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A short review: the immune system of the dairy calf and the importance of colostrum IGG

Abstract

The immune system of calves is a very complex system including neutrophils and macrophages, and adaptive cells, such as B cells and T cells. At birth the immune system of the calf is functionally limited, resulting in heavy reliance on nonspecific innate functions. Specific adaptive functions develop as calves age making the initial 4 to 5weeks after birth the most likely time for calves to experience disease. Colostrum feeding after birth provides IgG, which enhances the innate responses by joining them with adaptive specificity provided by the maternal immune system. Research continues to understand the complex immune system of the dairy calf and how colostrogenesis and the absorption of colostrum provide the needed immunity that the dairy calf requires. Despite extensive investigation into factors affecting IgG absorption, the exact mechanism of absorption is yet to be elucidated, which could improve our ability to enhance immune function in the young dairy calf.

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Overview of the immune system

The cells of the immune system can be divided into innate cells, including neutrophils and macrophages, and adaptive cells, such as B cells and T cells. Each of these groups of cells is important for recognizing and removing foreign organisms from the host. The innate cells recognize foreign antigens based on patterns found on the surface of foreign cells that are not present on host cells.[1] Lipopolysaccharide is an example of an antigen expressed on the surface of multiple different types of bacterial cells, but not mammalian cells. Due to the general nature of these receptors, innate cells have no "memory" and cannot distinguish specific organisms. They simply determine whether an encountered cell is "self" or "nonself".[1] In contrast, adaptive immune cells produce receptors that recognize specific antigens and thus are able to distinguish and remember individual foreign species and generate different types of immune responses depending on the type of antigen.[2]

Upon recognition of a foreign antigen, neutrophils and macrophages will initiate phagocytosis and release cytokines and reactive oxygen species into the surrounding area.[3] Phagocytosed organisms will be digested within the lysosome resulting in multiple antigenic particles which can then be presented by macrophages and dendritic cells to B and T cells to initiate cell replication and production of receptors specific for the presented antigen.[2] Upon initial activation, B cells begin to secrete large numbers of antigen-specific Ig molecules. The first Ig subclass produced is IgM, which has lower antigen-binding affinity compared to other Ig subclasses but can efficiently activate complement proteins to assemble and disrupt pathogenic membranes.[2] As the immune response continues, B cells will switch to produce other subclasses of Ig, including IgG.[4] CD_4+ helper T cells assist in this process through receptor stimulation and cytokine production.[5] Similar to IgM, IgG also activates complement proteins, but is a smaller molecule than IgM.[2] Thus, while IgM remains mainly in circulation, IgG is readily transferred across various membranes within the body.[6] In addition to complement activation, IgG can also neutralize antigens and mark them for phagocytosis by macrophages and neutrophils thereby increasing the efficiency of the innate immune response.[3,7]

Cytokines are protein signaling molecules that may be secreted by multiple cell types, but immune cells are the main producers of cytokine signals; receptors exist on the surface of most cells in the body.[1] Interleukin 1β (IL_{1B}), tumor necrosis factor α(TNF) and the T cell secreted interferon γ (IFNG) are three examples of generally pro-inflammatory cytokines. Interleukins 10 (IL_{10}) and 4 (IL_4) are examples of generally anti-inflammatory cytokines. Both IL_{1B} and TNF are secreted by activated macrophages to induce acute inflammation including fever, blood vessel dilation, and acute phase protein production.[2,8] These cytokines are also important in the process of antigen presentation in macrophage-dependent T cell activation.[8,9] Despite similar source and systemic response, IL_{1B} and TNF differ in the kinetics of their response. Release of TNF accelerates rapidly following exposure to antigen, peaking within 2hours and is hastily eliminated such that it is no longer detectable 8hours after initial exposure.[10,11] In contrast, IL_{1B} production occurs more slowly reaching detectable concentration approximately 4hours after exposure and remaining high for severaldays.[10]

While IL1B and TNF are generally associated with innate cell response, IFNG is produced by cytotoxic (CD_8+) and helper 1 (CD_4+) T cells and directs the ensuing adaptive response. Production of IFNG promotes a CD_4+ T helper 1-type immune response, which is driven by recognition and removal of pathogen by macrophages and elimination of injured or infected host cells by CD_8+ T cells.[12,13] This is accomplished by down regulating antibody production by B cells, activating macrophages and enhancing T cell function by increasing the expression of major histocompatibility complex (MHC) molecules on immune and non-immune cells.[13] A CD_4+ T helper type-2 immune response is characterized by less systemic inflammation, reduced T cell activity, high antibody production by B cells and occurs in the presence of high IL_4 and IL_{10}.[14] Both of these cytokines are produced by cells of the placenta and thus, the immune response of the newborn calf is predominantly a CD_4+ T helper type-2 response.[15]

Immune system of the neonatal calf

Early in the study of immunity, researchers began investigating whether protection from disease was transferable from mother to

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offspring. Results from these early studies were summarized by Ratner et al.[16] In some species, when the neonate was infected immediately after birth with a disease to which the mother had recovered, the newborn was not severely affected; however, this mechanism did not seem to function in goats, cattle, or sheep.[16] Subsequent experiments, measuring what were first called "agglutinins" and eventually Igs, reported that these molecules were undetectable in calf plasma at birth but increased if calves consumed colostrums.[17,18] Ratner et al.[16] were among the first to suggest that the absence of these protective molecules in neonatal calves was due to placental structure.[16]

As a result of placental inhibition of Ig transport and protection from foreign antigen in utero, calves are born with an immune system that is antigenically naïve. Thus, the adaptive immune cells in neonatal calves are incapable of recognizing foreign antigens until the foreign cells are first recognized, phagocytosed, digested, transported, and antigens are presented by innate immune cells in lymphoid tissues. The adaptive system is further handicapped by high concentrations of hormones (e.g. cortisol and prostaglandin E_2) and cytokines (e.g. IL_4 and IL_{10}) produced during pregnancy and parturition, which suppress T cell function and bias the adaptive response towards a CD_4+ T helper type-2 response.[13,15,19] Unfortunately, neonatal B cells, the focal point of this type of response are present in very low numbers at birth and not completely functional until 4 to 5weeks of age.[20]

In addition to low B cell numbers, CD_4+ T cells are also low in newborn calves making up only 16% of the peripheral T cell population. These cells account for 30% of peripheral T cells in adult cattle.[21] In place of these adaptive cells, neonatal calves have greater numbers of circulating neutrophils and γδ+ T cells.[22,23] It is likely that, given the limitations of the adaptive immune response, neonatal calves have evolved to depend more heavily on the innate functions of their immune system. This may explain the very high proportions of peripheral γδ+ T cells, which are able to recognize antigen using receptors similar to those of innate immune cells.[24] This allows γδ+ T cells to generate T cell type responses to foreign cells without the added step of antigen presentation. γδ+ T cells are also able to perform a wider array of functions than either CD_4+ or CD_8+ T cells including recruitment of innate cells, induction of cell death, and production of proinflammatory and anti-inflammatory cytokines.[24] High numbers of γδ+ T cells in circulation grants the neonatal calf much more flexibility in immune response and may help compensate for the slower response observed by other members of the adaptive system.

Importance of immunoglobuling in the dairy calf

Benefits of an adaptive system include a rapid, targeted, multifaceted response utilizing multiple cell types and the complement protein system to eliminate the foreign body. Adaptive cells also produce a wider array of specific receptors, which reduce the risk of invading cells passing unnoticed by the immune system. This response is a cell-mediated, specific response that can effectively eliminate foreign cells with minimal destruction to host cells.[25] In contrast, the innate response is limited mainly to the neutrophilic release of reactive oxygen species and phagocytosis, which can result in excessive inflammation and damage to host tissues,[1] Secreted Ig molecules can partially bridge the gap between the innate and adaptive systems by broadening the array of antigens recognized to alert innate cells to the presence of an invading organism and by activating the system of complement proteins to assist in eliminating the organism.[2,7]

Immunoglobulin G molecules are produced by activated B cells following exposure to a specific antigen.[2] Upon secretion, these molecules enter general circulation via lymph fluid and may be transported from the blood into most tissues with the exception of the brain.[6,7] There are 2 regions to each IgG molecule: the variable or antigen-specific region (F_{ab}) and the constant or signaling region (F_c). The F_{ab} region is specific, binding only to the antigen to which its parent B cell was activated. Regardless of the antigen recognized by the F_{ab} region, the F_c region translates an identical signal to neutrophils, macrophages, and other immune cells to initiate phagocytosis.[7] If the F_c region is not quickly recognized by a phagocytic cell, circulating complement proteins may also recognize the bound IgG molecule and initiate a cascade of proteins leading to eventual lysis of the foreign cell.[26] These two regions allow IgG to combine the innate response with adaptive specificity. During the period of colostrogenesis, approximately 3 to 4weeks prior to parturition, the bovine mammary gland begins to selectively transfer IgG from blood circulation into the forming colostrums.[27] There are two subclasses of bovine IgG: IgG_1 and IgG_2.[28] Both subclasses are present in colostrum; however, IgG_1 makes up 85 to 90% of the total IgG thus the majority of this reveiw will focus on IgG.[29–31] The total concentration of IgG in bovine colostrum is highly variable ranging from 11mg/mL to 221mg/mL.[32,27] Factors that can affect colostrum IgG concentration include time when colostrum is collected relative to parturition, parity, dry period length and energy intake during pregnancy.[32–34]

Early researchers observed that when calves were fed colostrum within 24 after birth, the IgG molecules that were in the colostrum appeared and were functional in the blood of the calves.[35,18] Since then a plethora of studies have been done investigating various means of increasing calves' ability absorb IgG. Hall et al.[36] and Kamada et al.[37] demonstrated enhanced IgG absorption with selenium supplementation directly in colostrum or via inclusion in the diet of the prepartum cow. Others supplemented pregnant cattle with nicotinic acid, iodine, lactoferrin and fatty acids with little to no effect on IgG absorption.[38–41]

Despite extensive investigation into factors affecting IgG absorption, the exact mechanism of absorption is yet to be elucidated. Based on data from several studies showing a consistent increase in serum IgG with increasing ingestion of IgG from colostrum, a nonspecific mechanism has been assumed for IgG absorption in neonatal calves.[42–44] This assumption is reflected in the terms successful and failure of "passive transfer of immunity" used to describe calves that achieve serum IgG concentrations above or below 10mg/mL, respectively.[45] Htun et al.[46] reported increased serum IgG and IgG absorption efficiency when difructose anhydride III, a molecule that interacts with tight junctions to improve nutrient absorption, was included in the colostrum. This implies that tight junctions may be at least partially involved in absorption. Data from rodents indicate that at least 80% of IgG present in the serum of neonatal mice and rats is selectively transported in vacuoles via the neonatal Fc receptor (FcRn) present in the neonatal gut lumen.[47] Studies conducted using neonatal ruminants have identified FcRn on crypt cells but not enterocytic cells, implying FcRn involvement in IgG recycling into the gut lumen, rather than absorption.[48] Studies have not been done to determine presence of FcRn within the intestine of the neonatal calf; however, the inability of calves to absorb insulin-like growth factor-1 (IGF_1) with the same efficiency as IgG implies that the neonatal bovine gut exhibits some degree of selectivity of absorption.[49] Further research is needed to fully characterize the mechanism of absorption and factors that may manipulate it.

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Conclusion

The immune system of calves at birth is functionally limited, resulting in heavy reliance on nonspecific innate functions. Specific adaptive functions develop as calves age making the initial 4 to 5weeks after birth the most likely time for calves to experience disease. Feeding colostrum immediately after birth provides IgG, which enhances the innate responses by joining them with adaptive specificity provided by the maternal immune system. Further research is necessary to understand how passage of maternal immunity occurs to enable more directed studies for improving the process.

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Conflict of interest

Author declares that there is no conflict of interest.

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