Inflammation in the transition dairy cow: adaptation or pathology?

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Introduction

Recent research in dairy cattle has highlighted the role of systemic inflammation in infectious diseases and has suggested that inflammation is involved in metabolic diseases as well. A key role for inflammation in numerous transition cow disorders may help to explain links between these diverse conditions. On the other hand, inflammatory pathways play important roles in normal immune function, metabolism, and reproduction. An improved understanding of the necessary and pathological aspects of inflammatory pathways in transition cows may improve our ability to predict and prevent transition disorders.

What is Inflammation?

During infections such as mastitis or metritis, immune cells in the body recognize invading pathogens and become activated. When the infection is caused by Gram-negative bacteria, lipopolysaccharide (LPS) released by the bacteria also activates immune cells. The activation of local and systemic host defense mechanisms requires cross-talk between numerous types of immune cells, and one component of this response is inflammation. The host of signaling molecules released by activated immune cells includes inflammatory mediators such as nitric oxide, prostaglandins, and cytokines. While many of these molecules promote local inflammation and increased blood flow to the infected tissue, inflammatory cytokines play a key role in stimulating systemic inflammatory responses, including increased body temperature, increased heart rate, and decreased feed intake (Dantzer and Kelley, 2007). Cytokines are able to alter many physiological systems because nearly all cell types express cytokine receptors. Key inflammatory cytokines include tumor necrosis factor alpha (TNFα), interleukin (IL) 1β, and IL-6; these inflammatory cytokines act through many of the same signaling cascades and often produce similar responses in cells.

One effect of cytokines is to activate production of acute phase proteins. Primarily produced by the liver, this class of proteins includes haptoglobin, serum amyloid A, and C-reactive protein. Proteins that participate in the acute phase response to infection are generally found in very low abundance in the bloodstream, but are greatly elevated during systemic activation of the immune system. The importance of acute phase proteins in the response to infection is somewhat unclear, but they have gained widespread acceptance as markers of inflammation.

It is clear that mammary and uterine infections result in both local and systemic inflammation. Coliform mastitis results in release of LPS into the bloodstream and increased plasma concentrations of cytokines and acute phase proteins (Hoeben et al., 2000). Likewise, metritis is associated with an acute phase response in transition cows (Huzzey et al., 2009); in fact, plasma haptoglobin is elevated prior to clinical

signs of metritis. Furthermore, monocytes are known to become more responsive to inflammatory stimulants during the transition period, resulting in greater secretion of inflammatory cytokines when stimulated (Sordillo et al., 1995). Mastitis and metritis can therefore result in systemic inflammation.

Systemic inflammation is common in the first week of lactation

The presence of an acute phase response in postpartum dairy cows is well-established. Although early studies focused on associations between inflammatory markers and diseases such as mastitis and metritis, numerous studies in the past decade have demonstrated that inflammatory and acute-phase mediators are elevated in the days after parturition, even in cows that are apparently healthy (Humblet et al., 2006; Bionaz et al., 2007; Huzzey et al., 2009; Graugnard et al., 2012; Mullins et al., 2012). This growing body of evidence suggests that either the processes of parturition and galactopoiesis induce inflammation directly or that infections or endotoxin affect far more postpartum cows than is currently recognized.

Elevations in inflammatory markers are linked to lower productivity

Although most transition dairy cows apparently experience a period of inflammation, the magnitude of this inflammatory condition varies greatly between cows. Bertoni et al. (2008) assessed the importance of this variation by measuring a panel of inflammatory markers and separating transition cows into quartiles for degree of inflammation. Cows in the highest quartile had significantly lower milk yields than those in the lowest quartile throughout the first month of lactation, differing by 20% on day 28 of lactation (Bertoni et al., 2008).

One metric that has been used in this respect is paraoxanase, a plasma biomarker that is potently suppressed by a variety of inflammatory stimuli. Transition cows with high paraoxanase concentrations, in addition to having lower concentrations of acute phase proteins and reactive oxygen metabolites, produced 24% more milk (4,346 lb.) over 305 days than those in the lowest quartile for paraoxanase (Bionaz et al., 2007). Likewise, plasma concentrations of haptoglobin (an acute phase protein) greater than 1.1 g/L were associated with a 2,088 lb. decrease in 305-day mature equivalent milk yield, and also with decreased risk of conception(Huzzey et al., 2012).

Testing the impact of sterile inflammation

The problem with associative data is that its interpretation is difficult. While it is possible that the studies described above identified cows with primary inflammatory conditions that impaired milk production capacity, it is also possible that the primary issue was a health disorder (i.e. metritis, displaced abomasum) that was the causative factor underlying both inflammation and the decrease in milk production (Ingvartsen, 2006). To carefully determine the effects of transition cow inflammation on milk production, experimental strategies to alter inflammation in apparently healthy cows must be employed.

In 2 recent studies, inflammatory mediators were administered to directly test the impact of inflammation on metabolic function of lactating cows. Trevisi and colleagues (2009) orally administered interferon-α (a cytokine) daily during the final 2 weeks of gestation, which caused liver inflammation and elevated acute phase proteins. Compared to control cows, treated cows had significantly higher plasma ketone concentrations in the first 2 weeks after calving. Our own lab recently reported that subcutaneous injection of TNFα for 7 days doubled liver triglyceride content in late-lactation dairy cows (Bradford et al., 2009). We also observed evidence of gene expression alterations promoting fatty acid uptake and storage, and decreased fatty acid oxidation. These results strongly support the hypothesis that inflammation disrupts normal metabolism, because although both of the above treatments were considered low-dose and short-term, they nevertheless promoted ketosis and fatty liver, respectively.

Is gut-derived endotoxin a key inflammatory signal?

Recent research indicates that feeding high-grain diets to dairy cows alters the environment and microbiota in the gut, leading to the release of large amounts of LPS from bacteria, and subsequently induces inflammatory responses. Emmanuel et al. (2008) reported that feeding increasing proportions of barley grain decreased feed intake and rumen pH, and increased ruminal LPS concentrations by more than 10-fold in lactating dairy cows. This response was associated with elevated plasma concentrations of acute phase proteins, indicating that liver inflammation occurred. If this scenario mimics what happens in transition cows that experience a sudden shift from dry cow diets to high-grain lactation diets, the altered rumen environment and increased inflammatory responses may promote the development of metabolic disorders.

In contrast to the negative effects caused by elevated ruminal LPS concentrations, a recent study (Zebeli et al., 2012) reported that repeated oral administration of LPS around calving improved the profile of plasma metabolites. The authors administered LPS at increasing doses (0.01, 0.05, and 0.1 µg/kg BW on weeks -2, -1, and 1 relative to calving), and showed that treated cows had greater plasma concentrations of glucose and insulin, and decreased NEFA and BHBA in the transition period, consistent with reduced body fat mobilization. In addition, a companion paper from the same experiment reported that LPS administration did not affect feed intake, plasma concentrations of cortisol, serum amyloid A or haptoglobin (Ametaj et al., 2012). It is possible that oral LPS treatment induced an immune refractory state, known as LPS tolerance, resulting in a reduced inflammatory response to subsequent LPS exposure. Indeed, pretreatment of the udder with a low dose of LPS protected against experimental *E. coli* mastitis (Petzl et al., 2012). Metabolic benefits in transition cows, however, may require LPS exposure at the mucosal surface in the gut. When LPS was administered i.v. in increasing doses (Zebeli et al., 2011), it decreased feed intake and milk production and triggered metabolic alterations that typically occur during transition disorders. The efficacy of the oral LPS tolerance protocol suggests that LPS may be a key contributor to the inflammation that is so common in transition cows. Furthermore, oral LPS "vaccination" may be useful tool for

preventing inflammation and metabolic disorders in transition dairy cows.

Anti-inflammatory treatments in transition cows

A third approach to understand the effect of transition cow inflammation has been to block these signals using non-steroidal anti-inflammatory drugs (NSAIDs). Multiple studies have demonstrated that anti-inflammatory treatments can improve long-term milk yield responses. In an initial study, Bertoni et al. (2004) treated 11 cows/treatment with lysine acetyl-salicylate (aspirin) or placebo for the first 5 days postpartum and monitored milk production through day 126 of lactation. Peak milk yield tended to increase with aspirin treatment. The same group subsequently conducted a similar study with 23 cows/treatment and found that aspirin treatment over the first 5 days of lactation increased milk yield through day 60 of lactation, with a 13% increase in peak milk yield (Trevisi and Bertoni, 2008). Though these studies were lacking in mechanistic detail, they nevertheless showed the potential for anti-inflammatory treatments to increase milk yield for a sustained period of time.

Our lab recently reported results from a study with 78 Holstein cows assigned to control or sodium salicylate (SS) treatment 12 to 36 hours after calving, continuing through the first 7 days of lactation (Farney et al., 2012b). Salicylate was delivered in drinking water, providing 123 g/cow daily. Milk production was unaffected during the week of SS treatment, but by week 3 of lactation, SS-treated cows produced significantly more milk fat than controls. To gain insight into sustained responses to treatment, we used DHIA records to quantify 305-day yields of milk and milk components. Milk yield was 5,444 lb. greater over the lactation in $\geq 3^{rd}$ parity SS cows compared to controls (21% increase), although milk yield tended to decrease by 8% in primiparous cows treated with SS. Furthermore, $\geq 3^{rd}$ parity SS cows produced 30% more milk fat over the lactation and tended to produce 14% more protein than controls in this parity group.

Surprisingly, the production responses to SS were not apparently a result of improved metabolic function. In contrast to our hypothesis that SS would improve liver function and decrease fat mobilization, SS-treated cows displayed decreased plasma glucose and increased plasma NEFA and BHBA concentrations in early lactation (Farney et al., 2012a). Intriguingly, the decrease in plasma glucose concentration coincided with increased measures of insulin sensitivity, suggesting that SS had interrupted the normal, and possibly necessary, insulin resistance that occurs in fresh cows.

What is the role of inflammation in the transition period?

Like many aspects of biology, the responses to inflammation in the transition cow are probably not linear. Although it is apparent that high levels of inflammation can limit milk production, other findings suggest that low levels of inflammation may be adaptive in very early lactation. Indeed, inflammatory pathways and compounds are critical to many aspects of physiology. Activation of inflammatory pathways can promote resolution of problems, even those that do not result in overt

disease. During infections, inflammatory signals promote activation and recruitment of immune cells, increasing the delivery of cells that can engulf bacteria, produce extracellular traps, and increase blood flow to the site of infection. Even in conditions that don't involve pathogens, inflammatory pathways can be beneficial. Our recent finding that inflammation underlies the beneficial, mild insulin resistance that occurs in early lactation cows is a novel example of this (Farney et al., 2012a).

Another critical role of inflammatory pathways in the transition cow is to promote labor and expulsion of the placenta. Like many reproductive processes, signaling molecules known as prostaglandins are critical in this process. Production of prostaglandins can be limited by availability of fatty acid substrates, but is also highly regulated by enzyme activity. The same inflammatory pathways that alter liver function and activate immune cells also stimulate prostaglandin synthesis. This is a critical process in the term fetus, as prostaglandin E_2 synthesis in the fetal membranes is thought to act directly on cervical tissue and myometrial cells to dilate the cervix and induce contraction, contributing to the initiation of parturition (Challis et al., 2009). Inhibition of such mechanisms may explain why flunixin treatment at 2 and 24 hours post-calving increased the incidence of retained placenta by 2.5-fold (Duffield et al., 2009). Therefore, our goal in the future is to develop strategies to prevent excessive inflammation without blocking the low-level inflammation that is likely necessary in transition cow physiology.

Nutritional strategies to influence inflammation

Antioxidants. Dietary antioxidants, notably vitamin E and selenium, are important for their ability to neutralize reactive oxygen species (ROS) and prevent oxidative stress. Oxidative stress can induce inflammation, so antioxidants can impede the progression toward inflammation. This is particularly important in fatter cows, because both the transition to lactation and high body condition are associated with increased plasma ROS (Bernabucci et al., 2005). Plasma concentrations of vitamin E decrease through the transition period (Weiss et al., 1990a), and low antioxidant status is associated with transition cow disorders (Mudron et al., 1997; LeBlanc et al., 2004). Supplementing vitamin E in the dry period improves antioxidant status (Weiss et al., 1990b). Multiple studies have shown that supplementing vitamin E in excess of traditional recommendations decreases the incidence and severity of clinical mastitis (Smith et al., 1984; Weiss et al., 1990b). Additionally, a meta-analysis showed that supplemental vitamin E is effective at preventing retained placenta (Bourne et al., 2007).

Lipid modulating compounds. Dietary compounds that reduce liver lipid concentrations may attenuate oxidative stress, primarily by decreasing the amount of fatty acid substrates available for lipid peroxidation. For example, rumen-protected choline (RPC) has been shown to decrease plasma NEFA concentration and liver fat in feed-restricted (Cooke et al., 2007) as well as in transition dairy cows (Zom et al., 2011). Supplementation of rumen-protected niacin (RPN) has also been shown to improve lipid metabolism in transition dairy cows. Morey et al. (2011) reported that cows supplemented with RPN had a 43% reduction in plasma NEFA on day 4 after calving. Similarly, Yuan et al. (2012) reported

that RPN decreased plasma NEFA by 39% on day 1 postpartum, and reduced liver TG accumulation by and 42 and 53% on d 1 and 21 postpartum, respectively. By limiting liver lipid content, additives such as RPC and RPN may protect transition cows against oxidative stress by limiting lipid peroxidation, but direct evidence to support this hypothesis is still lacking.

Bioactive fatty acids. A class of long-chain fatty acids, omega-3 fatty acids include alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid. Although these fatty acids are typically found in low abundance in ruminant diets, a number of recent studies have evaluated the use of flaxseed or fish oil-derived products to increase dietary supply of omega-3s. One reason for the interest in these compounds is that they can suppress inflammatory pathways. This effect has traditionally been ascribed to the idea that increasing supply of omega-3 fatty acids decreases the production of inflammatory compounds from omega-6 fatty acids. However, a cell surface receptor was recently characterized that more directly mediates anti-inflammatory effects of omega-3 fatty acids (Oh et al., 2010).

Lessard et al. (2003) reported that feeding fresh cows with flaxseed (a source of alpha-linolenic acid) increased serum omega-3 fatty acid concentration, resulting in a marked reduction in the omega-6 to omega-3 fatty acids ratio compared with those fed omega-6 fatty acid supplements (i.e. soybeans or Megalac). Interestingly, on day 5 after calving, the lymphocyte proliferative response of cows fed flaxseed was reduced compared with cows received soybeans or Megalac, suggesting an anti-inflammatory effect was achieved, albeit not necessarily a beneficial one.

Thatcher and colleagues have attempted to promote immune function in the transition period by supplementing omega-6 fatty acids compared to omega-3 fatty acids, supplied in the form of calcium salts of fatty acids. Although this form of fatty acid protection does not make the fatty acids inert in the rumen, biohydrogenation is slowed enough for these supplements to alter fatty acid composition of tissues. Increasing the ratio of omega-6 to omega-3 fatty acids increased the production of hydrogen peroxide and phagocytosis of bacteria by neutrophils (Silvestre et al., 2011), which could be due to increased supply of omega-6 precursors of inflammatory compounds and/or decreased supply of anti-inflammatory omega-3 fatty acids. This treatment also increased plasma concentrations of 2 acute phase proteins (Silvestre et al., 2011), indicating a more inflamed state of the liver during the transition period. While the observed effects on neutrophil function would be expected to improve the ability of the immune system to ward off infection, liver inflammation is associated with impaired metabolic function (Bertoni et al., 2008; Bradford et al., 2009). Like the other strategies discussed above, the potential benefits of such an approach may depend on the incidence of metabolic vs. infectious diseases on a given farm, the metabolic state of the cows in question, and even the diet to which the fatty acid supplement is added.

Conclusions

In summary, research in the fields of metabolism, reproduction, and immunology are uncovering a growing list of physiological functions

influenced by inflammatory pathways. The acute phase response is common in transition cows, indicating the presence of an inflammatory state. A state of mild inflammation can help support the cow's ability to calve, expel the placenta, conserve glucose, and fight off infection. On the other hand, excessive inflammation may also strain the metabolic system that is critical for handling mobilized fatty acids and providing nutrients to support lactation, ultimately impairing lactation performance. Consistent with this idea, various anti-inflammatory strategies have shown promise for minimizing metabolic disease and improving productivity, while also increasing the risk of retained placenta and perhaps infection. Moving forward, defining and promoting a healthy degree of inflammation in transition cows may allow the dairy industry to limit transition disorders while improving production.

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