produce a complete immune response. First, a B cell must bind its cognate antigen before it can become activated. B cells typically reside in lymph nodes where they can sample antigens in lymph fluid draining from sites of inflammation. Once antigen is bound, B cells internalize the antigen and express it on MHCII. When displayed to a T cell recognizes the antigen bound on the B cell, the T cell can become activated itself and can also provide stimulation to the B cell to allow differentiation in to

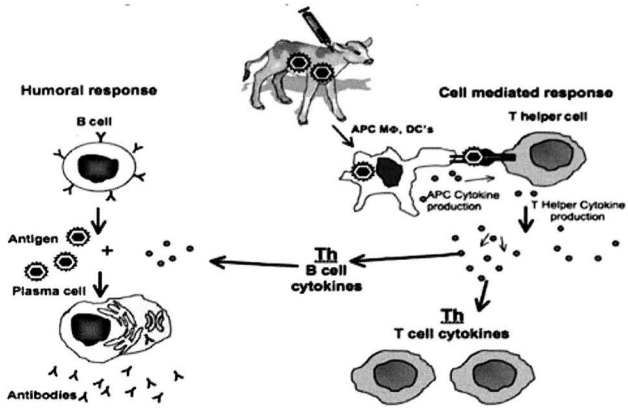


Figure 1. Summary of an immune response. Courtesy of Dr. Chris Chase, South Dakota State University. Used with permission.

an antibody secreting plasma cell. See Figure 1 for a schematic summarizing an immune response.

As the immune system gains the upper hand against the pathogens, the process of winding down the immune response begins. Specialized cells, including macrophages and regulatory T lymphocytes down-regulate inflammation and initiate tissue repair and healing. Simultaneously, memory T and B lymphocytes develop in order to provide

long-lived immune memory so that if the pathogen in question is encountered again, it can be quickly removed before it can damage the host.

Conclusion

Immunity of pathogens is a carefully orchestrated balance between destroying invading organisms and protecting host tissues and homeostasis. The structure of immune tissues allows rapid identification and response to pathogens and well-regulated effector cells and molecules are produced to quickly remove the invader and protect the host from further damage.

Acknowledgements

The author gratefully acknowledges the assistance and contributions of material from Dr. Chris Chase. The author declares no conflict of interest.

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