Alteration in Immune Responsiveness During the Peripartum Period and Its Ramification on Dairy Cow and Calf Health

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ABSTRACT

Substantial evidence indicates that innate and acquired defense mechanisms are lowest from 3 wk precalving to 3 wk postcalving. This lowered responsiveness includes aspects of systemic and mammary gland immunity that may account, at least in part, for the increased incidence of peripartum disease. The physical and metabolic stresses of pregnancy, calving, and lactation may contribute to this decrease in host resistance and the subsequent increase in disease incidence. However, variation among cows in their host resistance mechanisms suggests that genotype and phenotype may possibly be used to identify cows that are able to mount beneficial immune responses over the periparturient period. Our own studies suggest that cows may be categorized as high or low responders based on the peripartum antibody responses to ovalbumin and Escherichia coli J5. Low responders were hyporesponsive to these test antigens and had a higher incidence of peripartum diseases, particularly mastitis. In many species, a functional link exists between the immune and endocrine systems, and, during periods of stress or physical injury, neuropeptides and neuroendocrine hormones function as immunomodulators. Initial investigations of peripartum cows reveal positive relationships between growth hormone kinetics and profiles of antibody response. Whether hormone fluctuations during the periparturient period are responsible for the alterations observed in immune responsiveness remains uncertain.

(Key words: immune response, periparturient period, health, mastitis)

Abbreviation key: BoLA = bovine lymphocyte antigen, GH = growth hormone, IL = interleukin, MHC = major histocompatibility complex, PBL = peripheral blood lymphocytes, PMN = polymorphonuclear neutrophilic leukocyte.

INTRODUCTION

The modern dairy cow is unique in her experience of repeated lifetime cycles of pregnancy and parturition, followed by lengthy lactations producing high volumes of milk. Alterations in host defense mechanisms that occur during the periparturient period and associated with changes in hormone profiles and metabolic and physical stresses of parturition. These changes may contribute to the high incidence of disease experienced by the periparturient cow. Evidence that changes in both immune function(35, 36, 38) and nonspecific host defense mechanisms (24, 27, 37, 56, 70) occur in the peripartum dairy cow have been accumulating for some time. Previous and ongoing investigations that report impairment of periparturient immune mechanisms and innate host resistance mechanisms are described, as is the current understanding of how neuroendocrine and genetic factors interact during the peripartum period to influence immune system homeostasis. The potential function of these factors to alter host defense mechanisms and influence cow and calf health is also discussed. Because of the prevalence and economic relevance of mastitis, emphasis is placed on the role of these factors in resistance to mastitis. A comprehensive description of the ruminant immune system and the characterization of the response within the bovine mammary gland are reviewed elsewhere and are mentioned here only as they relate to the health of periparturient cows or calves.

THE PERIPARTURIENT COW

The alteration of immune and innate host resistance mechanisms of the dairy cow normally begins approximately 3 wk prior to calving, is maximal
at parturition, and continues until 3 wk after calving. Although this pattern is somewhat dependent upon the parameter under investigation, it serves as a useful criterion for defining the peripartum period when various aspects of host defense may be depressed and disease incidence is high.

The Immune System in Local and Systemic Infection

Early work by Newbould (56), Guidry et al. (27), and others (37, 54) showed that polymorphonuclear neutrophilic leukocyte (PMN) function was impaired during the peripartum period. Those researchers speculated that attenuated PMN function contributed to the increased incidence of mastitis postpartum. Although the role of PMN and peripheral blood lymphocytes (PBL) in systemic immunity and host response to infectious disease had been established, it was important to link the functional role of these cells with local protection of the mammary gland. Parallel and subsequent studies went on to show that the incidence of clinical mastitis is higher in cows with low respiratory burst activity of PMN (31, 88) and that the severity of Escherichia coli mastitis depends on the speed at which PMN are mobilized from the peripheral blood, as well as the opsonic activity within the gland (32). A recent study of 46 healthy dairy cows and 51 diseased dairy cows reported that impaired PMN function was clearly associated with the establishment of peripartum metritis and mastitis (11), that some PMN functional defects were apparent before calving in these cows, and that impaired function may be a predisposing factor in the development of these disorders (11). Clearly, PMN chemotaxis, diapedesis, phagocytosis, and killing each contribute to ability of the neutrophils to provide an effective first line of defense for the bovine mammary gland.

It is also apparent that peripartum changes in subpopulations of lymphocytes vary between peripheral blood and supramammary lymph nodes from normal and mastitic cows (87). By use of simple immunofluorescence techniques, decreases in absolute numbers of B and T lymphocytes (63 and 40%, respectively) in peripheral blood were noted during acute bacterial mastitis. Conversely, the draining supramammary lymph nodes of mastitic cows, but not healthy cows, showed increases in numbers of B and T cells (319 and 117%, respectively) that were likely due to local multiplication or recruitment from other lymphoid sites (87). Although changes in lymphocyte number or proportion do not necessarily relate directly to lymphoid function, alterations in lymphocyte subsets, particularly the ratios of CD4 to CD8 have been associated with immunosuppressive diseases in various species.

That concentrations of Ig-bearing plasma cells, cytophilic IgG2, and specific antibody increase with IMI has been consistently reported (4, 64, 74, 82, 83). However, whether antibody is truly relevant to protection against mastitis is still debated. Three antibody-mediated mechanisms that may associate with mastitis protection have been proposed: the opsonizing ability of cytophilic IgM and IgG on phagocytic cells entering the mammary gland, the production of specific antibody against surface antigen structures, and enhanced priming of early inflammatory responses in the gland following intramammary challenge (83). In addition, colonization of the teat end and teat sinus by bacteria, such as Staphylococcus aureus, seems dependent on its adhesive properties, which can be blocked by specific antibody (42, 83). Although mammary gland colonization by Gram-negative bacteria is not generally dependent on adhesions, a surface structure on E. coli (curli) may be involved in colonization of fibronectin-coated surfaces (42). In either case, it has proved difficult to develop efficacious mastitis vaccines that induce antibodies, except for the most recent Gram-negative core mutant products. This situation likely reflects the complex nature of immunity and the lack of understanding concerning the induction of protective immunity in unique immunological compartments, such as the mammary gland.

Previous investigations have revealed that serum IgG concentrations decreased at parturition (19, 38) and suggested that low IgG2 was associated with an increased incidence of pyogenic mastitis (74) and calf pneumonia (16). More recent studies also showed that Holstein cows in the peripartum period that had high antibody responses to ovalbumin in blood and milk had lower incidence of disease, including clinical mastitis, than did cows with lower antibody responses (51, 81). Several studies demonstrated the ability of bovine cytokines, such as interleukin-2, to increase the number of antibody secreting cells in the mammary gland (57, 64) and to enhance the responsiveness of mononuclear cells of the mammary gland (78). Other cytokines were employed in vivo or in vitro, including interferon-γ, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor, and have been shown to enhance nonspecific aspects of mammary gland defense (64, 68, 75). However, recombinant cytokines have often been expressed in E. coli systems, which make it difficult to distinguish precisely the cytokine effects from
lipopolysaccharide contamination, particularly because lipopolysaccharide is known to induce a tumor necrosis factor-α, interleukin (IL)-1, and IL-6 cascade. Nonetheless, selective cytokine therapy may be applicable for enhancing particular aspects of mammary gland defense during the peripartum period.

Although a number of integrative factors mediate host defense, collectively these studies demonstrate that leukocytes or their secreted products—derived from blood or mucosal sites (such as the gut) or produced locally—can contribute to protection of the bovine mammary gland against infectious agents.

**Lymphocyte Proliferative Responses**

Lymphocytes, broadly categorized into B- and T-cell subsets, are the cells of the immune system that are responsible for specific recognition of antigen. The B lymphocytes express surface Ig and are the precursors of plasma cells that synthesize antibodies. Each individual must be able to produce thousands of different antibody molecules in order to identify the large array of potential antigens and pathogens. Briefly, the effector functions of antibodies include their ability to bind to antigen and to increase phagocytosis or killing by PMN and macrophages, complement activation, direct inactivation of virus or toxin, and enhancement of antigen clearance.

The T lymphocytes are divided into discrete subpopulations based on the expression of cell surface receptors. Different T-cell subpopulations function to aid in antibody production and cytolytic cell function (T-helper cells), to induce particular inflammatory responses (T-delayed type hypersensitivity), and to kill specific target cells (T-cytotoxic cells). These functions are mediated by the production of a wide range of cytokines and enzymes. Both B- and T-lymphocyte populations exhibit immunological memory for antigen, which accounts for the more rapid and heightened response following repeated exposure to antigen. Measures of lymphocyte activity, such as antibody and cytokine production, cytotoxicity, and proliferation, have been used to indicate the functional status of the immune system.

Numerous investigations (35, 36, 38, 55, 70) have reported diminished lymphocyte responsiveness around calving. Studies by Kehrli et al. (38) utilizing Holstein heifers demonstrated that PBL response to mitogen declined steadily from 2 wk prepartum until the week of calving and then began to increase again at wk 2 postcalving. This diminishing response was substantiated by Saad et al. (70), who reported a steady decline in lymphocyte response of Swedish Red and White cows to mitogen from 3 wk precalving through to parturition and recovery at about wk 2 or 3 postpartum. Those groups (38, 70) speculated on the ability of reproductive hormones and glucocorticoids to modulate this response in vivo. It was also suggested that reduced blastogenesis of milk lymphocytes might be due to the presence of cells or molecules that have suppressive capacity (28). Another study (55) of 10 lactating Holsteins indicated that cows could be grouped based on changes in lymphocyte blastogenic responses during acute clinical mastitis and that these response profiles were associated with changes in cortisol concentrations. Those observations provide some support for the notion that altered lymphocyte responsiveness around calving is linked to increased mastitis susceptibility and that peripartum hormone changes may be influential.

Recent unpublished studies of Canadian Holsteins further confirm a decrease in lymphocyte blastogenic response to the T-cell mitogen concanavalin A and the ovalbumin antigen around calving (81). Cortisol, growth hormone (GH), IGF-I, and disease incidence each contributed (P ≤ 0.05) to the variation in PBL proliferative response to mitogen from 3 wk precalving to 3 wk postcalving (81). Only cortisol influenced the response to ovalbumin (81). Previous studies by Burton et al. (9) and Chang et al. (13) also indicated that GH and IGF-I were associated with PBL blastogenic responses; however, in vitro addition of hormones to PBL blastogenesis cultures or injectable recombinant bST can have effects opposing those associations that exist in vivo. Cumulative studies lend support to the concept that hormone fluctuations are involved in the alterations occurring during peripartum PBL blastogenesis, but those studies do not necessarily confirm a cause and effect relationship. More definitive studies need to be designed to determine the precise effects of these hormones on immune status during the peripartum period.

**Antibody Responses**

An examination (51, 81) of antibody response to ovalbumin and *E. coli* J5 (Rhône-Merieux, Lenexa, KS) indicates that cows can be categorized by phenotypes for high or low immune response, based on the magnitude and kinetics of the response during the peripartum period. Approximately one-third of the cows in this trial showed no indication of depressed serum antibody responses to ovalbumin peripartum but had responses that were above average after the immunizations given at 8 and 3 wk precalving and at calving. The remaining cows exhibited varying patterns of hyporesponsiveness following peripartum im-
munization. One group did not respond to ovalbumin given at calving and the other group did not respond to ovalbumin given 3 wk precalving or at calving. All cows responded to the ovalbumin immunization given 8 wk precalving. These patterns of response were independent of cow parity (51, 81). Noteworthy is that cows of the high responding phenotype also tended ($P \leq 0.10$) to have higher antibody responses to E. coli J5 at calving (51, 81). If higher peripartum antibody responses are confirmed to be of benefit, then, because of the generally moderate to high heritability estimates for specific antibody responses, it should be possible to select genetically for increased antibody responsiveness of peripartum cows.

Correlation analysis indicated that peripartum responses to ovalbumin in serum and whey antibody were positively associated with GH concentration in serum but negatively associated with IGF-I (51, 81). Our unpublished observations showed that the associations between hormone and peripartum antibody response tended to be opposite of those associations with PBL blastogenesis during the same period. Positive associations between GH and antibody have been previously reported in dairy cows treated with recombinant bST (8, 10, 40). A recent study by Eppard et al. (21) indicated that bST administered to peripartum Jersey cows decreased the incidence of clinical mastitis, but not ketosis. Again, this result may reflect certain immunoenhancing properties of GH, and, therefore, it may be pertinent to identify cows that have innately higher peripartum concentrations of GH.

**Lymphocyte Subsets and Adhesion Molecule Profiles**

Using flow cytometry and specific monoclonal antibodies, mononuclear cell subpopulation in peripheral blood, mammary gland tissue, and mammary gland secretions of dairy cows have been shown to vary over the peripartum period (59, 72, 77). Specifically, the percentage of T cells was lowest in milk (16%) during the peripartum period, but increased to 62% in late lactation. Conversely, the percentage of B cells and macrophages were reported as 25 and 69%, respectively, during the same period, but declined in late lactation to 7 and 21%, respectively (59). The ratios of CD4 to CD8 T cells in the blood of dairy cows have varied depending on stage of lactation, but can be as high as 3:1 around calving (33, 43, 59, 72). In general, the ratio of CD4 to CD8 was lower in milk than in blood, indicating a higher proportion of CD8+ cells in the mammary gland; however, no clear lactational patterns appear (33, 43, 59, 72, 77). In human colostrum from healthy individuals, the ratios of CD4 to CD8 were also low compared with ratios in peripheral blood (62, 69), and lymphocytes from mammary gland secretions were hyporesponsive to mitogens and antigens in a variety of species (28, 30, 62, 69). The reasons for these diminished responses are not entirely clear but are thought to relate to distinct lymphocyte subpopulations and to the high proportions of memory T cells in the lactating mammary gland. Similar unique combinations of lymphocyte subsets with immunomodulating capacity have recently been reported for cows (61).

Recent studies that examined the peripartum variation in mononuclear cell subsets in milk and blood from Holsteins support and extend the findings of Park et al. (59, 60) and Hurley et al. (33) in that the proportion of certain T-cell subsets decreased dramatically around calving, but B cells did not (43). In addition, the proportions of T lymphocytes precalving and at calving were also significantly lower than those of nonpregnant, nonlactating cows of the same breed (43). Our unpublished results showed that, in a subset of cows (n = 10), the proportion of CD2+, CD4+, CD8+, and major histocompatibility complex (MHC) class II+ lymphocytes were also markedly lower in milk than in blood following parturition and that GH and IGF-I may influence these cellular profiles (34). Conversely, the proportion of γδ T lymphocytes, as identified by the 215/230-kDa WC1 surface antigen (MAb-IL-A29; VMRD, Pullman, WA) was significantly greater in milk than blood at wk 0, 6, and 16 postcalving.

Park et al. (59) reported an increase in the number of CD8+ T cells expressing a unique activation molecule, ACT2, that was present in milk. Subsequent studies (61) revealed that this subset of cells also expressed the γδ TcR/N12, but not the γδ TcR/N6 marker (61). Results of those studies suggest that increases in this cell subset are linked to the dysfunction of CD4+ cell-mediated immune responses in the mammary gland because the removal of CD8+, ACT2+, and N12+ cells increased antigen responsiveness of mammary gland lymphocytes compared with that of PBL (60). Lower responses of mammary gland lymphocytes compared with PBL in dairy cows has previously been attributed to less efficient presentation of antigen by the antigen-presenting cells of the mammary gland. This deficiency is due in part to the presence of milk fat and casein within antigen-presenting cells and lowered expression of MHC class II (22), but other immunoregulatory factors, including CD8+, ACT2+ cells, are seemingly influential. Interestingly, the proportion of CD8+, ACT2+ cells
were also higher in mammary glands that were infected with *S. aureus* (60).

In a current study (43), peripartum infectious disease, predominately mastitis, influenced the proportion of certain PBL subsets, particularly CD2 (*P* < 0.02) and CD8 (*P* < 0.05). Earlier studies by Yang et al. (87) reported increased percentages of T cells in blood from mastitic cows (71.2 ± 7.1%) compared with those in blood of healthy cows in the control group (65.8 ± 7.2%), although the absolute number of T cells was substantially lower in the mastitic group (1.49 vs. 2.47 × 10⁶ cells/ml). However, whether the number and function of leukocytes are altered around parturition as a result of peripartum factors or whether increased disease incidence at calving is the cause of leukocyte dysfunction is still debated. That certain subsets of lymphocytes in blood decline in both healthy and diseased cows may argue in favor of the former; however, whether augmenting the number and responsiveness of any subsets would help prevent local or systemic infection is not clear. Of particular interest are some of the unique distribution patterns and immunoregulatory features of the γδ (WC1+ and CD8+, N12+, ACT2+) and CD8+ lymphocyte subsets reported during the peripartum period (59, 60, 61). These need to be defined further to ascertain more specifically if they play a role in protection against peripartum disease.

Others have postulated that the different proportions of lymphocyte subsets in peripartum blood and mammary gland secretions might be due to selective trafficking and migration of cells through interactions with specific adhesion molecules (6, 61, 77). These interactions are no doubt influenced by neuroendocrine and cytokine alterations as well as by the effects of chronic antigen exposure in the mammary gland (6, 61, 77). In dairy cows, the majority of T lymphocytes in milk have been reported to express the CD8+/CD45R memory phenotype (77). In mice, the changes from naive to memory cell phenotypes and the antibody and cell-mediated immune responses are regarded as functional differences that relate at least partially to differential cytokine production (41). Indeed, various cytokines and hormones are also known to influence the expression of adhesion molecules important in leukocyte trafficking (12, 17). Interestingly, decreased concentrations of critical regulatory bovine cytokines, such as IL-2 and IFN-γ, have been associated with diminished cell function of leukocytes and increased susceptibility to peripartum mastitis (64, 76). Initial studies from our laboratory, which examined peripartum expression of adhesion molecules on PBL and mammary gland lymphocytes, show that the mean percentage of L-selectin+ and LFA-1+ cells vary little over time, but proportions are substantially (*P* ≤ 0.0001) lower in milk than in blood (Figure 1). Lower proportions of L-selectin+ cells in the mammary gland are consistent with the concept that memory T cells preferentially accumulate in skin, gut, lung, and the mammary gland and have reduced expression of L-selectin (61, 85). The activation of T cells also leads to decreased L-selectin, which presumably prevents reentry of T cells into lymph nodes but permits accumulation in various tissues (85). Results of a recent study by Burton and Kehrli (6) using a dexamethasone stress model to examine circulating populations of T cells in Holstein bulls suggested that glucocorticoids cause a reduction and redistribution of γδ T cells that are independent of L-selectin, but the WC1 molecule itself may act as a trafficking molecule that is responsible for preferential migration to epithelial tissue. Whether differential expression of adhesion molecules between PBL and mammary gland lymphocytes relates to diminished leukocyte function as a result of redistribution of leukocyte subsets, altered peripartum cytokine profiles, antigen exposure, or other peripartum stress factors remains to be determined.

**ASSOCIATIONS BETWEEN HEALTH OF THE PERIPARTUM COW AND HEALTH OF HER CALF**

The vital role of the mammary gland in providing local host defense and passive protection to the newborn has long been recognized (3, 82). As is true of other ungulates, the calf is born with a functional immune system and is capable of responding to certain antigenic stimuli (35), but the system does not yet operate at optimum capacity; therefore, colostrum is largely responsible for providing protective antibody (82) and possibly lymphocytes to the calf (66, 67). Because passive immunity is highly dependent on mechanisms that allow the transport of antibody and cells from the blood across the endothelium into epithelial tissue and then into mammary gland secretions, the status of the immune system of the peripartum cow has an important influence on calf health. For example, whether the cow has been vaccinated or exposed to infectious disease, has produced protective antibodies, and has transported these into the gland would influence colostral quality and subsequent calf health.

Given that the placenta of the cow is epitheliochorial and that the uterine epithelium is maintained throughout pregnancy, there is no transfer of antibody, cells, or other large proteins to the calf prior to birth. Instead, the newborn calf experiences relative immunological naivete, requiring
antibody-rich colostrum to support its own defense mechanisms until they fully mature under genetic and environmental influences. The period of colostrogenesis begins about 15 d prepartum and is characterized by active and selective transport of Ig—or antibody, which is Ig of particular specificity—generally of the IgG1 subclass into the mammary gland (15, 82). As the newborn ingests colostrum, Ig is absorbed into its blood, and the calf is provided with a set of antibodies that absolutely reflects the repertoire of maternal antibodies. Thus, not only is the quantity of Ig important to the neonate, but the specificity of the set of transferred antibodies also dictates the breadth of protection available to the calf. Colostrum is also rich in a variety of growth factors, such as IGF-I, which help to regulate growth in the newborn (58). Recent data (9, 58) show that these growth factors also act as factors involved in immune regulation, and, in colostrum, these hormones may enhance early neonatal immune responses. However, specific studies feeding colostrum with and without these growth factors have not been conducted.

It is also important to realize that the rate at which maternal antibody declines in the calf is dependent on a number of factors, including the amount of antibody transferred and the half-life of Ig. Normally, the amount of maternal antibody declines substantially in the calf by 6 to 8 wk of age as the ability of the calf itself to respond to a wide range of antigen increases. Because passive immunity of the newborn, mediated by maternal antibody, also inhibits active antibody responses of the calf, an optimum program for calf vaccination may involve multiple immunizations between 6 and 8 wk of age to ensure response in each calf without specific knowledge of individual maternal antibody concentrations. Despite the tremendous variability in maternal antibody concentrations among calves, this relatively simple vaccination schedule should confer protection to most calves.

Leukocyte profiles also change during colostrogenesis. The number of cells in mammary gland secretions declines from $1.8 \times 10^7$ cells/ml during the early dry period to approximately $2.0 \times 10^6$ cells/ml just prior to parturition (15). The types of cells found in mammary gland secretions also vary between early dry-off (43% macrophages, 38% lymphocytes, and 19% PMN) and the formation of colostrum (50% macrophages, 25% lymphocytes, and 25% PMN) (15). Whether colostral leukocytes can be absorbed by the newborn calf and can aid in passive protection has often been disputed; however, current literature (65, 66, 67) would suggest that these cells can cross the intestine of the neonate and modulate host defense mechanisms.

Initial studies conducted using newborn piglets indicated that lymphoid cells (both T and B lymphocytes) originating from the common mucosal immune system of the dam were transported trans-epithelially into the mammary gland and then transferred via colostrum into the digestive tract of the neonate where they were absorbed into their circulation (79). Radiolabeling and electron microscopy revealed that the colostral cells were absorbed intercellularly and that only cells from the piglet’s own dam were able to pass the epithelial layers lining the gut (79). Interestingly, cells derived directly from maternal blood were not absorbed (79), although in some species...
radiolabeled lymphocytes derived from peripheral blood and intestinal pools injected intravenously are known to migrate into the lactating mammary gland via the alveolar epithelium and end up in mammary gland secretions (29). Subsequent studies using porcine maternal colorectal leukocytes that had been labeled with fluorescein isothiocyanate confirmed that these cells were able to migrate intercellularly between duodenal cells and jejunal cells, but not between ileal epithelial cells of the neonate (86). Within 24 h postpartum, maternal colorectal lymphocytes from sows were detected in liver, lung, lymph nodes, spleen, and gastrointestinal tissues (86).

Later studies by Reidel-Caspari and Schmidt (66, 67) indicated that calves fed milk containing colorectal cells had higher blastogenic responses to mitogen, higher lysozyme activity, and increased uptake of Streptococcus agalactiae than did calves fed with milk that had been depleted of leukocytes. Finally, in studies (65) in which neonatal calves were orally infected with E. coli and then fed colostrum, the calves receiving colorectal leukocytes shed significantly fewer bacteria. Collectively, those studies would indicate that colorectal leukocytes, preferentially from the calf's own dam, can enter the neonatal circulation and contribute to passive immunity and resistance to infectious disease. Whether the quality of this response is governed by the type and quantity of transferred cells or the status of the immune response in the periparturient cow remains to be elucidated. However, one might hypothesize that neuroendocrine immune interactions affecting the immune system of the periparturient cow, prepartum vaccination schedules, and the ability to transfer antibody and cells to the mammary gland are all important to ensure colorectal quality. Because many dairies fail to ensure that each calf receives adequate amounts of high quality colostrum (14), calf health might be compromised.

**GENETICS AND PERIPARTURIENT IMMUNE RESPONSIVENESS**

Breeding for disease resistance is not a new idea and was discussed as early as the 1950s by Lush (48) and by Legates and Grinnells (44) as an economical and prophylactic approach to improve dairy cattle health. However, the many diverse approaches have met with varying degrees of success. A noteworthy example of some success involved selection of chickens for resistance to Marek's disease based on specific MHC haplotypes (23). Still, there has always been the concern that selection for resistance to one disease may result in susceptibility to another. Therefore, to avoid the many problems associated with direct selection for disease resistance, including the concern of negative associations between resistance and susceptibility to various pathogens, many studies have focused on evaluating host defense mechanisms as indicators of broad-based resistance to disease (5, 39, 49, 52).

Early studies (5, 49, 52) of dairy genetics and health examined the variation of Ig concentrations and specific antibody responses in an attempt to quantitate their roles in protection and to determine whether genetic selection for altered humoral responses would be possible. The heritability of Ig concentration was generally low, but estimates for specific antibody responses were moderate to high, indicating that genetic selection would be possible if it were considered beneficial. Other research groups (39) conducted studies to ascertain whether differences in nonspecific defense mechanisms could explain the increased incidence of disease that has been associated with selection for high milk yield. Although results from these studies did not find differences between genetic lines of cattle, significant differences between sire progeny groups within lines were reported for lymphocyte blastogenesis, neutrophil functions, and serum conglutinin activity. Those researchers (39) also suggested that mechanisms of host defense could be useful as selection criteria to increase disease resistance if heritability estimates were reasonably large. This set of studies reinforced the idea of profiling young cows or bulls entering AI units using immunological tests that predicted their health or the health of their daughters.

At the same time, numerous research groups searched for associations between alleles of the bovine MHC (BoLA) and disease resistance (45, 47, 53, 71) or immune response parameters (25, 46, 50, 84). Although those studies clearly reported associations between BoLA and mastitis, the precise relationships varied among breeds because of a number of factors, including differences in BoLA allele frequencies. Also, because the MHC is a compilation of many closely linked genes, it is still not clear which gene or genes within the complex are actually responsible for the noted associations. Breeding strategies for dairy cattle that utilize information on BoLA alleles have not yet been implemented; however, systems that seek to maintain the natural polymorphism of the MHC are likely to be optimal. In addition, the possibility exists for selection of cattle expressing BoLA alleles or haplotypes that associate with resistance to mastitis, but such selection might be at the expense of suscepti-
bility to other infectious diseases. This potential problem still needs to be addressed before commercial selection based on BoLA information can be utilized. Nonetheless, the ability to utilize basic knowledge of MHC molecules to enhance response to vaccination is nearly within reach (73). Furthermore, ongoing mapping of the bovine genome should continue to allow identification of other genes involved in regulating the immune response and disease resistance (1). The challenge is to integrate effectively the information from molecular and quantitative genetics into existing breeding programs in order to improve health and performance of dairy cows.

Some of the most contemporary genetic studies conducted to improve dairy health have turned their attention to the periparturient cow. This sector of research involves evaluation of the genetic variation of innate and acquired responses during the period when many host defense mechanisms are impaired and disease incidence is highest (18, 19, 20, 51). The goal of these research programs is to determine whether cows exist that possess the inherent ability to maintain beneficial defense mechanisms during the peripartum period and whether this ability actually correlates with enhanced protection against infectious agents. If so, methods can be devised to identify cows that do not experience immune dysfunction during the peripartum period. The search for major genes that regulate these responses is focusing, in part, on connections within the neuroendocrine-immune axis.

The genetic variability of neutrophil functions, PBL blastogenesis, serum Ig, serum complement, and conglutinin activity were evaluated in 137 Holstein cows from 35 d prepartum until 35 d postpartum (20). Heritability estimates varied, depending on the time relative to calving, but, in general, the noted variability implied that genetic selection based on profiles of innate host defense could be achieved without negative effects on milk production. Because immune system dysfunction is thought to be responsible for the increase in infectious disease during the peripartum period, it is worth noting that in this study the period of maximal immunodepression coincided with the highest incidence of mastitis (20). Differences in numbers of circulating neutrophils and mononuclear cells and in neutrophil-directed migration were also noted in cows of this study from lines genetically selected for different milk production (19). Additionally, differences among sire progeny groups were noted for most of the parameters investigated (19).

Initial unpublished results, based on 100 cows from three research herds evaluated from 8 wk precalving until wk 6 postcalving, seem to confirm the hypothesis that not all cows experience the same degree of immunological impairment around calving (81). In fact, in one herd, approximately one-third of the cows did not experience any decrease in periparturient antibody response, and these cows also had the lowest disease incidence (51). Although initial studies are based on relatively few numbers of cows, the results are encouraging in that sufficient variation may exist to enable selection of animals with minimal peripartum immune system depression, and that this selection should correlate with an enhanced inherent ability to combat infectious disease.

CONCLUSIONS

Numerous studies confirm that aspects of both innate and acquired host resistance are suboptimal in the periparturient cow. Because the primary function of the immune system is to provide host defense against invading pathogenic organisms, it is logical to have hypothesized that impaired innate and immune function is at least partially responsible for the prevalence of disease during the peripartum period. Indeed, published evidence would substantiate this claim because cows with the greatest impairment in host defense tended to have the highest incidence of infectious disease.

The knowledge that dairy cows experience varying degrees of immunological dysfunction from approximately 3 wk precalving until 3 wk postcalving may have practical implications for health management practices. For example, in order to maximize the response to vaccination, it may be beneficial to vaccinate prepartum cows up to, but not past, 3 wk precalving. In this way, the appropriate protective response should develop before the onset of immune system dysfunction. Conversely, the use of immunomodulating agents, such as cytokines or immunostimulating nutrients (7, 76), could be restricted to the peripartum period when their effects are most warranted.

Although a complex set of interactions regulate host defense mechanisms, communication within the neuroendocrine-immune axis is known to have major influence (26, 63). During the peripartum period, a large number of reproductive, regulatory, and stress hormones are released from the anterior pituitary gland, which in turn stimulate other endocrine organs or target tissues, including those of the immune system. Glucocorticoids, for instance, have long been known to suppress immune response, delay wound healing, and depress numbers of circulating lympho-
cytes (26). Consequently, metabolic and physical stresses of pregnancy, parturition, and lactation that are associated with altered neuroendocrine profiles would be expected to have an impact on periparturient responses of the immune system. In fact, certain acute stresses are also known to reduce the rate of Ig transfer to the newborn calf (2, 80). Thus, peripartum immune dysfunction has ramifications for the health of both the cow and the calf. Further study is required to define more precisely the influence of neuroendocrine factors and the genes that regulate these effects on immune system homeostasis during the peripartum period.

Recent studies examining genetic and phenotypic variation in host defense mechanisms during the peripartum period conclude that not all cows experience the same degree of dysfunction of the immune system (18, 20, 51). Therefore, it may be possible to select cows or to identify genes that have positive influences on host resistance (17, 19, 70). Future research will no doubt focus on developing and implementing strategies to enhance periparturient defense mechanisms of the host as a means of disease prevention.

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