J. Dairy Sci. 98:6631–6650
http://dx.doi.org/10.3168/jds.2015-9683

Invited review: Inflammation during the transition to lactation: New adventures with an old flame

B. J. Bradford,[1] K. Yuan, J. K. Farney, L. K. Mamedova, and A. J. Carpenter
Department of Animal Sciences and Industry, Kansas State University, Manhattan 66506

ABSTRACT

For dairy cattle, the first several weeks of lactation represent the highest-risk period in their lives after their own neonatal period. Although more than 50% of cows during this period are estimated to suffer from at least one subclinical disorder, the complicated admixture of normal adaptations to lactation, infectious challenges, and metabolic disorders has made it difficult to determine which physiological processes are adaptive and which are pathological during this time. Subacute inflammation, a condition that has been well documented in obesity, has been a subject of great interest among dairy cattle physiologists in the past decade. Many studies have now clearly shown that essentially all cows experience some degree of systemic inflammation in the several days after parturition. The magnitude and likely persistence of the inflammatory state varies widely among cows, and several studies have linked the degree of postpartum inflammation to increased disease risk and decreased whole-lactation milk production. In addition to these associations, enhancing postpartum inflammation with repeated subacute administration of cytokines has impaired productivity and markers of health, whereas targeted use of nonsteroidal anti-inflammatory drugs during this window of time has enhanced whole-lactation productivity in several studies. Despite these findings, many questions remain about postpartum inflammation, including which organs are key initiators of this state and what signaling molecules are responsible for systemic and tissue-specific inflammatory states. Continued in vivo work should help clarify the degree to which mild postpartum inflammation is adaptive and whether the targeted use of anti-inflammatory drugs or nutrients can improve the health and productivity of dairy cows.

Key words: postpartum inflammation, transition, dairy cow, health and productivity

INTRODUCTION

The onset of lactation is a critical time for any dam. Lactogenesis, uterine involution, and the accompanying changes in endocrine and metabolic states create a unique set of adaptive challenges, and these challenges are particularly dramatic for the dairy cow. It is not uncommon for the 2 short weeks after parturition to account for 50% of morbidity on a dairy farm, and disease-related culling in early lactation remains a major problem from both economic and animal welfare perspectives.

In his influential review article, Drackley (1999) argued that the biology underlying the transition to lactation was the "final frontier" in our understanding of the dairy cow. This prescient assertion remains true today; although the field has made progress in alleviating clinical hypocalcemia, most other disorders common during the transition period remain as prevalent now as they were 20 yr ago (Goff, 2006; USDA, 2009). Rather than attempting to define the state of transition cow biology as a whole, the purpose of this review is to focus on inflammation as an emerging aspect of transition cow biology. Our goal is to summarize the current understanding of this phenomenon, how it contributes to physiology and pathology in early lactation, and to highlight critical questions that remain unanswered.

THE MOLECULAR KINDLING FOR INFLAMMATION

Inflammation is an evolutionarily conserved response underlying many physiological and pathological processes. In response to stimuli associated with infection and tissue injury, components of innate and adaptive immunity initiate coordinated responses and trigger inflammation (Medzhitov, 2008). Ideally, inflammation helps the body adapt to and overcome adverse stimuli, with the goal of restoring homeostasis. As inflammation has received increasing attention among biologists in recent decades, 2 somewhat distinct processes have

Received April 8, 2015.
Accepted June 6, 2015.
[1]Corresponding author: bbradfor@ksu.edu

been identified that we will refer to as acute and subacute inflammation.

Acute Inflammation

Classic signs of inflammation are redness, swelling, heat, and pain. In response to acute inflammatory stimuli, the body increases the expression and release of inflammatory mediators including cytokines, chemokines, adhesion molecules, eicosanoids, and complement proteins (Newton and Dixit, 2012). These molecules form complex regulatory networks to promote increased blood flow to the infected tissue, immune cell infiltration and activation, and systemic responses, including increased body temperature, increased heart rate, and decreased appetite (Dantzer and Kelley, 2007). Cytokines such as tumor necrosis factor α (**TNFα**), IL-1β, and IL-6 are produced by many cell types, especially macrophages and mast cells. They play important roles in the inflammatory response by activating leukocytes and endothelial cells as well as triggering the acute-phase response (Bannerman et al., 2009).

Much inflammation research has naturally focused on immune cells. However, most cell types across organ systems express receptors for inflammatory cytokines, and these parenchymal cells mediate many of the systemic responses to immune activation. For example, cytokines released by immune cells during infection travel through the bloodstream and stimulate prostaglandin E_2 production in endothelial cells, which in turn acts on neurons in the preoptic area of the brain to increase the set point for core body temperature (Nakamura, 2011). This mechanism for fever induction, which involves cross-talk between immune and nonimmune cells of various lineages, is similar to many inflammatory response cascades.

One key secondary response to inflammation is the acute-phase response. Produced in greatest quantity by the liver, acute-phase proteins include haptoglobin, ceruloplasmin, serum amyloid A, and C-reactive protein. Proteins involved in the acute-phase response are generally found in very low abundance in the bloodstream, but their concentrations are greatly elevated during systemic inflammation. At the same time, other proteins typically secreted by the liver (e.g., albumin) decline in concentration and therefore are sometimes known as negative acute-phase reactants. The importance of some acute-phase proteins in response to infection is somewhat unclear, but they have gained widespread acceptance as inflammation markers (Ceciliani et al., 2012).

The most costly inflammatory disease in dairy cows is mastitis, which commonly results from microbial infection of the mammary gland (Bannerman et al., 2009). If the infection is caused by gram-negative bacteria, LPS released from the bacterial outer membrane is the main pathogen component initiating inflammatory responses (Hogan and Smith, 2003). The subsequent production of pro-inflammatory cytokines induced by LPS (Schukken et al., 2011) elicits the migration of leukocytes (primarily neutrophils) to the site of infection. After they reach the afflicted tissue, neutrophils become activated and release the toxic contents of their granules, including reactive oxygen species, reactive nitrogen species, and proteases. These potent effectors are important in facilitating pathogen clearance, but they may also promote the breakdown of the blood–milk barrier and induce mammary epithelial tissue damage (Schukken et al., 2011). The reduced number and activity of secretory cells consequently contributes to decreased milk synthesis and secretion (Ballou, 2012). In addition to mastitis, uterine infections are common in early lactation. Essentially all cows have bacterial contamination of the uterus within 3 wk after calving, and the majority have at least one form of pathology of the reproductive tract (LeBlanc et al., 2011).

Although a controlled inflammatory process normally leads to recovery from infection, uncontrolled (e.g., sepsis) or chronic inflammatory conditions can be detrimental. Therefore, in an ideal acute inflammatory response, a rapid resolution phase following elimination of the infectious agents is necessary (Medzhitov, 2008). Important resolving signals include anti-inflammatory cytokines such as IL-10 (Fiorentino et al., 1991; Banchereau et al., 2012) and n-3 (omega-3) fatty acid derivatives such as resolvins and protectins (Spite et al., 2014).

Subacute Inflammation

Although dramatic elevation of inflammatory signals can induce a cytokine storm and even tissue damage, subacute inflammation causes mild increases in inflammatory mediators that contribute to chronic and progressive changes in tissue function. Low-grade chronic inflammation occurs in a wide variety of diseases, including obesity and type 2 diabetes in humans. The chronic inflammation associated with metabolic disorders is also referred to as metabolic inflammation (Hotamisligil, 2006). Unlike classical inflammation that is induced by infection and injury and then resolves, subacute inflammation is associated with tissue malfunction. In obesity, for example, subacute inflammation is initiated by excess nutrients in metabolic tissues (Gregor and Hotamisligil, 2011). This response eventually activates multiple types of immune cells and leads