Peripartum Inflammatory Response in Dairy Cows and Its Relationship with Immune Function and Energy Metabolism (Postprint)

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Abstract

Inflammation is an immune response triggered by stimulation from pathogenic microorganisms or alterations in metabolic function. Stimulation by pathogenic microorganisms induces acute inflammatory responses; under normal conditions, acute inflammation effectively clears pathogenic microorganisms through immune system activation and spontaneously resolves to a normal state. In contrast to acute inflammation, subacute inflammation is often initiated by alterations in tissue metabolic function, and once established, is difficult to self-resolve. In periparturient dairy cows, particularly during the first few weeks postpartum, dramatic changes in physiological status, nutrient metabolism, and immune function render inflammatory responses—especially subacute inflammation—relatively common, substantially increasing the risk of various infectious and metabolic diseases during this period. Understanding the development of inflammatory responses in periparturient dairy cows and the interactions between immune function and metabolism that influence inflammation is of significant theoretical and practical importance for implementing early interventions to control postpartum diseases and improve periparturient cow health. Therefore, this review summarizes the occurrence of inflammatory responses in periparturient dairy cows and their relationship with immune function and energy metabolism.

Full Text

Inflammation in Periparturient Dairy Cows and Its Relationship with Immunity and Energy Metabolism

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Abstract

Inflammation is an immune response triggered by pathogenic microbial infection or metabolic dysfunction. Microbial infection typically induces acute inflammation, which, under normal conditions, can effectively eliminate pathogens through immune system activation and self-resolve to restore homeostasis. In contrast, subacute inflammation is often associated with altered tissue metabolic function and tends to persist once initiated. In periparturient dairy cows, particularly during the first few weeks postpartum, dramatic physiological changes, metabolic shifts, and immune alterations make inflammatory responses—especially subacute inflammation—commonplace, substantially increasing the risk of both infectious and metabolic diseases. Understanding the mechanisms of inflammation in transition cows and how immunity and metabolism interact to influence inflammatory processes is crucial for developing early interventions to control postpartum diseases and improve periparturient health. This review summarizes current knowledge on inflammation in periparturient dairy cows and its relationship with immunity and energy metabolism.

Keywords: dairy cows; periparturient period; inflammation; immunity; energy metabolism

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Introduction

The periparturient period, defined as three weeks before to three weeks after calving, represents a critical physiological stage in the dairy cow production cycle. Health issues during this period have long been the primary factor limiting the sustainable development of dairy farming and milk processing industries. Statistics indicate that approximately 75% of diseases—including both infectious and metabolic disorders—occur during the periparturient period, particularly within the first month after calving [1]. Previously, infectious and metabolic diseases were often considered independent events without inherent connections. However, in reality, early lactation diseases frequently co-occur. For example, cows with ketosis exhibit a twofold higher risk of developing mastitis [2], while retained placenta substantially increases mastitis susceptibility [3].

From an inflammatory perspective, both metabolic and infectious diseases manifest varying degrees of inflammatory response. Pathogenic invasion typically triggers acute inflammation, which, when immune function is normal, effectively clears pathogens and resolves spontaneously. Metabolic stress, conversely, induces subacute inflammation that persists without self-resolution. Periparturient cows, especially in early lactation, commonly experience inflammatory responses that are slow to resolve or irreversible, markedly elevating the risk of infectious diseases (mastitis, metritis) and metabolic disorders (fatty liver, ketosis, retained placenta). The precise etiology of periparturient inflammation remains incompletely understood, though compromised immune function,

metabolic stress from dramatic nutrient metabolism changes, and oxidative stress likely represent primary triggers [4]. This review examines the pathogenesis of inflammation in transition dairy cows and its relationship with immunity and energy metabolism.

1.1 Acute Inflammation

When the body encounters pathogenic microbial invasion, gene expression and release of inflammatory mediators in immune cells increase markedly [5]. Key inflammatory mediators include cytokines, chemokines, adhesion molecules, eicosanoids, and plasma proteins. These molecules form complex regulatory networks that enhance blood flow to infected tissues, activate immune cells, and promote chemotactic migration to infection sites, thereby eliminating pathogens [6]. Such pathogen-induced inflammatory responses are typically acute; if uncontrolled, they may trigger systemic symptoms including fever, swelling, pain, increased heart rate, and reduced feed intake.

1.2 Relationship Between Acute Inflammation and Immunity

In dairy cows, mastitis represents the classic inflammatory disease. Despite significant progress in prevention and control, mastitis remains a major constraint on dairy industry development. Mastitis is an inflammatory response of mammary tissue to pathogenic infection, with particularly high incidence during early lactation [7]. When Gram-negative bacteria infect mammary tissue, they release lipopolysaccharide (LPS) from their outer membrane [8], which induces secretion of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1 , and IL-6. These cytokines trigger rapid neutrophil migration to infection sites [9]; upon arrival, neutrophils release reactive oxygen species, reactive nitrogen species, and proteases to eradicate pathogens.

The effectiveness of acute inflammatory responses in clearing pathogens depends on normal immune function, which in turn determines whether infected tissues can recover from inflammation. When immune function is robust, pathogen clearance is efficient and recovery is rapid. Conversely, compromised immunity prolongs and intensifies inflammation, potentially preventing self-resolution. Therefore, the goal is not to completely prevent inflammatory responses but to enhance immune function (i.e., phagocytic capacity) to reduce inflammation duration and accelerate recovery [10]. Unfortunately, periparturient cows typically experience immune suppression, increasing mastitis risk. This suppression manifests as reduced immune cell sensitivity and responsiveness to pathogens. Studies show that compared to mid-lactation, early-lactation mammary tissue shows minimal response to low-dose LPS infusion, while bacterial growth and concentration continue to increase. With higher LPS doses, body temperature and pro-inflammatory cytokines in colostrum increase significantly, accompanied by elevated *Escherichia coli* concentrations in mammary tissue [11-12].

Additionally, immune cell function is diminished. Research demonstrates that

compared to mid-lactation and 12 days prepartum, neutrophils from cows at 7 days postpartum exhibit significantly reduced intracellular, extracellular, and total reactive oxygen species content [13], indicating impaired bactericidal capacity. Postpartum neutrophil chemotactic activity and adhesion molecule gene expression are also significantly reduced [12].

2.1 Subacute Inflammation

Unlike classic acute inflammation, subacute inflammation is relatively mild. While pro-inflammatory cytokines and other mediators are elevated, the magnitude is smaller, and inflammation is typically localized to specific tissues. Studies in obese patients reveal that subacute inflammation is associated with altered tissue energy metabolism, often termed metabolic inflammation [14]. Although milder, subacute inflammation tends to persist, disrupting metabolic homeostasis and exacerbating metabolic stress [15].

2.2 Relationship Between Subacute Inflammation and Energy Metabolism

Subacute inflammation is common in periparturient cows, particularly from late pregnancy through early lactation. Research shows that serum haptoglobin, an inflammatory marker, increases significantly postpartum, with elevated mRNA and protein expression in liver and adipose tissue [16]. This inflammatory response occurs even without pathogen infection [17]. More direct evidence indicates that cows with mild or severe fatty liver (resulting from extensive lipolysis) exhibit significantly increased serum amyloid A, haptoglobin, and pro-inflammatory cytokine TNF , with prepartum serum TNF positively correlating with postpartum liver fat content [18-19].

While the precise mechanisms remain unclear, the dramatic increase in energy requirements during early lactation, coupled with inadequate dry matter intake, forces cows to mobilize body fat to meet milk production demands. This metabolic stress likely represents the primary trigger for subacute inflammation in transition cows. Additionally, as suggested by obesity research, subacute inflammation induced by metabolic stress may feedback to worsen metabolic stress.

2.2.1 Altered NEFA Composition from Lipolysis Triggers Subacute Inflammation Enhanced postpartum lipolysis markedly increases blood non-esterified fatty acids (NEFA) and alters their composition, potentially triggering subacute inflammation [4]. Studies show that postpartum NEFA profiles in cows closely resemble those in obese patients [20], whose adipose tissue exhibits persistent subacute inflammation. Postpartum NEFA composition shows increased saturated fatty acids (palmitic, stearic) and monounsaturated oleic acid, with decreased -3 polyunsaturated fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Blood NEFA composition reflects that

of immune cells involved in inflammation, thereby affecting inflammatory responses [20]. For example, bacterial LPS binds to Toll-like receptor 4 (TLR4) on immune cells, activating downstream nuclear factor- B (NF- B) signaling to initiate pro-inflammatory cytokine expression. Certain fatty acids—lauric, palmitic, and oleic acids—activate NF- B via TLR4 interaction [21], whereas EPA and DHA inhibit NF- B activation [22]. Peroxisome proliferator-activated receptors (PPARs), ligand-activated nuclear hormone receptors, are also regulated by fatty acids: -linolenic acid and DHA downregulate inflammation upon binding, while palmitic and stearic acids enhance inflammation through NF- B activation [23]. These findings demonstrate that altered NEFA composition affects inflammation. However, research in periparturient cows is scarce. In vitro studies on bovine vascular endothelial cells show that fatty acid mixtures mimicking postpartum NEFA profiles significantly increase pro-inflammatory cytokine gene expression, while increasing -3 polyunsaturated fatty acids attenuates this response, possibly due to differences in lipid-derived oxylipids [20]. -3 fatty acids generate protectins and resolvins with potent anti-inflammatory and pro-resolving activities, whereas -6 fatty acids produce pro-inflammatory prostaglandins, leukotrienes, and thromboxanes [24].

2.2.2 NEFA Accumulation from Lipolysis Triggers Subacute Inflammation While NEFA accumulation itself may not directly trigger subacute inflammation, excessive NEFA oxidation readily forms lipid hydroperoxides and generates reactive oxygen species. For example, arachidonic acid (-6 polyunsaturated fatty acid) released from membrane phospholipids is oxidized by lipoxygenase to form hydroperoxyeicosatetraenoic acids (HPETE, including 5-, 12-, and 15-HPETE depending on oxidation site) [25], generating substantial superoxide anions during lipid peroxidation [26]. These reactive oxygen and lipid hydroperoxides induce oxidative stress, triggering inflammation. Additionally, NEFA accumulation increases hepatic metabolic load, causing hepatic fat accumulation and elevated blood -hydroxybutyrate, which induces oxidative stress by increasing inducible nitric oxide synthase activity and reactive nitrogen species production, thereby triggering inflammation [27]. Oxidative stress enhances inflammation through NF- B activation and induces inflammatory responses via mitogen-activated protein kinase pathways; detailed mechanisms are reviewed elsewhere [28].

2.2.3 Persistent Subacute Inflammation Feedback Exacerbates Lipolysis and Metabolic Stress Studies show that oral low-dose interferon- during the last two weeks prepartum significantly increases postpartum plasma haptoglobin, NEFA, and -hydroxybutyrate [29]. Daily subcutaneous TNF injection for seven days in late-lactation cows increases hepatic TNF mRNA and protein expression and triglyceride content [30]. Recent research demonstrates that seven-day subcutaneous TNF injection during the first week of lactation significantly increases plasma haptoglobin and triples ketosis incidence despite no significant effect on plasma NEFA or -hydroxybutyrate [15]. These findings

suggest subacute inflammation induces and exacerbates metabolic stress, likely through inflammation-induced insulin resistance.

Normally, when energy demand increases, blood glucose decreases, reducing insulin secretion, which stimulates lipolysis and increases NEFA. Elevated NEFA then signals feedback to stimulate insulin secretion, reducing lipolysis. When insulin functions normally, this feedback prevents excessive NEFA accumulation and ensures complete hepatic oxidation. However, in periparturient cows, massive lipolysis often exceeds hepatic capacity, causing persistent NEFA accumulation that triggers subacute inflammation. Inflammatory signals directly induce insulin resistance, primarily because enhanced immune activity competes for glucose needed for milk production and physiological functions [31], further intensifying lipolysis and metabolic stress [32]. Limited studies show postpartum TNF negatively correlates with insulin but positively correlates with NEFA [19]. Insulin secretion depends on tyrosine phosphorylation of insulin receptor substrate (IRS) [33]; pro-inflammatory cytokines like TNF , IL-1 , IL-6, and interferon- phosphorylate IRS at serine rather than tyrosine residues. Serine phosphorylation inhibits tyrosine phosphorylation, weakening IRS binding to insulin receptors and downstream activation, thereby impairing insulin signaling and causing insulin resistance [34].

Conclusion

Moderate inflammation protects cows from pathogenic infection and tissue damage while facilitating adaptation to physiological and metabolic changes. However, unresolved persistent inflammation causes destructive consequences. Periparturient cows, due to immune dysfunction and metabolic disturbances, often experience an irreparable persistent inflammatory state that substantially increases disease risk. Management practices should focus on enhancing immune function and regulating energy metabolism to direct this inevitable inflammatory response toward beneficial outcomes or at least minimize its detrimental effects on health and productivity.

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