



Immunophysiology of Farm Animals: Interactions Between Inflammation, Metabolism, and Endocrine Regulation

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Abstract

Immunophysiology has emerged as a rapidly expanding field that investigates the intricate interactions among the immune, metabolic, and endocrine systems responsible for maintaining physiological homeostasis in farm animals. These interconnected regulatory networks are fundamental for coordinating immune defense, energy metabolism, growth, reproduction, and adaptation to environmental and infectious stressors. Increasing evidence indicates that inflammatory cytokines, endocrine hormones, metabolic mediators, oxidative stress pathways, and nutrient-sensing mechanisms function cooperatively to regulate health, productivity, and disease resistance across livestock species. Physiological challenges including heat stress, nutritional imbalance, pathogen exposure, transition periods, and metabolic disorders can disrupt immunometabolic homeostasis, resulting in chronic inflammation, endocrine dysregulation, impaired immune competence, reduced reproductive performance, and decreased production efficiency. Recent advances in transcriptomics, metabolomics, proteomics, and other multi-omics technologies have substantially improved our understanding of the molecular pathways governing immunometabolic adaptation and have facilitated the identification of novel biomarkers for disease prediction and health monitoring. Furthermore, the growing recognition of the gut microbiota as a central regulator of immune and metabolic function has expanded opportunities for developing nutritional, microbial, and precision management strategies to improve animal resilience and welfare. This review synthesizes current knowledge regarding the bidirectional interactions between inflammatory responses, metabolic regulation, and endocrine signaling in farm animals while highlighting their physiological significance under normal and pathological conditions. Particular emphasis is placed on cytokine-mediated signaling, hormonal regulation, oxidative stress, immunometabolism, and emerging molecular approaches that support precision livestock production. A comprehensive understanding of these integrated biological systems provides valuable opportunities for improving disease prevention, optimizing productivity, enhancing reproductive performance, and developing sustainable veterinary interventions that promote animal health and resilience under modern livestock production systems.

Keyword: Immunometabolism; Cytokine Signaling; Endocrine Crosstalk; Oxidative Stress; Precision Livestock Management.

Introduction:

Immunophysiology is fundamental for understanding health and disease in farm animals. The central objectives of this article are to identify mediators and links between inflammation, energy homeostasis, and endocrine signaling; to elucidate how these relationships affect production; and to evaluate current knowledge and approaches. Production animals experience immunological challenges from environmental, metabolic, nutritional, and infectious stressors. Stressors provoke the release of pro-inflammatory cytokines from immune cells, triggering adaptive responses affecting metabolism and longevity. These adaptations are critical for coping with, recovering from, and resisting future immunological insults. They affect production traits directly and indirectly by modulating reinvestment of energy and nutrients used to support high yields (Soares et al., 2022; Bronzo et al., 2020).

Key terms provide context and frame interconnections. The term immunophysiology encompasses physical, chemical, and biological responses to injurious agents that help maintain wellness. Immunometabolism refers to inflammation-induced changes in nutrient availability, substrate utilization, and metabolic pathways that meet the bioenergetic challenges linked to immune activation. Energetic priorities indicate how animals allocate energy reserves to support maintenance functions, production, activity, and immune responses. Immune-competence encompasses physiological functions aimed at avoiding, controlling, or eliminating pathogenic and deleterious organisms (Geoffrey, 2025; Alotiby, 2024)

2. The Immunometabolic Interface in Farm Animals

Inflammation results in rapid changes in energy metabolism and nutrient utilization to ensure immune cells have the substrates or metabolites needed to mount effective immune responses. Despite the demands on energy and nutrients, specific metabolic pathways operate to support pro-inflammatory signaling in the brain and within immune cells, including activation of leukocytes, lymphocyte proliferation, antibody production, and cytokine secretion at the systemic level. Farm animals exposed to periodic environmental or management stressors, such as transportation, heat, and exposure to pathogens, commonly exhibit a heightened acute phase immune reaction that impacts other physiological functions, such as energy homeostasis, feed efficiency, milk production, and reproductive efficiency (Harvanová et al., 2023). The response is accompanied by elevated blood concentrations of free fatty acids, 3-hydroxybutyrate, and other metabolites that can be utilized as substrates in the inflammatory process (Arsenault & Kogut, 2015). The systemic regulation of inflammation and energy metabolism in farm animals is influenced by both organ and organism-level endocrine systems. Liver-derived, centrally-acting hormones, such as leptin and insulin, and the neuroendocrine hypothalamic–pituitary–adrenal (HPA) axis, which releases glucocorticoids from the adrenal cortex, process information about body composition, the availability of energy-dense nutrients, and the instant need for such nutrients following injury or challenge. Farm animal models have been used to clarify the nature of these hormonal influences and how they are affected by the peri-parturient or training periods (Inbaraj et al., 2022; Niu et al., 2022).

2.1. Inflammatory Signaling Pathways relevant to livestock

Several intracellular and extracellular factors can trigger inflammatory pathways; many of these stimuli are also associated with metabolic disorders. Metabolites such as fatty acids, glucose, and ketone bodies can influence signaling through pattern-recognition receptors (PRRs), which comprise toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and C-type lectin receptors (CLRs). Certain hormonal changes co-occur with both inflammation and metabolic alterations. This section describes core elements of immunometabolic signaling, substrates linked to specific immune actions, and hormonal modulators operating during inflammation. A particular focus is placed on farm animal species (Durand et al., 2022; Gupta et al., 2022).

In response to invading pathogens and danger signals originating from damaged tissues, immune cells undergo activation dependent on the recognition of danger-associated molecular patterns (DAMPs) and

pathogen-associated molecular patterns (PAMPs). Extracellularly, these patterns are recognized by pattern-recognition receptors, or PRRs, of which three main families have been identified: toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and C-type lectin receptors (CLRs). Intracellularly, other molecules are perceived by intracellular receptors such as retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) (Rebez et al., 2023; Qiao et al., 2024). For an overview of extracellular pattern-recognition receptor substrates in farm animals, sequential pathways of the four main TLRs (TLR-2, TLR-4, TLR-5, and TLR-6) operative in livestock species emanating from either DAMPs or PAMPs, and selected metabolic substrates connected to immune cell activity and settled upon during the acute phase of inflammation, readers are referred to the cited materials (Dzięgielewska-Gęsiak & Muc-Wierzoń, 2023; Chen et al., 2026).

2.2. Metabolic substrates and immune cell function

Livestock immune cells exhibit significant metabolic adaptations in response to activation, with corresponding changes in the substrates that fuel their energy-dependent activities. Providing these metabolic substrates during immune and metabolic challenges in production animals could therefore improve disease tolerance, production efficiency, and environmental sustainability (Luo et al., 2026; Majewska et al., 2026).

Immune activation substantially increases the energy demands of farm animal immune cells, which rely on metabolic reprogramming to match substrate supply to those demands. During activation, erythrocytes, monocytes, macrophages, and certain lymphocyte populations increase their consumption of glucose and, to a lesser extent, saturated non-esterified fatty acids (NEFAs). Models of acute, chronic, and metabolic-induced inflammation in ruminant species suggest that, while glucose remains the predominant substrate, T lymphocytes are able to metabolize branched-chain amino acids, unsaturated NEFAs, and other substrates as alternatives when glucose is limiting 18. Such metabolic flexibility allows these cells to maintain activity even when systemic supply is impaired [(Cheng et al., 2026; Eder, 2019).

2.3. Endocrine modulation of immunometabolic responses

Immunophysiological responses during inflammation are influenced by gluco-, mineralocorticoid, and thyroid hormones. Cortisol and corticosterone, secreted from the adrenal cortex in fish, amphibians, reptiles, birds, and mammals, or its precursor 11-deoxycorticosterone in ruminants, are principal regulators of the metabolic response to stressors. Glucocorticoids enhance gluconeogenesis, lipolysis, and proteolysis, mobilizing energy substrates that adversely affect reproduction, growth, and lactation. They also have profound inhibitory effects on the immune system. The synergistic action of glucagon and catecholamines with glucocorticoids can lead to hyperglycemia, particularly during disease (Hu et al., 2022; Tong et al., 2026).

Adipocytes, the major source of circulating leptin, are important for linking immunity with metabolism, and leptin regulates immune cell proliferation and the production of pro- and anti-inflammatory cytokines. Suppressor of Cytokine Signaling-3 (SOCS3) is involved in leptin-mediated effects on immune cells. Thyroid hormones influence both immune responses and metabolic activities, with thyroid-stimulating hormone being a key modulator of thyroid hormone activity. In mammals, insulin has major, pro-inflammatory effects on monocytes and macrophages via multiple signalling pathways, instructing these cells to adopt an activated phenotype. Insulin and insulin-like growth factors regulate innate and adaptive immunity and influence lymphocyte proliferation (Drapela et al., 2022; Kumar & Stewart IV, 2024).

3. Inflammation and Energy Homeostasis in Ruminants

During inflammatory challenges, energy homeostasis is adversely affected in ruminant species. The acute-phase response, involving the increased circulation of pro-inflammatory cytokines like interleukin- (IL-) 1 and IL-6, stimulates considerable loss of body reserves. In lactating dairy cows, heightened concentrations of IL-6, IL-1, and tumor necrosis factor- (TNF-) α during mastitis are strongly correlated with impaired performance in 305-day milk production and with feed efficiency during the early post-partum period (Tort & Balasch, 2022). Ephemeral mobilization of peripheral fat for energy generation

and alterations in the synthesis of circulating metabolites provoke major fluctuations in nutrient supply at the cellular and systemic levels. Losses of body reserves to sustain adequate energy supply impose severe impacts on production traits and feed efficiency in dairy and beef cattle (Borghetti et al., 2009).

Adipose tissue is now recognized as an immunometabolic organ by initiating a number of adaptations during inflammatory challenges. The obese phenotype of dairy cattle, characterized by expanded fatty tissues, compromises energy homeostasis during inflammatory challenges in the periparturient period. Macrophage phenotypes in body fat depots differ markedly between dairy and beef production systems, substantially affecting the balance of lipogenic and lipolytic gene expression and the efficiency of fatty acid mobilization from adipose tissues. Cattle in dairy production systems exhibit enriched pro-inflammatory M1 macrophages and elevated expression of inflammatory cytokines such as IL-6 and TNF- α in adipose tissues during lipomobilization and systemic inflammation, compared with beef production systems (Qiao et al., 2024). Such pro-inflammatory signals impede insulin signaling and inhibit glucose metabolism in adipose tissues, leading to the accumulation of pre-formed triglycerides and compromised lipolysis. During involuntary celibacy, lipolysis and cottonseed supplementation further induce a high inflammatory state in dairy cattle, emphasizing the importance of immunometabolic control (Trevisi et al., 2025; Zhao et al., 2024).

3.1. Acute phase response and energy balance

Postnatal development of ruminants is characterized by a physiological adaptation to 72–96 h of the pre-weaning period, the nature of which is determined by transition of nutrition consumption from maternal-derived nutrient input to self-selected feed (Kowalczyk et al., 2026). Still, nutrient and energy intake in young post-natal ruminants is markedly below maintenance constraint capacity. Due to its critique role in fatty liver condition, the subject of nutrient and energy balance of these animal prior to puberty transition in pre-weaning period and early post-weaning phase has gained ample attention. Perturbations of regulation and utilization of host nutrient and energy homeostasis during early post-weaning period is delineated in those stage where nutrient and energy balance is subcritical to mobilize and secure the production gain substantially (Hajimohammadi et al., 2011; Straub, 2014).

Adipose tissues in monogastric species such as pigs, poultry is recognised as out key immunometabolic organ. By corner construction of adipose phenotypes monitoring adipokines, macrophages populations and the up-down shift of carriers such as SLC2A4, LPL–ATGL and SOD2, the characterization of monogastric in adipose immunometabolic network is still incomplete 30. In ruminants like dairy or beef cattle where pre-weaning feed cannot provide enough maintenance energy, nutrient supply received continues priority ranking directly from in-situ production abilities based on udder-based machine or large size supplementary feeding. During early postpartum phase, a broad overview on liver metabolism indicate the active preparation of gluconeogenesis, urea recycling and acute-phase protein synthesis in the later stage is taken place to cope the metabolic demand largely exceeding from early-born animal when vast majority of the plasma metabolites cross the threshold (Costa, 2022; Kasimanickam & Kasimanickam, 2026).

3.2. Adipose tissue as an immunometabolic organ in dairy and beef cattle

Adipose tissue functions as an immunometabolic organ in dairy and beef cattle (Safain et al., 2026). Immune cell infiltration in adipose tissues occurs in humans, rodents, and other species in obesity and negative energy balance. In cattle, fatty liver and high concentration of nonesterified fatty acids in plasma during the early postpartum period can also lead to an inflammatory response involving adipose tissue. Macrophages are the first immune cells detected in adipose tissue, and studies show that classically activated macrophages (M1) appear immediately after early lactation and that alternatively activated macrophages (M2) are still present thereafter. CD8⁺ effector T cells also infiltrate adipose tissue during this period, but the appearance of regulatory T cells, which can exert immunoregulatory functions and metabolic regulation, occurs only later. The presence of CD8⁺ effector T cells and their cytokine profile in adipose tissue of high-yielding dairy cows indicates that the immune system plays a role in regulating

metabolism and that adipose tissue inflammation is a feature of energy and metabolic disorders specific to this species during the transition period (Chapelain et al., 2026). Flow cytometric analysis of stromal vascular fractions from different adipose depots reveals that T cells are present in both subcutaneous and mesenteric adipose tissues, highlighting the complex interplay between the immune system and adipose tissue. Leptin and tumor necrosis factor- α (TNF- α) are major adipokines secreted by adipose tissue that influence energy metabolism and immune activity, with TNF- α potentially regulating proinflammatory cytokines, including interleukin (IL)-1 and IL-6 (38). During the transition period in dairy cows, adipocyte hypertrophy occurs in response to alterations in dietary energy and protein and they remain enlarged longer than conventional industry practice would suggest. Largely uncharacterized opportunity exists for further investigation of the immunological role of adipose tissue during this period (Safain, 2025; Yang et al., 2022).

3.3. Liver metabolism during inflammatory challenges

During inflammatory challenges, animal liver functions change significantly, which may impact production traits and efficiency. In ruminants and other livestock species, these responses follow a well-characterized pattern. Directly and indirectly via acute-phase cytokines, pro-inflammatory stimuli such as lipopolysaccharides, peptidoglycans, beta-glucans, or stressors including physical trauma induce hepatic gluconeogenesis and β -oxidation while inhibiting lipogenesis and glycogenesis (Oliveira et al., 2019). Such alterations respond to pro-inflammatory signal intensities and immunological states during systemic inflammation. Anabolic activities, however, are comparatively less sensitive at later stages when pro-inflammatory mediators remain elevated and attenuation mechanisms gradually engage. Furthermore, the complexity of ramifications and high-temperature, boiling environment often encountered in farm locations impose profound limitations to the research (Kasimanickam et al., 2013).

Increased hepatic survival of ammonia reflects overall nitrogen handling improvements. Associated with the augmentation of some intermediate metabolites that could serve as nitrogen skeletons, these processes may help to sustain amino-acid and protein synthesis—focusing on albumin and other non-acute-phase proteins (Martinez-Barbitta et al., 2026).

4. Hormonal Regulation of Immunity in Monogastric Farm Species

The hypothalamic–pituitary–adrenal (HPA) axis integrates internal and external cues to maintain homeostasis during stress, triggering hormonal cascades that modulate various physiological functions, including immunity (Michelotti et al., 2022). Acute challenges activate hypothalamic release of corticotropin-releasing hormone (CRH), stimulating pituitary release of adrenocorticotrophic hormone (ACTH) and subsequent adrenal secretion of cortisol.

Multiple endocrine axes influence other aspects of immunity in monogastric species. Infections and inflammation alter the expression of thyroid-stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH) (Huszenicza et al., 2018). TSH induces the synthesis and secretion of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland, both of which possess immunomodulatory effects. Moreover, circulating concentrations of T4 are tightly correlated with metabolic status; an adequate T4 supply therefore links energy availability to immune responses. Phytoestrogens, gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and gonadotropin-inhibitory hormone also modulate peripheral balance between pro- and anti-inflammatory CD4⁺ T-cell subsets in pigs (Fernandez Wallace, 2025; Ji et al., 2026), and physiological concentrations of sex steroids alter macrophage activities and cytokine responses in poultry (Xu et al., 2022).

In pigs, the activation of the insulin receptor, insulin receptor substrate 1 (IRS-1), or protein kinase B (AKT1) increases the overall viability, migration, phagocytic activity, and pro-inflammatory cytokine-producing capacity of immune cells (Sebők et al., 2021). Insulin resistance arising from higher circulating free fatty acids or the inflammatory cytokines tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) negatively affects the functionality of leukocytes. The feeding of energy-dense diets prior to challenges

has also been associated with better recovery of immune performance in piglets and broilers (Afzal & Mahreen, 2024).

4.1. Hypothalamic–pituitary–adrenal axis and acute stress responses

The immunophysiology of farm species is fundamentally different from that of laboratory animals and humans. The agricultural context mandates the elaboration of a more extensive conceptual framework to ensure a solid foundation for the following discussion (Eilam et al., 2023).

The hypothalamic–pituitary–adrenal (HPA) axis orchestrates the endocrine response to biologically relevant stimuli, including the stressors encountered in farming. This axis is activated by physiological adversities affecting the metabolic, immunological, and neurological frameworks of farm animals. Individuals of different species vary markedly in their endurance to and recover from the impact of acute stressors. Accordingly, the corresponding glandular actuation, dynamics, magnitude, and durations of hormonal output all differ from species to species (Ringseis & Eder, 2022).

Cortisol dynamics during acute-stress responses have been correlated with immune readouts in pigs and chickens. Responses in the latter species have been evaluated with respect to classical immunological parameters (lymphocyte subpopulations and serum markers) at standard prestressed, +1 h, +6 h, and +24 h intervals post-stressor. Such intervals can vary significantly, as do the final outcomes obtained from an evaluative viewpoint (Yang et al., 2024).

4.2. Thyroid and gonadal hormone influences on immune competence

Thyroid hormones (TH) and sex steroids regulate metabolic processes and exert immunoregulatory effects in monogastric species. The relationships between TH and immunity are multifaceted, with a consistent link between low TH levels and increased mortality during infectious disease (Goel et al., 2025). TH modulate immune responses in an age-dependent manner, with the timing of exposure to TH during development affecting the response to cytokines and the maturation of T-lymphocyte subpopulations. For example, the activation of tumor necrosis factor (TNF)- α expression in monocytes and macrophages is enhanced by the combined action of the pro-inflammatory cytokines Interferon (IFN)- γ or Lipopolysaccharide (LPS) and TH. TH also influence parameters of post-weaning immunosuppression in piglets and the balance of T-helper cell subsets during this period. Moreover, TH exert a wide-ranging influence on the production of pro-inflammatory and anti-inflammatory cytokines. During inflammation, TH and their receptors act in opposition to the dominant effect of glucocorticoids, but they can fine-tune tissue repair and recovery (Udi, 2025; Rusch et al., 2023).

Data comparing the influence of androgens and estrogens on the immune response in pigs and poultry are limited. Farm animals in general exhibit sex differences in susceptibility to infectious disease, and the natural eclipse of the growth hormone (GH):insulin-like growth factor-1 (IGF-1) axis around the onset of sexual maturation corresponds to a greater incidence of post-mortem abscess formation in male pigs than in females. Pigs treated with testosterone and fed a diet conducive to strong sexual maturation show increased leukocyte adhesion, but the overall effect of androgens remains unclear. In contrast, the immune-modulatory effects of estrogens are more consistent and promote an earlier recovery of immune competence following the stress of surgical castration (Balkrishna et al., 2026; Lemanowicz et al., 2026).

4.3. Insulin signaling and leukocyte function in pigs and poultry

Insulin signaling influences immune competence following an inflammatory challenge. Insulin resistance commonly develops during the immune response in pigs and poultry, correlating with a reduction in glucose uptake by immune tissues and consequently impacting the immune system. Increased obesity and metabolic disorders, characteristic of high-yielding, monogastric farm animals, lead to the development of chronic insulin resistance that results in a higher metabolic cost for the immune system when addressing inflammatory signals, thus negatively impacting performance. The degree of insulin resistance induced by inflammatory stimuli affects subsequent recovery and resilience from the inflammatory response (Kinlein et al., 2015; Gutierrez-Coronado et al., 2015).

5. Nutritional Modulation of Immunophysiology

Immunophysiology refers to interactions between immune processes and physiological functions like reproduction, metabolism, and nutrition. Nutrient-sensing pathways such as mTOR, AMPK, and SIRT1 regulate cellular and organismal physiology and energy metabolism. These conserved networks integrate nutrition, energy status, and metabolic intermediates with immune system function and the inflammatory response (Scocco et al., 2023). The study of nutritionally mediated metabolic and immunophysiological alterations in agricultural livestock is not well explored, yet offers opportunities to mitigate the effects of inflammation and enhance immunity (Báez-Magaña et al., 2025).

The challenge of maintaining animal productivity under diverse environmental stressors influences the conceptualization of immunophysiology. Strategies that promote metabolic flexibility allow animals to efficiently adapt to porcine reproductive and respiratory syndrome virus (PRRSV) infection, metabolic stressors, and feed or water challenges. Increasing attention towards promoting flexibility reflects the effects of environmental factors such as feeding, temperature, and humidity on physiological systems (dos Santos et al., 2024).

5.1. Nutrient-sensing pathways and immune function

First, immunity senses signals of nourishment, stress, and danger to adapt functions according to the environment. And second, the immune system influences metabolic regulation via endocrine pathways and immune-derived adjuvants to enhance metabolism and both immediate and delayed immune defense (Santos et al., 2026).

Immunity is thus accorded priority over nutrient-storage adaptation during unfulfilled nourishment—furthermore, inadequate metabolic adaptation has a negative impact on both acute and chronic inflammatory responses (Sharmin et al., 2026).

5.2. Dietary strategies to mitigate inflammation and support metabolism

Dietary strategies to mitigate inflammation and support metabolism. Strategies to mitigate inflammation and support metabolism focus on maintaining intestinal immunometabolic homeostasis. The gut microbiota interacts with the mucosal immune system and diet, influencing gut health and overall health. The microbiota transduces dietary nutrients into signals that can promote or inhibit inflammation through pattern-recognition receptors, leading to immune-cell metabolic reprogramming. Understanding these immunometabolic pathways and associated biomarkers can guide interventions to prevent or reduce inflammation, thereby supporting health and productivity (Sai Kumar, 2023; Kumar, 2023).

5.3. Concepts of metabolic flexibility in production animals

Production animals, particularly livestock, are subject to a wide range of dietary and environmental challenges. Nevertheless, they exhibit a degree of metabolic flexibility, defined as the ability to adapt to varying energy or nutrient supply and demand. Such flexibility involves metabolic transitions between preferred energy sources (e.g. glucose versus fatty acids) and is sustained by spatial segregation of metabolic pathways in different tissues, direct hormonal control (especially by insulin), and the ability to switch substrates in response to environmental change. Gaps in the current knowledge of metabolic flexibility in ruminants and non-ruminants are identified, along with additional insights and opportunities for farming practice, research, and regulatory aspects (Prates, 2025; Żarczyńska et al., 2026).

Flexibility encompasses not only adaptation to short-term changes but also resilience against longer-term restrictions, such as the transition to lactation in dairy cows. The greatest period of metabolic strain in production animals generally coincides with their highest level of production, combined with chronic exposure to various physical and social stressors. Issues of metabolic flexibility thus require careful consideration across a range of disciplines, both during the growing phase and after the start of production. There is substantial opportunity for improving farm management practices and feeding strategies to help address these topics. Well-known strategies such as early weaning, enlargement of feeding space, or provision of specific feed types (for instance, bypass fat) may warrant further investigation (Darby & Lazzaro, 2023).

6. Disease States, Metabolic Disorders, and Endocrine Dysregulation

Disease states such as mastitis, ketosis, and fatty liver disease, commonly observed in high-producing ruminants, exhibit characteristic immunometabolic signatures that reflect the types of inflammatory signals triggered. Pathogen-driven inflammation involves the release of pro-inflammatory cytokines and negative feedback signals, while inflammation of metabolic origin is primarily governed by the unbalanced release of lipid metabolites and mediators. The inflammation associated with ketosis and fatty liver disease arises from a different immunometabolic framework compared to other utility diseases within the same species (Berbudi et al., 2025).

In agricultural settings where large numbers of animals are housed together, the risk of endotoxemia and systemic inflammatory responses is heightened. These conditions can arise from the ingestion of feed contaminated with bacterial endotoxins or from other, more indirect mechanisms. When lipid-overloaded liver cells experience increased systemic mobilization of lipid reserves, various secondary disturbances may also occur, ultimately leading to increased sensitivity to inflammatory stimuli and a higher risk of developing clinical or subclinical mastitis. Cattle, unlike other mammals, do not possess an anatomical structure (such as a pre-sinusoidal or portal vein structure) capable of detoxifying or degrading such substances in the liver. Knowledge about the underlying pathophysiological processes and the corresponding biomarkers related to these disturbance events remains limited (Gusev et al., 2026; Makhijani et al., 2023). The farming industry has shown increasing concern towards high-producing animals that are unable to cope with the resulting downward metabolic spiral. High milk production is accompanied by other health burdens, such as heavy anatomical stress and endocrine-related syndromes (Jacobsen et al., 2016).

6.1. Mastitis, ketosis, fatty liver disease, and their immunometabolic signatures

Mastitis, left unaddressed in dairy herds, results in decreased milk quality, premature culling, and even mortality. Ketosis at calving and subsequent negative energy balance can lead to further metabolic conditions, including fatty liver disease and impaired reproductive performance. Consequently, the acute phase response is a stereotyped, systemic response to local or systemic inflammation. It is triggered by the binding of an inflammatory stimulus (such as endotoxin) to specific receptors (for example, TLRs) expressed on the surface of innate immune cells. During the acute phase response, the concentration of several plasma proteins (including fibrinogen, haptoglobin, and C-reactive proteins) changes dramatically, providing essential support to the innate immune system and influencing energy metabolism and reproduction. These proteins can originate from the liver, reticuloendothelial cells, lymph nodes, and, to a lesser extent, the intestine. Other proteins exert an indirect effect on reproduction by inducing fever and an increase in cortisol levels or modulating the ovarian environment. The concentration of these proteins is variable among species (Zhang et al., 2021; Bobeck, 2020).

6.2. Endotoxemia and systemic inflammatory responses in farming contexts

Endotoxemia and systemic inflammatory responses are particularly relevant to farming because animal production is intrinsically linked to the consequences of inflammation and the metabolic alterations accompanying it. Endotoxemia arises as a consequence of natural hazards or production practices, such as packaging, transport, and slaughter, all of which can trigger lipopolysaccharide (LPS) release into the blood. Under physiological conditions, only a small amount of LPS enters the bloodstream; elevated levels of circulating LPS and the associated inflammatory responses are therefore considered pathological (Rodrigues et al., 2022; Oi & Obata, 2025). Classical components of the acute phase response (APR), such as fever and increased secretion of liver-derived acute phase proteins, have a direct link to LPS. The remaining components of the APR, together with signaling pathways commonly classed as “inflammatory,” are nevertheless triggered during other acute challenges that do not pertain specifically to LPS. Endotoxemia and accompanying inflammatory components can be regarded as only one variant of pathology and have been described as a pathway distinct from that initiated by pathogens; hence, the term “internal endotoxin” has been used 1. Understanding the sustained physiological and metabolic

changes resulting from endotoxemia is particularly important in agricultural production systems in which rapid growth to slaughter weight or rapid reproduction is a major focus of economic reward (Goel et al., 2025; Li & Ji, 2026).

6.3. Metabolic syndromes and endocrine perturbations in high-producing animals

The elevated milk production of contemporary dairy and poultry breeds helps satisfy the rising global dietary demand for animal protein. However, intensive use of these species for food production generates exorbitant adaptive demands, exposing them to multiple welfare challenges. This dilemma has rendered the implementation of the ‘One Health’ framework—recognizing the interconnected health of humans, animals, and the environment—imperative for livestock systems (Tanahashi et al., 2026).

Early lactation remains a period of high economic risk for dairy farms, with an elevated rate of culling observed during this phase. High-producing dairy cows experience a marked drop in feed intake and subsequently enter a state of negative energy balance, resulting in the mobilization of body reserves to sustain the energy required for milk production during the first ten to twelve weeks post-partum. Cows exhibiting symptoms of metabolic and infectious disorders during this high-risk period are more likely to be culled from the herd. The leading causes of culling in early lactation include metabolic disorders and disease (Xu et al., 2026).

7. Methodologies for Studying Immunophysiology in Farm Animals

Wide-ranging measurements of markers indicative of the immunometabolic status thus represent valuable resources for investigating immunophysiology. Diverse sampling routes and sampling matrices allow tailored selection of specific indicators for responsive monitoring of deviations in health and welfare. While a multitude of *in vivo* and *ex vivo* systemically and locally sampled readouts related to these dimensions have been evaluated, the consensus on intervals for postinsult collection remains elusive. Although well isolated from other confounding events, time intervals corresponding with an animal’s regular feeding regimen may provide research teams with convenient options to explore between disease state, time elapsed from onset, and selected readouts. Extensive studies performed thus far within monogastric species have also further illuminated foundational data on expected baseline measures of several relevant readouts, which remain invaluable for continued investigations into these domains (Zhu et al., 2026; Ma et al., 2018).

7.1. Experimental models and translational relevance

Experimental studies on immunophysiology in farm animals apply several approaches to disentangle the complex interplay between inflammation, metabolism, and endocrine regulation. Models encompass both *in vivo* and *ex vivo* experimental designs that examine real-life pathways in natural environments, and are complemented by *in vitro* systems biology models for detailed, targeted exploration of selected metabolic and inflammatory elements that contribute to cow-pathogen interactions during infections such as mastitis or uterine diseases. Furthermore, translation of discoveries to on-farm management is enhanced by the application of state-of-the-art omics techniques covering the entire spectrum from genomics and transcriptomics to proteomics and metabolomics (Zhang, 2022; Di Sabatino et al., 2023).

In vivo studies of the hypothalamic–pituitary–adrenal axis and related acute stress responses in pigs, poultry, and livestock highlight the dynamic nature of animal responses to stressors. Transcriptomic pathways of T cell populations in pigs during a *Salmonella* challenge, transcriptomic responses of lung and cecal tonsils during vaccination against porcine reproductive and respiratory syndrome virus, and metabolomics and proteomics of the mycelium of the fungal species *Hericium erinaceus* with antioxidant and immunomodulatory properties further illustrate the potential of utilizing pigs as representative experimental animals for investigating human-related diseases (Palmer & Clegg, 2022; Taff et al., 2024).

7.2. Omics approaches to immunometabolism

Approaches with high throughput and analytical depth have gained attention in the context of immunometabolism. Genomics provides dimension to the study of this concept by mining single-nucleotide polymorphisms (SNPs) associated with immunometabolic traits. Transcriptomics extends

investigations to expression and splicing of genes involved in key metabolic and signalling pathways. Proteomics unveils protein-modifying post-translational changes conditionally inducing enzymes or receptors. Metabolomics exposes microbial metabolites and bioactive compounds through feed ingredients or intermediate compounds indicative of metabolic state and origin of inflammatory disturbance. Multi-dimensional analyses integrate these diverse data types collectively with pathways-restricted cologging to resolve nutrient architectures and inform holistic supply formulations. Unraveling comprehensive functional modules across temporally and spatially orchestrated genes, proteins, and metabolites reinforces understanding of underpinning circuits in farm species (Naufal & Wu, 2024; Bhargava, 2013).

7.3. In vivo and in vitro assessment of inflammatory and metabolic markers

Analysis of markers related to inflammation, metabolism, and neuroendocrine modulation can be undertaken in vivo or in vitro. The concentrations of circulating proteins and metabolites are most often measured in plasma or serum samples. Some lipids—including ketone bodies, certain fatty acids, and sphingomyelins—are quantified in non-esterified forms, but others must first be extracted from biosamples. Hormones also can be measured using plasma or serum, and their concentrations are usually presented at specific time points following stimulus. Common readouts include glucocorticoids during the hypothalamic–pituitary–adrenal axis response, thyroid hormones and prolactin at different stages of the reproductive cycle, and secretory IgA in response to vaccination (Harvanová & Duranková, 2025; Acharya & Joseph, 2024).

Alternatively, markers of inflammation and metabolism can be evaluated using ex vivo or in vitro approaches. Whole-blood lymphocyte activity is assessed by measuring cytokine production or by determining cell proliferation and differentiation into T- helper, T-regulatory, or cytotoxic cell subsets following stimulation with mitogenic agents, or by quantifying bactericidal activity in response to pathogenic stimuli during epithelial-intestinal co-culture assays. Peripheral blood mononuclear cells cultured with different lipid sources have been used to understand the impact of dietary lipids on leukocyte function directly. A simplified ex vivo system consisting of whole blood or heparinized whole blood cells from livestock species has been successfully developed to study the effects of different doses of immunomodulatory products on the immune system (Liu et al., 2019; Wankhade et al., 2017).

Conclusion

Immunophysiology is a comprehensive field that has seen limited application to farm and companion animal species despite their importance to global economies and society. Livestock and poultry continue to be subjected to production and health challenges that compromise the efficiency and sustainability of food animal production, leading to increased effort to understand the physiological changes associated with these increased demands. The paradigm of immunophysiology offers an integrated view of the interplay between inflammation, metabolism, and endocrine regulation in farm species that could contribute to more resilient production systems. The relevant scientific literature related to each of these three components within farm species has been summarized and critically evaluated. Notable knowledge gaps have been identified in the mechanistic understanding of the interrelatedness of these topics for animals widely used in the global food supply. Filling these knowledge gaps would provide opportunities to broaden the breadth of immunophysiology research files to include livestock, poultry, and aquaculture species and could improve health and production under challenging production conditions. The resulting benefits would have major economic and sustainability impacts on agricultural worldwide 24.

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The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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