



OPEN ACCESS

EDITED BY

Carlos Angulo,
Northwestern Center of Biological Research,
S.C. (CIBNOR), Mexico

REVIEWED BY

Lija Satheesan,
National Dairy Research Institute (ICAR), India
Kandasamy Rajamanickam,
Tamil Nadu Veterinary and Animal Sciences
University, India

*CORRESPONDENCE

Zhipeng Zhang
✉ zhipengzhang@yzu.edu.cn

RECEIVED 08 November 2025

REVISED 18 January 2026

ACCEPTED 19 January 2026

PUBLISHED 12 February 2026

CITATION

Ye C, Zhang Z and Yang Z (2026) A new type of biomarker for heat stress: insights from immunology. *Front. Immunol.* 17:1742202. doi: 10.3389/fimmu.2026.1742202

COPYRIGHT

© 2026 Ye, Zhang and Yang. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A new type of biomarker for heat stress: insights from immunology

Chunmei Ye¹, Zhipeng Zhang^{1,2*} and Zhangping Yang^{1,3}

¹College of Animal Science and Technology, Yangzhou University, Yangzhou, China, ²Experimental Farm, Yangzhou University, Yangzhou, China, ³Zhejiang Key Laboratory of Cow Genetic Improvement and Milk Quality Research, Wenzhou, China

Global warming exacerbates heat stress in dairy cows, while traditional indicators like the Temperature-Humidity Index (THI) struggle to accurately reflect individual physiological response variations. This review systematically analyzes the dynamic changes in the bovine immune system under heat stress and proposes immune-related biomarkers as a novel strategy for early warning and individualized assessment. Research reveals that heat stress compromises the innate immune barrier function of cows, suppressing neutrophil chemotaxis and antimicrobial peptide synthesis, leading to a decline in the opsonophagocytic index and endotoxin translocation. Expression of intestinal tight junction proteins (e.g., Claudin-1, Occludin) is significantly downregulated (by ~40%), causing endotoxin translocation (serum LPS increases ~3-fold) and disruption of the blood-milk barrier, increasing mastitis risk by 2–3 times. Regarding adaptive immunity, the proliferation and differentiation of T/B cells are impaired, the CD4+/CD8+ T cell ratio decreases, antibody affinity maturation is suppressed, and the efficiency of immune memory formation post-vaccination is reduced. Concerning mammary immunity, the number of viable granulocytes in milk decreases, mammary epithelial cells increase, pro-inflammatory cytokine levels rise, and the risk of clinical mastitis increases 2–3 fold. Furthermore, heat stress induces metabolic reprogramming, gut microbiota dysbiosis, oxidative stress, and activation of the hypothalamic-pituitary-adrenal (HPA) axis. Novel biomarkers, such as Heat Shock Proteins (HSPs), Neutrophil-to-Lymphocyte Ratio (NLR), cytokine profiles (e.g., IL-6/TNF- α), acute-phase proteins (e.g., Haptoglobin, Hp), and epigenetic markers, provide crucial targets for heat-tolerant breeding and early intervention, promising to enhance the climate resilience of the dairy industry.

KEYWORDS

dairy cow, gut-mammary axis, heat stress, immune biomarkers, thermotolerance

1 Introduction

The stark reality of global warming poses unprecedented systemic challenges to animal husbandry, particularly highly intensive dairy farming (1). According to authoritative data from the Intergovernmental Panel on Climate Change (IPCC), the current global average temperature has risen by approximately 1°C compared to pre-industrial levels. This seemingly modest increase has directly led to a significant rise in the frequency, intensity,

and duration of extreme heatwave events (2, 3). Dairy cows, as core production animals, exhibit heightened sensitivity to high-temperature environments due to their unique physiology, large body size, thick hide (hindering heat dissipation), and relatively underdeveloped sweat gland system (relying primarily on respiratory cooling) (4). When environmental temperatures persistently exceed their thermoneutral zone (TNZ, typically considered between 5 °C and 25 °C), the cow's thermoregulatory mechanisms become overwhelmed, rapidly triggering the Heat Stress Response (HSR) (5).

Heat stress is far more than mere discomfort; it initiates a cascade of complex physiological, metabolic, and immune dysfunctions, ultimately translating into substantial economic and production losses (6). Long-term assessment of dairy cow heat stress has primarily relied on traditional metrics like rectal temperature measurement and the Temperature-Humidity Index (THI) (7). While a THI >68 is widely regarded as the critical threshold for heat stress, this approach has significant limitations: it is inherently an environmental parameter incapable of precisely capturing individual variations in physiological responses to heat stress (8). For instance, high-yielding cows, due to greater metabolic heat production, may exhibit significant metabolic disturbances (e.g., exacerbated oxidative stress, negative energy balance) and physiological changes (e.g., sharply elevated respiratory rate, increased core body temperature) at an environmental THI as low as 65, well before the average herd threshold is reached (Figure 1) (9).

Consequently, the development and application of novel biomarkers capable of enabling early warning, possessing high specificity, and accurately reflecting the internal physiological state of the organism have become a forefront hotspot and urgent need in current dairy heat stress research. In this exploration, the immune system, serving as the body's first line of defense and central regulator

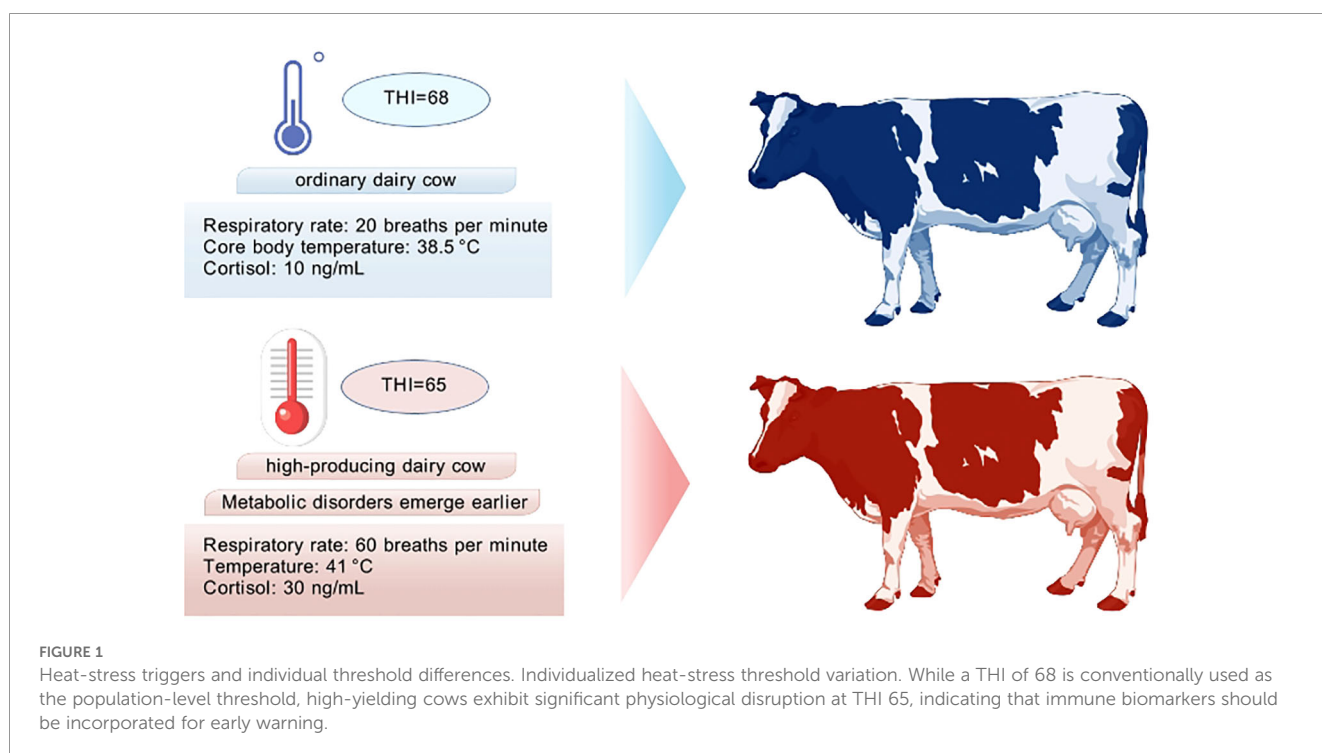
against external environmental stimuli (including heat stress), exhibits dynamic activation states intricately linked to the onset, progression, and consequences of heat stress (10–12). Changes in immune-related indicators (e.g., quantity and activity of specific immune cell subsets, cytokine profiles, acute-phase proteins, immune-related gene expression profiles) often precede or accompany noticeable declines in production performance and the emergence of clinical symptoms, providing a valuable window for early intervention (13–15).

The core objective of this review is to systematically focus on the complex and dynamic changes occurring in the bovine immune system under heat stress conditions. By synthesizing the latest research advances, we will elaborate on the discovery pathways, validation processes, and application potential in research and practice for a range of novel immune-related biomarkers (e.g., specific inflammatory cytokines, heat shock proteins, immune cell functional indicators, epigenetic markers). These markers not only facilitate more precise and individualized assessment of a cow's heat stress status and tolerance capacity but, more importantly, provide a solid scientific foundation and powerful technical support for breeding new dairy cattle varieties with enhanced thermotolerance (molecular breeding), ultimately bolstering the resilience and sustainability of the dairy industry in the face of global warming.

2 Overview of the bovine immune system

2.1 Innate immunity

The innate immune system serves as the primary barrier of the cow's immune defense mechanism, activating rapidly within hours



of pathogen invasion. It comprises key components including physical barriers, humoral factors, and immune cells, which collaborate to mount a swift response against invading pathogens (16).

Physical barriers constitute the outermost line of innate defense, encompassing the skin and mucous membranes. The skin's keratinized layer blocks pathogen entry, while mucous membranes of the respiratory, gastrointestinal, and urogenital tracts clear pathogens via ciliary movement and mucus secretion (17). For example, relaxation time of the teat sphincter increases under heat stress, elevating mastitis risk (18). Humoral factors also play vital roles in innate immunity. Lysozyme in serum disrupts bacterial cell walls, lactoferrin inhibits bacterial proliferation by chelating iron ions, and the complement system lyses pathogens via classical and alternative pathways (19, 20). These humoral factors not only directly kill pathogens but also enhance the phagocytic activity of immune cells (21). Phagocytic cells are core components of innate immunity, including neutrophils and macrophages (22). Neutrophils constitute 40-50% of blood leukocytes and rapidly migrate to infection sites via chemotaxis to phagocytose and kill pathogens (23). Heat stress can reduce neutrophil chemotactic capacity by 30%, impairing their pathogen clearance efficiency (24). Macrophages clear pathogens via phagocytosis and participate in antigen presentation, activating subsequent adaptive immune responses (25).

Through mechanisms involving physical barriers, humoral factors, and immune cells, the bovine innate immune system rapidly responds to pathogen invasion, reducing infection and activating adaptive immunity (26). In production settings, an efficient innate immune system significantly lowers disease incidence in cows, prevents ailments like mastitis, reduces veterinary drug use, improves production performance and milk quality, and increases economic returns (27). However, factors like heat stress can weaken its defensive functions, increasing disease risk.

2.2 Adaptive immunity

The bovine adaptive immune system is a crucial component of its immune defense, characterized by high specificity and memory, primarily mediated by B cells and T cells (28). It plays a key role in cow health and productivity, effectively recognizing and eliminating pathogens while providing long-term immune protection (29).

B cells are primarily responsible for humoral immune responses in adaptive immunity, producing specific antibodies to recognize and neutralize pathogens (30). Antibodies (immunoglobulins) are products of B cells and exist in various types, including IgM, IgG, IgA, IgD, and IgE (31). In cows, IgG1 and IgG2 are predominant types, playing significant roles in neutralizing viruses and toxins, and in bacterial agglutination and opsonization (32). IgA primarily functions at mucosal sites like the respiratory and gastrointestinal tracts, preventing pathogen adhesion and invasion (33). T cells are mainly responsible for cell-mediated immune responses, including cytotoxic T cells (CTLs) and helper T cells (Th cells) (34). CTLs

directly kill pathogen-infected cells, while Th cells regulate the activity of other immune cells by secreting cytokines (30). In cattle, $\gamma\delta$ T cells also play important roles, particularly in neonates, where they may compensate for the immaturity of functions like neutrophils (35).

The adaptive immune system is vital for bovine health and productivity. An efficient adaptive immune system significantly reduces disease incidence, effectively prevents common diseases like mastitis, thereby decreasing veterinary drug use frequency, and subsequently enhances cow productivity and milk quality. For instance, vaccination can induce adaptive immune responses, establishing immune memory and enhancing resistance to specific pathogens (36). Moreover, the long-term persistence of immune memory cells provides sustained protection for cows.

3 Impact of heat stress on bovine innate immunity

3.1 Impact of heat stress on bovine immune barriers

You may insert up to 5 heading levels into your manuscript as can be seen in “Styles” tab of this template. These formatting styles are meant as a guide, as long as the heading levels are clear, Frontiers style will be applied during typesetting. The bovine immune barrier comprises multi-layered defense mechanisms including the skin barrier, respiratory barrier, and intestinal barrier, which play crucial roles in defending against pathogen invasion and maintaining overall health (37). Heat stress, as a common environmental stressor, can compromise the integrity of these immune barriers through various mechanisms, significantly reducing the cow's disease defense capacity (38).

The skin, as the first line of immune defense, effectively blocks pathogen entry under normal physiological conditions (39). Under heat stress, cows dissipate heat through sweating and increased respiratory rate; this process can disrupt skin barrier integrity, leading to increased water loss from the skin surface, dryness, and impaired barrier function (40). High temperature and humidity environments alter the skin surface microbiome, increasing the abundance of pathogenic bacteria (e.g., *Staphylococcus aureus*) and the probability of penetration through the damaged stratum corneum (41, 42). This decline in barrier function facilitates easier pathogen penetration into the body. Prolonged exposure to high temperatures may alter the structure of the skin surface microbial community, significantly increasing the risk of bacterial or fungal infections, further weakening the skin's defensive capabilities (41). Heat stress exacerbates rumen epithelial sloughing, disrupting its physical barrier, and interferes with pathways related to DNA replication/repair and amino acid metabolism, though no specific impact on tight junction protein or TLR4 signaling expression was found (43). Heat stress may maintain rumen epithelial barrier integrity by upregulating HSP expression, and increased amino acid metabolism in the rumen could affect systemic nutrient utilization (44).

The respiratory immune barrier is also significantly affected by heat stress. High temperatures cause a marked increase in respiratory rate and depth in cows, a physiological cooling mechanism, but frequent respiration also increases opportunities for pathogens to enter the respiratory tract (45, 46). Simultaneously, microbial concentrations in the air may rise under high-temperature conditions, further exacerbating the risk of respiratory infections (47). Studies show that drying mucosa develops micro-fissures, making it easier for airborne pathogenic microbes (e.g., *Mycoplasma*, *Streptococcus pneumoniae*) to adhere and invade, thereby increasing clinical respiratory infection rates (48). The respiratory mucosa is a vital barrier against pathogen invasion; its surface mucus layer and ciliary motion effectively clear inhaled pathogens (49). Heat stress can cause drying of the respiratory mucosa and reduced ciliary motility, weakening its defense capacity and increasing the incidence of respiratory infections (50). Research indicates heat stress forces cows to double their respiratory rate (from 20-30/min to 60-80/min), accelerating water evaporation from the respiratory mucosa, increasing mucus viscosity, reducing ciliary motility efficiency by over 50%, and weakening pathogen clearance capacity (51, 52).

The intestinal barrier is a key component of the bovine immune barrier impacted by heat stress. Heat stress can downregulate the expression of tight junction proteins (e.g., Claudin-1, Occludin) in intestinal epithelial cells, impairing barrier function and increasing intestinal permeability (53). This barrier dysfunction allows antigens like bacteria and toxins from the gut lumen to more easily enter the bloodstream, triggering systemic immune responses (Figure 2) (54). For example, heat stress downregulates Claudin-1 and Occludin expression, increasing paracellular permeability and widening intestinal barrier “leaks” (55). Heat stress may also alter the structure and function of the gut microbiota, leading to a reduction in beneficial bacteria and an increase in harmful bacteria, thereby disrupting gut microbial balance (56). For instance, increased intestinal permeability allows endotoxin (LPS) and Gram-negative bacteria to translocate into the circulation, elevating serum LPS concentrations and triggering systemic inflammation (57). Gut dysbiosis not only affects digestive and absorptive functions but may also reduce disease resistance by impacting the development and function of the gut mucosal immune system (58). For example, the abundance of beneficial bacteria (e.g., *Lactobacillus*) in the gut decreases by ~60%, while conditional pathogens (*E. coli*) proliferate 2.8-fold, exacerbating intestinal inflammation (59–61). Dysbiosis leads to decreased production of short-chain fatty acids (SCFAs, e.g., butyrate), weakening their role in energy supply and anti-inflammatory regulation for gut epithelial cells (62).

3.2 Impact of heat stress on bovine innate immune factors

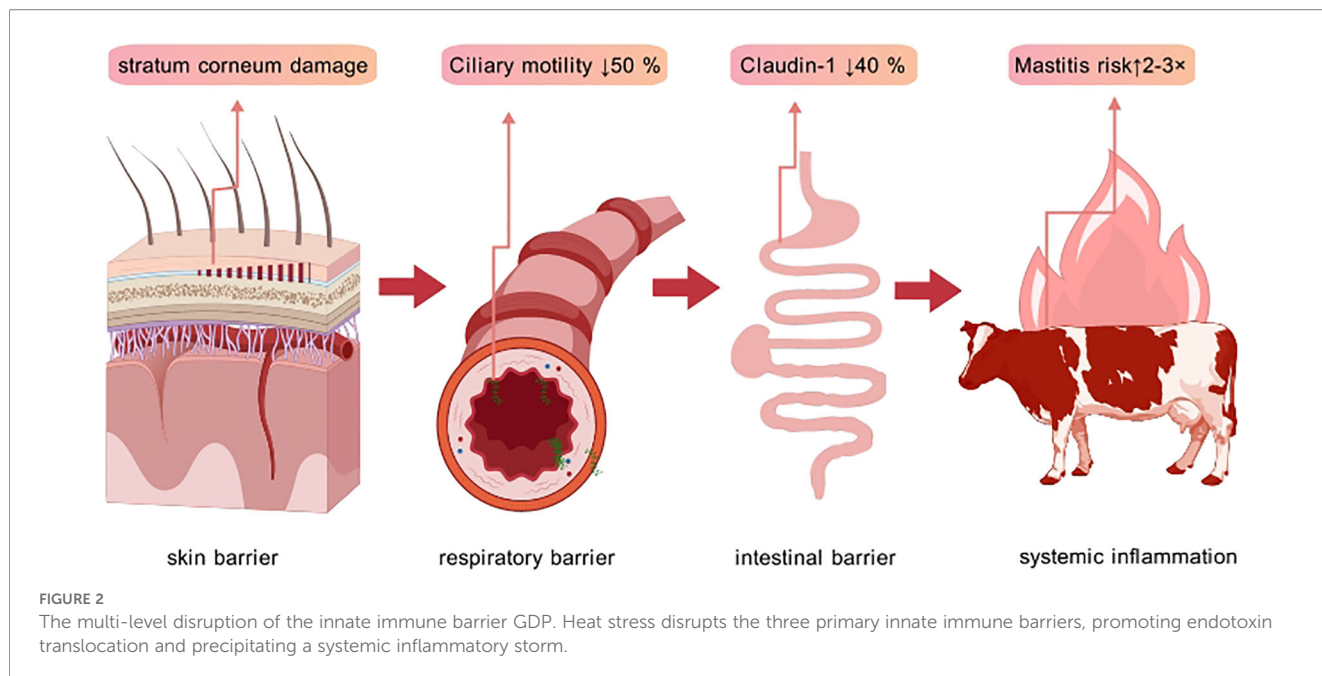
Heat stress impairs innate immune function through multiple avenues. It significantly compromises the function of innate immune cells, including the phagocytic capacity and chemotaxis

of macrophages, monocytes, and neutrophils, reducing the cow's pathogen clearance ability and the speed of local immune responses (63). Studies show heat stress alters cytokine levels: pro-inflammatory cytokines (e.g., TNF- α , IL-6) increase, while changes in immunosuppressive factors (e.g., IL-10) can lead to immune system imbalance, placing cows in a suboptimal health state (64, 65). Heat stress also suppresses the synthesis and secretion of antimicrobial peptides (e.g., defensins, cathelicidins), reducing the cow's direct defense capability against pathogens (24). Research indicates a decline in the opsonophagocytic index (OPI), reduced efficiency of membrane attack complex (MAC) formation, and prolonged clearance cycles for Gram-negative bacteria (66, 67).

Regarding blood immune parameters, heat stress causes a decrease in leukocyte counts, particularly lymphocytes and neutrophils, while also affecting the synthesis and secretion of immunoglobulins (e.g., IgG, IgM), further weakening humoral immune responses (68). Heat stress upregulates the glucocorticoid-induced protein GILZ, suppressing neutrophil chemotactic activity, and excessive ROS reduces phagocytic capacity by ~50% (69, 70). M2 polarization of macrophages is hindered, IL-10 secretion decreases, while TNF- α secretion increases, exacerbating tissue oxidative damage (71–73).

Oxidative stress is another key mechanism of heat stress impact. Heat stress increases free radical generation, causing oxidative damage that directly harms cells and impairs immune cell function, reducing the synthesis of immune factors (74). Chronic heat stress may lead to reduced immune tolerance, increasing the cow's susceptibility to infections like mastitis and respiratory diseases (75). Concerning mammary immunity, heat stress impairs the function of mammary leukocytes, reduces concentrations of innate immune factors like whey immunoglobulins and lysozyme, and weakens the innate immune defense capacity of the mammary gland (76).

In summary, heat stress significantly impairs the phagocytic capacity and chemotaxis of macrophages, monocytes, and neutrophils, reducing the cow's pathogen clearance ability and the speed of local immune responses. Concurrently, heat stress alters cytokine profiles: increased pro-inflammatory cytokines (e.g., TNF- α , IL-6) and altered immunosuppressive factors (e.g., IL-10) may cause immune system imbalance, placing cows in a suboptimal health state. Additionally, heat stress suppresses the synthesis and secretion of antimicrobial peptides (e.g., defensins, cathelicidins), reducing the cow's direct defense against pathogens. Heat stress causes a decline in the opsonophagocytic index (OPI), reduced membrane attack complex (MAC) formation efficiency, and prolonged clearance cycles for Gram-negative bacteria. Blood immune parameters show decreased leukocyte counts, particularly lymphocytes and neutrophils, alongside impaired immunoglobulin (e.g., IgG, IgM) synthesis and secretion, further weakening humoral immunity. Oxidative stress markers increase; heat stress elevates free radical generation, causing oxidative damage that directly harms cells and impairs immune cell function, reducing immune factor synthesis. In mammary immunity, heat stress impairs mammary leukocyte function, reduces concentrations of innate immune factors like whey immunoglobulins and lysozyme, and



weakens mammary innate defense capacity. Heat stress impairs bovine innate immune function through multiple mechanisms; these changes serve as potential biomarkers for monitoring and assessing the impact of heat stress on cow health.

4 Impact of heat stress on bovine adaptive immunity

Heat stress exerts significant negative effects on the bovine adaptive immune system, primarily manifesting as suppression of immune cell function, imbalance in immune factor expression, and enhanced immune tolerance (77). Regarding immune cells, heat stress markedly inhibits the proliferation and differentiation capacity of T cells and B cells; specifically, CD4⁺ T cell proliferation declines, thymocyte apoptosis increases, leading to significantly weakened cytotoxic responses (78). B cell antibody affinity maturation is impaired, activation-induced cytidine deaminase (AID) expression decreases, serum IgG titers fall, and the efficiency of immune memory formation post-vaccination is reduced (79).

Adaptive immunity, the core defense mechanism for specific pathogen recognition and clearance, shows significant functional suppression under heat stress (80). Bovine adaptive immunity, mediated by T and B lymphocytes, exhibits acquired characteristics, memory, and high specificity, playing a key role in maintaining immune homeostasis (81). Heat stress disrupts the functional balance of this system through multiple pathways. For T cells, thymic microenvironment disturbances lead to decreased CD4⁺ T cell proliferation capacity, Th1/Th2 cytokine imbalance, and significantly weakened cytotoxic responses (82). B cells exhibit impaired antibody affinity maturation, reduced serum IgG titers, and decreased efficiency of immune memory formation post-vaccination (83). Heat stress-induced elevation of glucocorticoid

levels suppresses the NF- κ B signaling pathway, downregulating macrophage phagocytic activity and natural killer (NK) cell cytotoxicity, creating a state of systemic immunosuppression (84). Chronic heat stress can further lead to enhanced immune tolerance, increasing the risk of mastitis and respiratory diseases. Studies show that selenium and vitamin E supplementation can partially reverse heat stress damage (85).

4.1 Impact of heat stress on bovine cell-mediated immunity

Heat stress is a common physiological stress response in cows exposed to high temperatures, significantly impacting their immune system, particularly cell-mediated immunity. Heat stress disrupts immune cell function and immune factor balance through multiple mechanisms, thereby weakening the cow's disease resistance. Heat stress alters immune cell function and distribution. Changes in peripheral blood leukocyte distribution manifest as increased neutrophil counts and decreased lymphocyte counts; this shift may promote chronic inflammation and weaken disease resistance (86, 87). Macrophage phagocytosis, antigen presentation, and cytokine secretion functions are suppressed, reducing immune response capacity (88). The proliferation and differentiation capacities of T cells and B cells are also inhibited, further impairing adaptive immune responses (89, 90).

Heat stress reprograms the bovine immune system through multiple pathways. When exposed to high temperatures, the hypothalamic-pituitary-adrenal (HPA) axis is rapidly activated, leading to a significant rise in glucocorticoid levels (primarily cortisol) (91). Cortisol, a core stress hormone, binds to glucocorticoid receptors (GRs) on immune cells, suppressing the transcription of pro-inflammatory cytokines (e.g., IL-2, IFN- γ)

while inducing lymphocyte apoptosis, ultimately establishing a state of immunosuppression (92). Research confirms that serum cortisol levels in heat-stressed cows can be 2–3 times higher than in non-stressed periods, showing a significant negative correlation with decreased total leukocyte count and reduced neutrophil phagocytic function (93).

Simultaneously, heat stress induces mitochondrial dysfunction, prompting excessive accumulation of reactive oxygen species (ROS) and triggering oxidative stress (94). This directly causes protein denaturation, lipid peroxidation, and DNA damage, accompanied by the collapse of the antioxidant enzyme system—superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity significantly decrease, while levels of the oxidative end-product malondialdehyde (MDA) significantly increase (95, 96). Studies show SOD concentration is significantly negatively correlated with THI ($r=-0.406$), while MDA content is significantly positively correlated with THI ($r=0.381$), highlighting the close link between oxidative stress and heat load (97).

Heat stress also affects immune cell function via metabolic reprogramming. For example, key metabolites like linoleic acid and fructose are downregulated during heat stress; these molecules are not only energy substrates but also immunoregulatory signaling molecules (98). Metabolic disturbances form a vicious cycle with gut dysbiosis (e.g., reduced *Prevotella*), further impairing intestinal barrier function, increasing endotoxin translocation risk, and ultimately leading to systemic inflammation (99, 100).

The Neutrophil-to-Lymphocyte Ratio (NLR), an indicator of systemic inflammation, significantly increases during heat stress (101). Neutrophil numbers decrease, and their chemotaxis and phagocytic function are impaired, while lymphocyte subset ratios become imbalanced: the CD4+/CD8+ T cell ratio decreases, and B cell antibody production capacity is reduced (102). Research indicates lymphocyte counts in heat-stressed cows are significantly lower than in non-stressed groups ($P<0.05$), while levels of pro-inflammatory cytokines like IL-2, IL-6, and TNF- α are significantly elevated ($P<0.05$) (103).

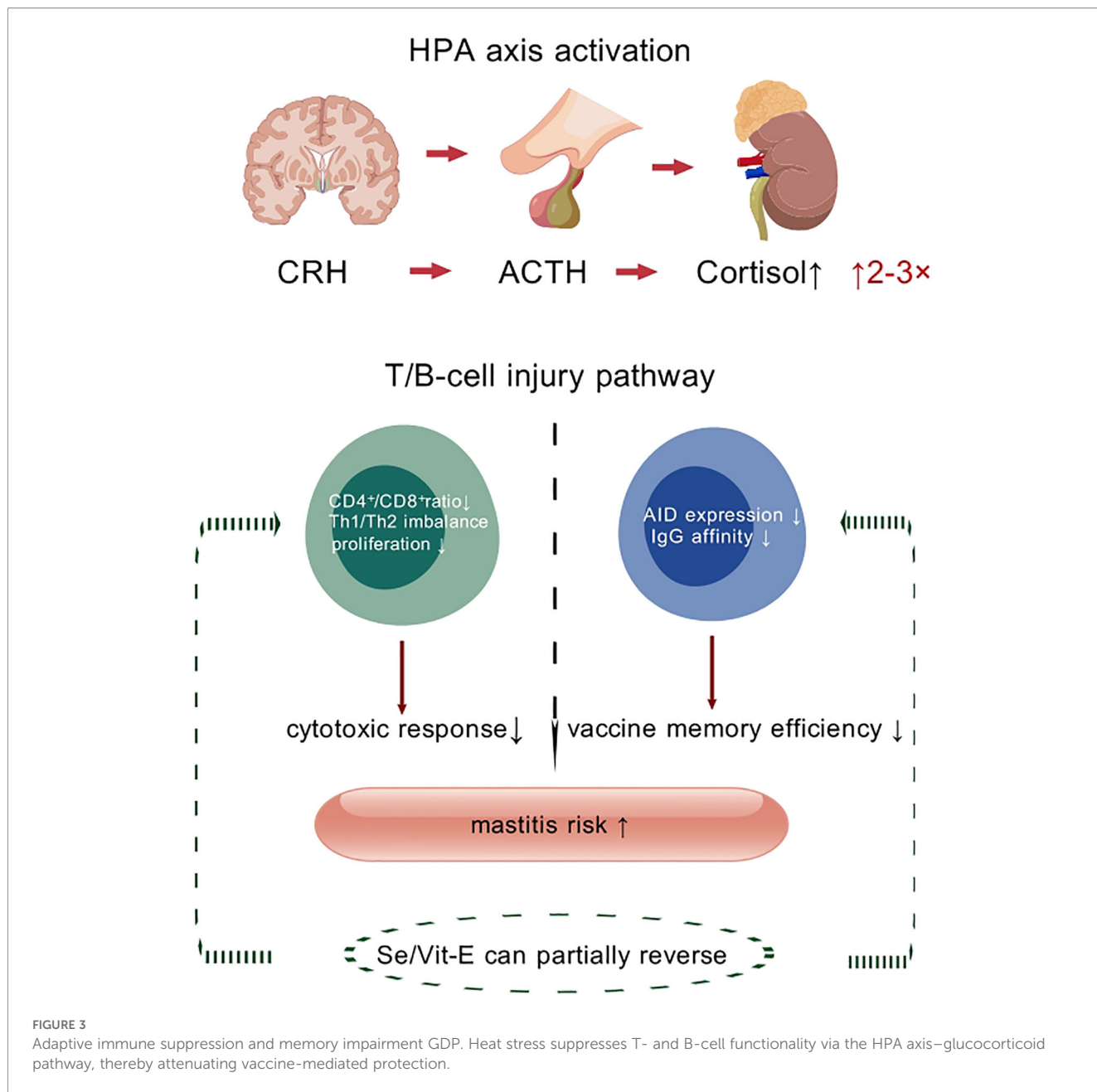
A shift in monocyte functional phenotype is also significant. Heat stress induces monocyte differentiation towards anti-inflammatory M2-type macrophages, highly expressing arginase 1 (Arg1) and IL-10, thereby suppressing Th1-type immune responses (104). While this phenotypic shift helps limit inflammatory damage, it concurrently weakens the body's ability to clear pathogens, increasing the risk of mastitis and metritis.

A burst increase in pro-inflammatory cytokines is a core feature of the early pathophysiology of heat stress in cows. Research finds plasma levels of IL-6, TNF- α , and IL-1 β are significantly elevated in heat-stressed cows, with TNF- α showing a significant positive correlation with the THI index ($r=0.423$) (103, 105). These cytokines amplify inflammatory cascades by activating signaling pathways like NF- κ B and mediate typical symptoms such as fever and anorexia (106). Notably, IL-6 plays a dual role: as a pro-inflammatory cytokine in the acute phase response, and by inhibiting thyroid hormone secretion to reduce heat production, forming an adaptive feedback loop (107, 108).

Acute-phase proteins (APPs) like haptoglobin (Hp) and serum amyloid A (SAA) rise significantly during heat stress, serving as sensitive indicators of tissue damage (109, 110). They are primarily synthesized by the liver in response to inflammatory signals and participate in processes like opsonization and free radical scavenging (111). Studies show Hp levels in heat-stressed cows correlate positively with rectal temperature (RT), suggesting their potential as markers for assessing inflammatory load (112, 113) (Figure 3).

4.2 Impact of heat stress on bovine humoral immunity

Innate immune factors rapidly recognize and respond to foreign pathogens. In high-temperature environments, the cow's humoral immune system is significantly affected. Heat stress suppresses the function of key immune cells like T cells, B cells, and macrophages. T cell numbers decrease, proliferation declines, weakening cell-mediated immune responses (114); B cell antibody synthesis and secretion capacity is impaired, affecting immune memory establishment (115); macrophage phagocytic ability and inflammatory cytokine generation are also suppressed, reducing the overall defensive capacity of the immune system (116). Heat stress significantly impacts antibody production in cows, particularly the synthesis and secretion of immunoglobulins like IgG, IgA, and IgM (117). IgG is the most important antibody in milk; its decreased level weakens immune protection for newborn calves (118). Reduced antibody production is closely linked to endocrine changes induced by heat stress (e.g., elevated cortisol). Cortisol suppresses B and T cell function, further impacting antibody production (119). Heat stress triggers a series of inflammatory reactions, elevating levels of cytokines like IL-1 β , IL-6, and TNF- α (120). While these cytokines help initiate acute immune responses, chronic inflammation can lead to immunosuppression and disrupt immune system balance (121). Oxidative stress induced by heat stress increases free radical generation, damaging immune cell function (122). Heat stress also affects mammary blood circulation in cows, reducing the delivery of immune cells and transport of antibodies, thereby impacting the levels of immune components in milk (123). Decreased levels of IgG and IgA in milk weaken immune protection for newborn calves (124). Heat stress also increases the risk of mammary inflammation, further affecting milk quality and the cow's immune status (125). Heat stress causes elevated levels of stress hormones like cortisol (126). Cortisol has immunosuppressive effects, reducing immune cell proliferation and cytokine secretion, thereby suppressing normal immune system function (127). Chronically elevated cortisol levels are a major contributor to reduced immunity in cows (128). Heat stress impairs the function of mammary immune cells (e.g., macrophages, lymphocytes), reduces the mammary gland's ability to secrete immune factors, and increases the risk of mammary infection (129). Chronic heat stress may also reduce the number of local mammary immune cells, further impacting milk immunity (130).



5 Impact of heat stress on mammary system immunity

Heat stress exerts multifaceted effects on the mammary system immunity of milk-producing animals like dairy cows. It causes a reduction in immune function, weakening the animal’s defense against pathogens, increasing the risk of udder infection by pathogenic bacteria, and thereby predisposing to mastitis. Studies indicate that under heat stress conditions, immunoglobulin concentrations decrease and cytokine levels increase in cow blood, suppressing overall immune function (131). At the cellular level, heat stress alters the composition and activity of immune cells within the mammary gland. Lengi et al. (2022), using flow cytometry analysis, found that compared to cows under

thermoneutral conditions, heat-stressed cows had significantly elevated concentrations of mammary epithelial cells in milk, while viable granulocytes and total viable CD45⁺ cells decreased by 17% and 12%, respectively. This indicates heat stress affects the relative numbers and viability of certain somatic cell populations in milk; reduced immune cell viability may negatively impact mammary immune capacity in cows (15). Heat stress also interferes with the normal physiological functions and defense mechanisms of the mammary gland. It induces physiological and metabolic disturbances in cows, including altered blood circulation and endocrine dysregulation; these changes may impair normal mammary function, creating favorable conditions for pathogen invasion and proliferation (132). For example, reduced feed intake during heat stress leads to insufficient nutrient intake,

affecting systemic immunity and defense; excessive water intake dilutes antimicrobial components in milk, reducing the udder's ability to resist infection (133). During the dry period, heat stress may negatively impact mammary involution due to endocrine changes (decreased estrogen, increased prolactin). Immune cells play a crucial role in preparing mammary tissue for the next lactation during this stage; heat stress disruption of this process may impair immune protection in the subsequent lactation (134). Under heat stress, milk retention and reduced flow within the udder favor pathogen colonization and proliferation in the mammary gland, thereby inducing mastitis (135). Research indicates that heat load significantly influences the occurrence of clinical mastitis in dairy cows; higher milk yield, later lactation stage, and greater parity increase the risk of clinical mastitis under heat stress (136).

5.1 Impact of heat stress on bovine mammary immune homeostasis

Heat Stress is a significant environmental stress factor in modern dairy farming, adversely affecting cow productivity, mammary immune function, and milk quality (137). The impact of heat stress on the bovine immune system is multifaceted, particularly concerning mammary immune homeostasis (138). Immune system dysregulation can lead to mammary infections, subsequently affecting milk quality (27). Heat stress alters immune cell function, including reduced numbers or impaired function of peripheral blood leukocytes, and weakened phagocytosis by macrophages and dendritic cells, increasing mastitis risk (139). Heat stress also leads to enhanced inflammatory responses and elevated levels of stress hormones (e.g., cortisol, epinephrine) (140, 141), suppressing normal immune cell function, especially anti-infective capacity (142). Chronic heat stress may induce chronic low-grade systemic inflammation; local mammary inflammatory responses are consequently heightened, predisposing to immune-related diseases like mastitis (143). Heat stress also reduces the secretion of immunoglobulins (e.g., IgG, IgA), weakening local mammary immune defense and making cows more susceptible to pathogenic microorganisms (144). Cytokine imbalance is another significant effect of heat stress: pro-inflammatory cytokine levels (e.g., TNF- α , IL-1 β , IL-6) rise (145), while anti-inflammatory cytokine levels (e.g., IL-10) fall, promoting inflammation onset and exacerbating immunosuppression (146).

Specific impacts of heat stress on mammary health include increased mastitis incidence, mammary microbial dysbiosis, and reduced milk quality (147). Mastitis is a common mammary infectious disease, typically caused by bacteria (148, 149). Heat stress-induced decline in immune system function weakens mammary defense against pathogens, thereby increasing mastitis incidence (150). The mammary gland harbors a microbial community that plays a role in maintaining immune homeostasis (151). Heat stress may alter the normal mammary microbiota (152), increasing the proliferation of harmful bacteria (e.g., *Staphylococcus aureus*, *Streptococcus* spp.), leading to mammary infection (153). Due to impaired mammary immune function, cows under heat stress may secrete more immune-related molecules (e.g.,

lactoferrin, enzymes), which can affect milk composition, leading to reduced milk quality (44). For example, milk fat and protein content may decrease (154), while levels of casein, lactose, etc., may change, affecting final dairy product quality (155).

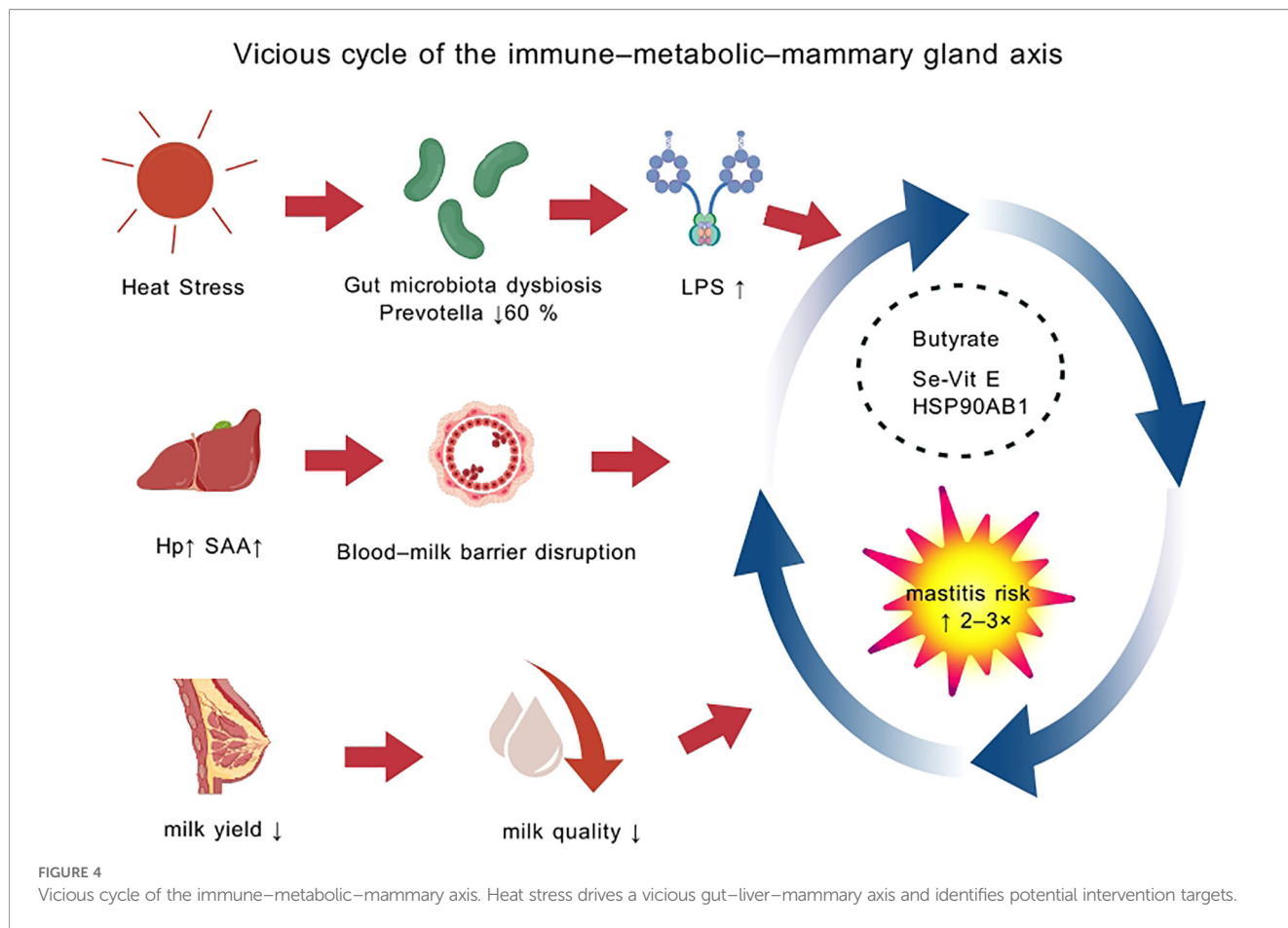
The impact of heat stress on bovine mammary immune homeostasis is multifaceted. By reducing the defensive capacity of the immune system, exacerbating inflammatory responses, and altering the mammary microbiota, it contributes to mammary health problems and affects dairy product quality (156, 157). Improving the environment, optimizing management, and enhancing immunity can effectively mitigate the negative impacts of heat stress, ensuring cow productivity and milk quality.

5.2 Impact of heat stress on bovine mastitis

The impact of heat stress on bovine mastitis is a complex, multi-dimensional issue. Particularly under hot and humid conditions, heat stress significantly affects the cow's physiological state, immune system, and mammary health, thereby adversely influencing mastitis incidence, severity, and treatment efficacy (158). Heat stress causes elevated body temperature and increased respiratory rate; these physiological changes not only impair immune cell function but also reduce the defensive capacity of skin and mammary tissues, increasing the risk of pathogen invasion (159). Research shows that under heat stress, the somatic cell count (SCC) in cow milk significantly increases, directly correlating with mastitis incidence (136). Due to immune system impairment by heat stress, the mammary defense capacity is significantly reduced when encountering bacterial infections, leading to a marked rise in mastitis incidence (160). Studies demonstrate a clear correlation between heat stress and mastitis, especially during summer or hot, humid seasons, when the risk of mastitis outbreaks increases (161). Heat stress not only aggravates clinical mastitis but also worsens subclinical mastitis symptoms, causing chronic inflammation to progress to clinical mastitis (160). Heat stress may also affect milk quality, manifesting as increased udder temperature, reduced milk yield, and altered milk composition (162). Mastitis itself elevates mammary tissue temperature, further impacting milk quality (163). Heat stress negatively impacts the cow's overall physiological state, leading to reduced milk production (164). Mastitis and heat stress may also increase bacterial content in milk, leading to decreased protein, fat, and lactose levels, affecting dairy product quality (165).

Heat stress not only weakens the cow's immune system but also creates favorable conditions for pathogen growth and dissemination. It increases free radical generation and decreases antioxidant enzyme activity (e.g., SOD, GSH-Px); oxidative damage impairs immune cell function (166). This oxidative stress state directly damages cells and disrupts immune-metabolic processes, reducing immune cell proliferation and differentiation capacity (167, 168).

Heat stress damages tight junction proteins (e.g., Claudin-3, Occludin) in mammary epithelial cells, increasing paracellular permeability and impairing blood-milk barrier function (169) (Figure 4). This barrier disruption allows pathogens and



inflammatory factors to penetrate mammary tissue more easily, significantly increasing infection risk (170). Heat stress increases serum levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6) while decreasing anti-inflammatory cytokines (e.g., IL-10), causing immune system imbalance; this inflammatory dysregulation further affects metabolic processes, creating a vicious cycle (171). Under heat stress, the disruption of mammary epithelial tight junctions, reduced concentrations of antimicrobial substances like lysozyme and lactoferrin in milk, and increased colonization by pathogens like *S. aureus* occur (172). Elevated levels of IL-8 and TNF- α in milk trigger excessive inflammatory responses, while insufficient anti-inflammatory factors exacerbate mammary tissue damage, potentially increasing clinical mastitis incidence by 2–3 fold (173, 174). Heat stress significantly increases mastitis incidence in dairy cows through multiple mechanisms: weakening the immune system, disrupting mammary barrier function, and exacerbating inflammation.

To mitigate the negative impact of heat stress on bovine mastitis, farm managers need to implement measures including environmental control, water management, nutritional modulation, enhanced udder care, and regular health monitoring. These strategies help improve cow living conditions and immune status, effectively reducing heat stress-related mastitis risk and enhancing production efficiency and milk quality (175). The impact of heat stress on bovine mastitis is multifaceted, involving both decreased immune system function and

compromised mammary health (176). To reduce its negative effects, adopting scientific environmental control, nutritional supplementation, and mammary health management is crucial. Optimizing management and preventive measures can effectively lower heat stress-induced mastitis risk and improve cow productivity and milk quality.

6 Impact of heat stress on bovine immunometabolism

Heat stress profoundly impacts bovine immunometabolism, involving multifaceted changes in immune cell function, oxidative stress, endocrine regulation, and overall metabolic status. At the immune cell level, heat stress significantly suppresses neutrophil chemotaxis and bactericidal capacity, reduces macrophage phagocytic activity, and impairs lymphocyte proliferation and differentiation (177). These changes weaken the cow's pathogen clearance ability, increasing infection risk. Increased oxidative stress is another key mechanism, characterized by excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), exceeding the clearance capacity of antioxidant systems, leading to cellular damage and further suppression of immune cell function (178). Regarding endocrine regulation, heat stress activates the hypothalamic-pituitary-adrenal (HPA) axis, elevating cortisol levels, which subsequently suppresses immune cell activity and

cytokine secretion (179). Heat stress also alters thyroid hormone levels, reducing basal metabolic rate and energy supply for immune cells. At the systemic metabolic level, heat stress causes negative energy balance, lowering serum glucose and non-esterified fatty acid (NEFA) levels while increasing lactate accumulation, impairing normal immune system function (180). These combined effects not only weaken the cow's immune defense but also significantly negatively impact production performance and health (181).

6.1 Overview of bovine immunometabolism

Bovine immunometabolism refers to the metabolic processes involved in the immune system maintaining normal physiological function and responding to pathogen invasion (182). It encompasses not only energy metabolism and nutrient allocation but also involves oxidative stress, endocrine regulation, and the functional state of immune cells (183). Proper functioning of immunometabolism is crucial for maintaining cow health and productivity. At rest, immune cells rely on highly energy-efficient processes like the tricarboxylic acid (TCA) cycle, while activated immune cells shift towards glycolysis. This metabolic reprogramming not only affects immune cell function but may also influence systemic metabolism through metabolites and signaling molecules (184–186).

The periparturient period is a critical phase for immunometabolic changes in cows. During this stage, cows undergo physiological processes like placental expulsion, uterine involution, fat mobilization, and lactogenesis, all accompanied by tissue remodeling and inflammatory responses (187). Fat mobilization promotes inflammatory responses in adipose tissue, releasing large amounts of non-esterified fatty acids (NEFA), thereby affecting systemic metabolism (188, 189). Circulating glucose in postpartum cows is preferentially allocated to immune cells and the mammary gland; the activated immune system further consumes glucose, exacerbating negative energy balance (190). Immunometabolism is closely linked to bovine health. Mastitis is a common immunometabolic disease; its major pathogen, *Staphylococcus aureus* (SA), evades host immunity by secreting metabolic and virulence factors like lipases (191–193). Periparturient cows often experience metabolic inflammation, characterized by elevated serum levels of pro-inflammatory cytokines (e.g., IL-6, TNF- α) and acute-phase proteins (e.g., Serum Amyloid A, SAA); this inflammatory state affects the appetite center, leading to hypoglycemia, hypoinsulinemia, and reduced feed intake, further worsening negative energy balance (194, 195). Immunometabolic regulation can be achieved through nutritional and immunological interventions. For example, Niacin, a known inhibitor of fat mobilization, can reduce fat mobilization during the transition period, alleviating metabolic inflammation, while also influencing immune cell metabolic state, promoting a shift from pro-inflammatory to anti-inflammatory phenotypes (196–198). By reducing inflammatory factor production, fat mobilization and hepatic metabolic disturbances can be mitigated (199).

Bovine immunometabolism exhibits significant dynamic changes during the periparturient period; its dysregulation is

closely associated with various diseases. Nutritional and immunomodulatory approaches can effectively improve metabolic and immune status, providing a theoretical basis for healthy dairy farming.

6.2 Immunometabolic biomarkers in the heat stress environment

Heat stress increases free radical generation in cows and decreases the activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px); oxidative damage impairs immune cell function (200). This oxidative stress state directly damages cells and disrupts immunometabolic processes, reducing immune cell proliferation and differentiation capacity (201). Heat stress reduces feed intake, decreasing energy intake, while the energy required to maintain body temperature increases, leading to negative energy balance (202). This shift in energy metabolism affects immune system function, as immune responses demand substantial energy support. Studies show heat stress lowers serum glucose and non-esterified fatty acid (NEFA) levels while increasing lactate accumulation (203). Heat stress significantly impacts immune cell function, including neutrophils, macrophages, and lymphocytes. Research indicates it suppresses neutrophil chemotaxis and bactericidal capacity, reduces macrophage phagocytic activity, and impairs lymphocyte proliferation and differentiation (63, 74). Heat stress also increases immune cell apoptosis, further reducing immune system function (204). Heat stress activates the hypothalamic-pituitary-adrenal (HPA) axis, elevating cortisol levels (205, 206). Cortisol has immunosuppressive effects, reducing immune cell proliferation and cytokine secretion (207). Heat Shock Proteins (HSPs) are among the most important molecules in the heat stress response; they not only exert protective effects during cellular damage but also mitigate cell injury and enhance immune defense against pathogens by regulating protein folding, antioxidant responses, and immune reactions (208). Heat stress also suppresses thyroid function, reducing thyroid hormone (T3, T4) levels, lowering basal metabolic rate and energy supply for immune cells (209). Heat stress affects not only local immunometabolism but also systemic immunometabolism through multiple mechanisms. Studies show it increases serum levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6) while decreasing anti-inflammatory cytokines (e.g., IL-10), causing immune system imbalance (145). This immune dysregulation further impacts metabolic processes, creating a vicious cycle. Heat stress also affects gut microbiota structure, alters intestinal barrier function, increases the risk of endotoxemia, and further disrupts systemic immunometabolism (210, 211).

Heat stress causes significant alterations in the plasma metabolome. Targeted metabolomic analysis reveals that 9 metabolites, including linoleic acid and fructose, are downregulated during heat stress; these molecules are not only energy sources but also signaling molecules regulating immune cell function (2, 212). Linoleic acid, a polyunsaturated fatty acid,

participates in synthesizing anti-inflammatory mediators like resolvins; decreased fructose levels are directly linked to gut dysbiosis, affecting short-chain fatty acid production (213).

The gut microbiota-immune axis plays a key role in heat stress. Genus-level analysis shows a significant decrease in *Prevotella* abundance in the feces of heat-stressed cows; this genus is a major player in dietary fiber fermentation and butyrate production (214). Butyrate, a primary energy source for colonocytes, has multiple functions: maintaining intestinal barrier integrity, inducing regulatory T cell differentiation, and inhibiting NF- κ B activity (215). Its reduction leads to increased intestinal permeability, endotoxin translocation, and triggers systemic low-grade inflammation. Conversely, the relative abundance of opportunistic pathogens like *Escherichia* increases, further elevating infection risk (216).

7 Discussion

Heat stress impacts the bovine immune system multifariously, involving barrier function disruption, altered immune cell activity, and dysregulation of the metabolism-immune axis. Significant downregulation of intestinal tight junction proteins (Claudin-1/Occludin) causes endotoxin translocation, triggering systemic inflammation and disrupting the blood-milk barrier, markedly increasing mastitis risk. Reduced efficiency of respiratory mucosal ciliary movement also impairs pathogen clearance. Regarding immune cell function, decreased neutrophil chemotaxis and macrophage phagocytic activity, coupled with suppressed antimicrobial peptide synthesis, weaken innate immunity. Adaptive immunity is characterized by a reduced CD4+/CD8+ T cell ratio, impaired B cell antibody affinity maturation, and diminished vaccine-induced immune memory efficiency. Dysregulation of the metabolism-immune axis further exacerbates the problem; heat stress-induced metabolic reprogramming and gut dysbiosis form a vicious cycle, leading to heightened oxidative stress. These findings reveal the systemic impact of heat stress on bovine health, providing a crucial foundation for subsequent research.

The immune-related biomarkers proposed in this study demonstrate significant potential for early warning, individualized assessment, and breeding guidance. Changes in the Neutrophil-to-Lymphocyte Ratio (NLR), Heat Shock Proteins (HSP70/HSP90), and acute-phase proteins (Haptoglobin, Hp) precede declines in production performance, providing a basis for early heat stress intervention. Furthermore, high-yielding cows exhibit metabolic disturbances at a lower Temperature-Humidity Index (THI = 65), which traditional THI thresholds (>68) fail to capture, highlighting the value of novel biomarkers for individualized assessment. For breeding, the CD4+/CD8+ T cell ratio and HSP gene polymorphisms can serve as molecular markers for thermotolerance traits, accelerating the selection of heat-tolerant lineages and supporting the sustainable development of the dairy industry.

Despite the progress made, several unresolved questions and research bottlenecks remain. Firstly, the precise mechanisms by

which heat stress regulates epigenetic markers (e.g., DNA methylation) to influence immune gene expression are unclear and require further elucidation using multi-omics technologies. Secondly, detection thresholds for cytokine profiles (e.g., IL-6/TNF- α) are not standardized, and the lack of rapid, on-farm detection systems limits the widespread application of novel biomarkers. Additionally, current intervention strategies lack sufficient timeliness; for instance, selenium/vitamin E supplementation only partially reverses heat stress damage. Future research needs to develop targeted interventions focusing on the gut-mammary axis (e.g., butyrate formulations) to improve efficacy.

Based on these findings, this study proposes several practical recommendations. Firstly, integrating the Temperature-Humidity Index (THI) with immune biomarkers (e.g., NLR, HSP70) to construct a dynamic risk assessment model can enable individualized monitoring of cow heat stress, enhancing the precision of early warning systems. Secondly, optimizing nutritional intervention strategies, such as adding butyrate precursors (e.g., dietary fiber), can help maintain gut microbial balance, alleviate endotoxin translocation, and mitigate the negative health impacts of heat stress. Furthermore, incorporating indicators like HSP90AB1 gene polymorphism and CD4+ T cell activity into genomic selection indices holds promise for accelerating the breeding of heat-tolerant dairy cattle lines. For mammary health management, strengthening heat stress mitigation measures (e.g., cooling facilities) during the dry period can reduce the risk of abnormal mammary epithelial cell proliferation and safeguard udder health.

Against the backdrop of global warming, heat stress has become a major challenge for the dairy industry. The application of immune biomarkers offers a new paradigm shifting from “passive response” to “active prevention and control” in heat stress management. Future research requires deep integration of immunology, metabolomics, and epigenetics to construct cross-scale regulatory networks, driving the upgrade of climate resilience in dairy farming and providing solid scientific and technical support for the industry’s sustainable development.

Author contributions

CY: Writing – original draft. ZZ: Writing – review & editing. ZY: Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This study was financially supported by the National Natural Science Foundation of China (32372847 and 32402711), the Postdoctoral Fellowship Program of CPSF (GZB20240634), Jiangsu Funding Program for Excellent Postdoctoral Talent (2024ZB446), and the Jiangsu Province Seed Industry Revitalization Project (JBGS [2021]115).

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial

intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Asmarasari SA, Widyasari A, Putra E, Prasetya A, Sari D, Dewi R, et al. A review of dairy cattle heat stress mitigation in Indonesia. *Veterinary World*. (2023) 16:1098–1108. doi: 10.14202/vetworld.2023.1098-1108
- Moore SS, Davis M, Wilson J, Taylor L, Anderson K, White S, et al. Effects of different temperature-humidity indexes on milk traits of Holstein cows: A 10-year retrospective study. *J Dairy Sci*. (2024) 107:3669–87. doi: 10.3168/jds.2023-23723
- Reuscher KJ, Miller C, Brown D, Green J, Harris L, Clark S, et al. Effect of different air speeds at cow resting height in freestalls on heat stress responses and resting behavior in lactating cows in Wisconsin. *J Dairy Sci*. (2023) 106:9552–67. doi: 10.3168/jds.2023-23364
- Wang H-L, Zhang Y, Li J, Zhao W, Chen L, Liu H, et al. Dihydropyridin attenuates heat stress-induced apoptosis in dairy cow mammary epithelial cells through suppressing mitochondrial dysfunction. *Ecotoxicology Environ Saf*. (2021) 214:112078. doi: 10.1016/j.ecoenv.2021.112078
- Chen X, Yang C, Zhang M, Wu Y, Huang J, Zhou H, et al. Impact of heat stress on blood, production, and physiological indicators in heat-tolerant and heat-sensitive dairy cows. *Anim (Basel)*. (2023) 13:2562. doi: 10.3390/ani13162562
- Ramon-Moragues A, Garcia M, Fernandez J, Lopez P, Martinez S, Ruiz C, et al. Dairy cows activity under heat stress: A case study in Spain. *Animals*. (2021) 11:2305. doi: 10.3390/ani11082305
- Richards D, Thompson R, Garcia N, Nelson K, Lee S, Wilson T, et al. Tree contributions to climate change adaptation through reduced cattle heat stress and benefits to milk and beef production. *Glob Chang Biol*. (2024) 30:e17306. doi: 10.1111/gcb.17306
- Pinto S, Silva F, Costa R, Mendes J, Almeida A, Santos P, et al. Critical THI thresholds based on the physiological parameters of lactating dairy cows. *J Therm Biol*. (2020) 88:102523. doi: 10.1016/j.jtherbio.2020.102523
- Blond B, Dubois M, Leroy J, Pety S, Moreau C, Lefevre G, et al. Influence of heat stress on body surface temperature and blood metabolic, endocrine, and inflammatory parameters and their correlation in cows. *Metabolites*. (2024) 14:104. doi: 10.3390/metabo14020104
- Guo W, Liu J, Zhang Q, Wang L, Chen Y, Huang L, et al. Rumen-bypassed tributyrin alleviates heat stress by reducing the inflammatory responses of immune cells. *Poult Sci*. (2021) 100:348–56. doi: 10.1016/j.psj.2020.10.006
- Miętkiewska K, Kordowitzki P, Pareek CS. Effects of heat stress on bovine oocytes and early embryonic development—An update. *Cells*. (2022) 11. doi: 10.3390/cells11112974
- Rodriguez-Venegas R, Gonzalez M, Perez L, Sanchez J, Torres R, Lopez C, et al. Effect of THI on milk production, percentage of milking cows, and time lying in Holstein cows in northern-Arid Mexico. *Anim (Basel)*. (2023) 13:1715. doi: 10.3390/ani13101715
- Yang J, Zhu X, Feng J. The changes in the quantity of lymphocyte subpopulations during the process of sepsis. *Int J Mol Sci*. (2024) 25:1902. doi: 10.3390/ijms25031902
- Dahl GE, Tao S, Laporta J. Heat stress impacts immune status in cows across the life cycle. *Front Vet Sci*. (2020) 7:116. doi: 10.3389/fvets.2020.00116
- Lengi AJ, Johnson S, Smith K, Davis M, Wilson J, Brown C, et al. Heat stress increases mammary epithelial cells and reduces viable immune cells in milk of dairy cows. *Anim (Basel)*. (2022) 12:2810. doi: 10.3390/ani12202810
- Pradeu T, Du Pasquier L, Eberl G, Vivier E, Quintana-Murci L, Casanova JL, et al. The conceptual foundations of innate immunity: Taking stock 30 years later. *Immunity*. (2024) 57:613–31. doi: 10.1016/j.immuni.2024.03.007
- Vlasova AN, Saif LJ. Bovine immunology: implications for dairy cattle. *Front Immunol*. (2021) 12:643206. doi: 10.3389/fimmu.2021.643206
- Paludan SR, Bowie AG, Hornung V, Latz E, Fitzgerald KA, Golenbock DT, et al. Constitutive immune mechanisms: mediators of host defence and immune regulation. *Nat Rev Immunol*. (2021) 21:137–50. doi: 10.1038/s41577-020-0391-5
- Kell DB, Heyden EL, Pretorius E. The biology of lactoferrin, an iron-binding protein that can help defend against viruses and bacteria. *Front Immunol*. (2020) 11:1221. doi: 10.3389/fimmu.2020.01221
- Legrand D. Overview of lactoferrin as a natural immune modulator. *J Pediatr*. (2016) 173 Suppl:S10–5. doi: 10.1016/j.jpeds.2016.02.071
- Martinez-Riaño A, Gomez C, Lopez M, Ruiz J, Fernandez P, Serrano L, et al. Role of Innate Immune Signaling in Host Defense Against Bacterial Pathogens. *EMBO Rep*. (2018) 19:123–35.
- Hatzfeld-Charbonnier AS, Dubois C, Leroy J, Moreau G, Petit M, Lambert D, et al. Influence of heat stress on human monocyte-derived dendritic cell functions with immunotherapeutic potential for antitumor vaccines. *J Leukoc Biol*. (2007) 81:1179–87. doi: 10.1189/jlb.0506347
- Auger JP, Boudreau J, Cote S, Dubois M, Fortin A, Giguere S, et al. Metabolic rewiring promotes anti-inflammatory effects of glucocorticoids. *Nature*. (2024) 629:184–92. doi: 10.1038/s41586-024-07282-7
- Worku D, Alemu G, Taye M, Assefa A, Belay T, Dessie T, et al. Candidate genes associated with heat stress and breeding strategies to relieve its effects in dairy cattle: a deeper insight into the genetic architecture and immune response to heat stress. *Front Vet Sci*. (2023) 10:1151241. doi: 10.3389/fvets.2023.1151241
- Gupta S, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. The impact of heat stress on immune status of dairy cattle and strategies to ameliorate the negative effects. *Anim (Basel)*. (2022) 13:107. doi: 10.3390/ani13010107
- Reid C, Wilson M, Taylor K, Brown S, Davis J, Moore L, et al. Bovine innate immune phenotyping via a standardized whole blood stimulation assay. *Sci Rep*. (2021) 11:17227. doi: 10.1038/s41598-021-96493-3
- Erskine RJ. Nutrition and mastitis. *Vet Clin North Am Food Anim Pract*. (1993) 9:551–61. doi: 10.1016/S0749-0720(15)30621-6
- Becker CA, Smith J, Johnson K, Williams L, Davis M, Taylor R, et al. Predicting dairy cattle heat stress using machine learning techniques. *J Dairy Sci*. (2021) 104:501–24. doi: 10.3168/jds.2020-18653
- Missiakas D, Winstel V. Selective host cell death by *Staphylococcus aureus*: A strategy for bacterial persistence. *Front Immunol*. (2020) 11:621733. doi: 10.3389/fimmu.2020.621733
- Zhang Z, Li Y, Wang J, Liu H, Chen W, Zhao X, et al. Assessment of adaptive immune responses of dairy cows with Burkholderia contaminans-induced mastitis. *Front Microbiol*. (2023) 14:1099623. doi: 10.3389/fmicb.2023.1099623
- Justiz Vaillant AA, Sabir S, Jan A. Physiology, immune response. In: *StatPearls*. StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC, Treasure Island (FL) (2025). with ineligible companies. Disclosure: Sarah Sabir declares no relevant financial relationships with ineligible companies. Disclosure: Arif Jan declares no relevant financial relationships with ineligible companies.
- MaChado VS, Silva TH. Adaptive immunity in the postpartum uterus: Potential use of vaccines to control metritis. *Theriogenology*. (2020) 150:201–9. doi: 10.1016/j.theriogenology.2020.01.040

33. Conrey PE, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. IgA deficiency destabilizes homeostasis toward intestinal microbes and increases systemic immune dysregulation. *Sci Immunol.* (2023) 8:eade2335. doi: 10.1126/sciimmunol.ade2335
34. Arshad U, Khan M, Ali S, Hussain T, Shah Z, Iqbal J, et al. Immune cells phenotype and bioenergetic measures in CD4(+) T cells differ between high and low feed efficient dairy cows. *Sci Rep.* (2024) 14:15993. doi: 10.1038/s41598-024-66345-x
35. Guzman E, Lopez M, Garcia J, Fernandez C, Ruiz L, Perez A, et al. Bovine $\gamma\delta$ T cells are a major regulatory T cell subset. *J Immunol.* (2014) 193:208–22. doi: 10.4049/jimmunol.1303398
36. Li M, Zhang Y, Wang Z, Liu J, Chen H, Zhao X, et al. Metagenomic analysis reveals microbial drivers of heat resistance in dairy cattle. *Anim Microbiome.* (2025) 7:35. doi: 10.1186/s42523-025-00399-8
37. Emam M, Abdel-Hamid A, Elsayed S, Ali M, Hussein H, Mohamed A, et al. Genetic and epigenetic regulation of immune response and resistance to infectious diseases in domestic ruminants. *Vet Clin North Am Food Anim Pract.* (2019) 35:405–29. doi: 10.1016/j.cvfa.2019.07.002
38. Kim JY, Dao H. Physiology, integument. In: *StatPearls*. StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC, Treasure Island (FL) (2025). ineligible companies. Disclosure: Harry Dao declares no relevant financial relationships with ineligible companies.
39. Cramer MN, Davis S, Wilson J, Thompson L, Garcia M, Martinez R, et al. Human temperature regulation under heat stress in health, disease, and injury. *Physiol Rev.* (2022) 102:1907–89. doi: 10.1152/physrev.00047.2021
40. Oliveira CP, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Heat stress in dairy cows: impacts, identification, and mitigation strategies-A review. *Anim (Basel).* (2025) 15:249. doi: 10.3390/ani15020249
41. Takahashi M. Heat stress on reproductive function and fertility in mammals. *Reprod Med Biol.* (2012) 11:37–47. doi: 10.1007/s12522-011-0105-6
42. Guo Z, Li H, Zhang Y, Wang Z, Zhao J, Chen L, et al. Effects of heat stress on the ruminal epithelial barrier of dairy cows revealed by micromorphological observation and transcriptomic analysis. *Front Genet.* (2021) 12:768209. doi: 10.3389/fgene.2021.768209
43. Koester LR, Miller K, Davis S, Wilson J, Thompson L, Garcia M, et al. Influence of a sodium-saccharin sweetener on the rumen content and rumen epithelium microbiota in dairy cattle during heat stress. *J Anim Sci.* (2023) 101:skac403. doi: 10.1093/jas/skac403
44. yrkäs-Palmu H, Niemi M, Rautio M, Karvonen A, Kinnunen K, Laine K, et al. The influence of weather and urban environment characteristics on upper respiratory tract infections: a systematic review. *Front Public Health.* (2025) 13:1487125. doi: 10.3389/fpubh.2025.1487125
45. Dash S, Mishra S, Patel R, Singh A, Kumar V, Joshi R, et al. Effect of heat stress on reproductive performances of dairy cattle and buffaloes: A review. *Vet World.* (2016) 9:235–44. doi: 10.14202/vetworld.2016.235-244
46. Ge Y, Zhang J, Li H, Wang Z, Zhao J, Chen L, et al. The impact of environmental factors on respiratory tract microbiome and respiratory system diseases. *Eur J Med Res.* (2025) 30:236. doi: 10.1186/s40001-025-02517-3
47. Celebi Sözen Z, Sözen H, Aydin S, Koc E, Yildirim M, Ciftci O, et al. Global warming and implications for epithelial barrier disruption and respiratory and dermatologic allergic diseases. *J Allergy Clin Immunol.* (2023) 152:1033–46. doi: 10.1016/j.jaci.2023.09.001
48. Whittsett JA. Airway epithelial differentiation and mucociliary clearance. *Ann Am Thorac Soc.* (2018) 15:S143–s148. doi: 10.1513/AnnalsATS.201802-128AW
49. Gleeson M. Immunological aspects of sport nutrition. *Immunol Cell Biol.* (2016) 94:117–23. doi: 10.1038/icb.2015.109
50. Bustamante-Marin XM, Ostrowski LE. Cilia and mucociliary clearance. *Cold Spring Harb Perspect Biol.* (2017) 9:a028241. doi: 10.1101/cshperspect.a028241
51. Shang X, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Global meta-analysis of short-term associations between ambient temperature and pathogen-specific respiratory infections, 2004 to 2023. *Euro Surveill.* (2025) 30:2400375. doi: 10.2807/1560-7917.ES.2025.30.11.2400375
52. Sun M, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. The mechanisms behind heatstroke-induced intestinal damage. *Cell Death Discov.* (2024) 10:455. doi: 10.1038/s41420-024-02210-0
53. Zuhl MN, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Effects of oral glutamine supplementation on exercise-induced gastrointestinal permeability and tight junction protein expression. *J Appl Physiol (1985).* (2014) 116:183–91. doi: 10.1152/jappphysiol.00646.2013
54. Fung AA, Chan E, Lee M, Wong C, Cheung H, Ng K, et al. Enhanced intestinal permeability and intestinal co-morbidities in heat strain: A review and case for autodigestion. *Temperature (Austin).* (2021) 8:223–44. doi: 10.1080/23328940.2021.1922261
55. Drake MJ, Johnson K, Williams L, Davis M, Taylor R, Moore S, et al. Effects of dietary zinc on the gut microbiome and resistance of the gestating cow and neonatal calf. *Anim Microbiome.* (2024) 6:39. doi: 10.1186/s42523-024-00326-3
56. Yu J, Cheon JH. Microbial modulation in inflammatory bowel diseases. *Immune Netw.* (2022) 22:e44. doi: 10.4110/in.2022.22.e44
57. Yu Z, Li H, Zhang Y, Wang Z, Zhao J, Chen L, et al. Heat stress-associated changes in the intestinal barrier, inflammatory signals, and microbiome communities in dairy calves. *J Dairy Sci.* (2024) 107:1175–96. doi: 10.3168/jds.2023-23873
58. Malmuthuge N, Guan LL. Understanding the gut microbiome of dairy calves: Opportunities to improve early-life gut health. *J Dairy Sci.* (2017) 100:5996–6005. doi: 10.3168/jds.2016-12239
59. Malmuthuge N, Griebel PJ, Guan le L. The gut microbiome and its potential role in the development and function of newborn calf gastrointestinal tract. *Front Vet Sci.* (2015) 2:36. doi: 10.3389/fvets.2015.00036
60. Cao C, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. The microbiota-gut-brain axis during heat stress in chickens: A review. *Front Physiol.* (2021) 12:752265. doi: 10.3389/fphys.2021.752265
61. Welch CB, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Utilizing the gastrointestinal microbiota to modulate cattle health through the microbiome-gut-organ axes. *Microorganisms.* (2022) 10:1391. doi: 10.3390/microorganisms10071391
62. Cantet JM, Yu Z, Rius AG. Heat stress-mediated activation of immune-inflammatory pathways. *Antibiotics (Basel).* (2021) 10:1285. doi: 10.3390/antibiotics10111285
63. Mohyuddin SG, Khan M, Ali S, Hussain T, Shah Z, Iqbal J, et al. Effect of chitosan on blood profile, inflammatory cytokines by activating TLR4/NF- κ B signaling pathway in intestine of heat stressed mice. *Sci Rep.* (2021) 11:20608. doi: 10.1038/s41598-021-98931-8
64. Neurath MF. Strategies for targeting cytokines in inflammatory bowel disease. *Nat Rev Immunol.* (2024) 24:559–76. doi: 10.1038/s41577-024-01008-6
65. Heesterbeek DA, van der Pol S, Bakker J, van den Berg B, Janssen L, Meijer A, et al. Bacterial killing by complement requires membrane attack complex formation via surface-bound C5 convertases. *EMBO J.* (2019) 38:e100852. doi: 10.15252/emboj.201899852
66. Xie CB, Jane-Wit D, Pober JS. Complement membrane attack complex: new roles, mechanisms of action, and therapeutic targets. *Am J Pathol.* (2020) 190:1138–50. doi: 10.1016/j.ajpath.2020.02.006
67. Tao S, Su H, Zhang Y, Wang Z, Zhao J, Chen L, et al. Symposium review: The influences of heat stress on bovine mammary gland function. *J Dairy Sci.* (2018) 101:5642–54. doi: 10.3168/jds.2017-13727
68. Mortimer PM, Mc Intyre SA, Thomas DC. Beyond the extra respiration of phagocytosis: NADPH oxidase 2 in adaptive immunity and inflammation. *Front Immunol.* (2021) 12:733918. doi: 10.3389/fimmu.2021.733918
69. Moghadam ZM, Henneke P, Kolter J. From flies to men: ROS and the NADPH oxidase in phagocytes. *Front Cell Dev Biol.* (2021) 9:628991. doi: 10.3389/fcell.2021.628991
70. Kang H, Lee J, Kim S, Park M, Choi Y, Jung H, et al. Enhanced engraftment and immunomodulatory effects of integrin alpha-2-overexpressing mesenchymal stromal cells in lipopolysaccharide-induced acute lung injury. *Stem Cell Res Ther.* (2025) 16:286. doi: 10.1186/s13287-025-04423-1
71. Peng Y, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Regulatory mechanism of M1/M2 macrophage polarization in the development of autoimmune diseases. *Mediators Inflamm.* (2023) 2023:8821610. doi: 10.1155/2023/8821610
72. Xu X, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Targeting macrophage polarization by inhibiting Pim2 alleviates inflammatory arthritis via metabolic reprogramming. *Cell Mol Immunol.* (2025) 22:418–36. doi: 10.1038/s41423-025-01268-9
73. Bagath M, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. The impact of heat stress on the immune system in dairy cattle: A review. *Res Vet Sci.* (2019) 126:94–102. doi: 10.1016/j.rvsc.2019.08.011
74. Guo Z, Li H, Zhang Y, Wang Z, Zhao J, Chen L, et al. Impacts of heat stress-induced oxidative stress on the milk protein biosynthesis of dairy cows. *Anim (Basel).* (2021) 11:726. doi: 10.3390/ani11030726
75. ao S, Su H, Zhang Y, Wang Z, Zhao J, Chen L, et al. Effect of heat stress during the dry period on mammary gland development. *J Dairy Sci.* (2011) 94:5976–86. doi: 10.3168/jds.2011-4329
76. Heled Y, Fleischmann C, Epstein Y. Cytokines and their role in hyperthermia and heat stroke. *J Basic Clin Physiol Pharmacol.* (2013) 24:85–96. doi: 10.1515/jbcpp-2012-0040
77. Park DS, Kim J, Lee S, Park M, Choi Y, Jung H, et al. Dynamic changes in blood immune cell composition and function in Holstein and Jersey steers in response to heat stress. *Cell Stress Chaperones.* (2021) 26:705–20. doi: 10.1007/s12192-021-01216-2
78. Kelsoe G, Haynes BF. What are the primary limitations in B-cell affinity maturation, and how much affinity maturation can we drive with vaccination? Breaking through immunity's glass ceiling. *Cold Spring Harb Perspect Biol.* (2018) 10:a029397. doi: 10.1101/cshperspect.a029397
79. Reolon HG, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Proteomic changes of the bovine blood plasma in response to heat stress in a tropically adapted cattle breed. *Front Genet.* (2024) 15:1392670. doi: 10.3389/fgene.2024.1392670
80. Özmen Ö, Yildirim M, Ciftci O, Aydin S, Koc E, Sözen H, et al. Profiling of milk miRNAs associated with the innate immune system and pathway analysis in dairy cows with *S. aureus*-infected subclinical mastitis. *J Dairy Res.* (2025) 16:1–6.
81. Damasceno LEA, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. PKM2 promotes Th17 cell differentiation and autoimmune inflammation by fine-tuning STAT3 activation. *J Exp Med.* (2020) 217:e20190613. doi: 10.1084/jem.20190613

82. Hou Y, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Insights into vaccines for elderly individuals: from the impacts of immunosenescence to delivery strategies. *NPJ Vaccines*. (2024) 9:77. doi: 10.1038/s41541-024-00874-4
83. Paszek A, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Heat shock response regulates stimulus-specificity and sensitivity of the pro-inflammatory NF- κ B signalling. *Cell Commun Signal*. (2020) 18:77. doi: 10.1186/s12964-020-00583-0
84. Phillips MC, Olson LR. The immunologic role of the gastrointestinal tract. *Crit Care Nurs Clin North Am*. (1993) 5:107–20. doi: 10.1016/S0899-5885(18)30590-2
85. Zhou N, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. The dietary inflammatory index and its association with the prevalence of hypertension: A cross-sectional study. *Front Immunol*. (2022) 13:1097228. doi: 10.3389/fimmu.2022.1097228
86. Xiao G, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Eicosapentaenoic acid enhances heat stress-impaired intestinal epithelial barrier function in Caco-2 cells. *PLoS One*. (2013) 8:e73571. doi: 10.1371/journal.pone.0073571
87. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat Rev Immunol*. (2019) 19:369–82. doi: 10.1038/s41577-019-0127-6
88. Dimeloe S, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. T-cell metabolism governing activation, proliferation and differentiation; a modular view. *Immunology*. (2017) 150:35–44. doi: 10.1111/imm.12655
89. Liu R, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Allogeneic mesenchymal stem cells inhibited T follicular helper cell generation in rheumatoid arthritis. *Sci Rep*. (2015) 5:12777. doi: 10.1038/srep12777
90. Bellavance MA, Rivest S. The HPA - immune axis and the immunomodulatory actions of glucocorticoids in the brain. *Front Immunol*. (2014) 5:136. doi: 10.3389/fimmu.2014.00136
91. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol*. (2017) 17:233–47. doi: 10.1038/nri.2017.1
92. Yang Y, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Molecular regulation of whole genome DNA methylation in heat stress response of dairy cows. *BMC Genomics*. (2025) 26:464. doi: 10.1186/s12864-025-11683-x
93. Emami NK, Rahimi M, Safari M, Ghorbani M, Hashemi S, Rezaei A, et al. Radical response: effects of heat stress-induced oxidative stress on lipid metabolism in the avian liver. *Antioxidants (Basel)*. (2020) 10:35. doi: 10.3390/antiox10010035
94. Jomova K, Valko M, Rhodes CJ, Izakovic M, Cuperlovic-Culf M, Koska J, et al. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol*. (2024) 98:1323–67. doi: 10.1007/s00204-024-03696-4
95. Li Pomi F, Conti M, Pinto S, Silva M, Costa J, Ferreira L, et al. Oxidative stress and skin diseases: the role of lipid peroxidation. *Antioxidants (Basel)*. (2025) 14:555. doi: 10.3390/antiox14050555
96. Li H, Wang Y, Zhang Z, Zhao J, Chen L, Liu J, et al. Effect of seasonal thermal stress on oxidative status, immune response and stress hormones of lactating dairy cows. *Anim Nutr*. (2021) 7:216–23. doi: 10.1016/j.aninu.2020.07.006
97. Kim H, Lee J, Kim S, Park M, Choi Y, Jung H, et al. Inflammatory response in dairy cows caused by heat stress and biological mechanisms for maintaining homeostasis. *PLoS One*. (2024) 19:e0300719. doi: 10.1371/journal.pone.0300719
98. Abdelsalam NA, Hegazy SM, Aziz RK. The curious case of *Prevotella copri*. *Gut Microbes*. (2023) 15:2249152. doi: 10.1080/19490976.2023.2249152
99. Iljazovic A, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Perturbation of the gut microbiome by *Prevotella spp.* enhances host susceptibility to mucosal inflammation. *Mucosal Immunol*. (2021) 14:113–24. doi: 10.1038/s41385-020-0296-4
100. Ji J, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Immune cells characteristics and their prognostic effects in exertional heatstroke patients: A retrospective cohort study. *Front Med (Lausanne)*. (2022) 9:867774. doi: 10.3389/fmed.2022.867774
101. Tang Y, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Clinical relevance of neutrophil/lymphocyte ratio combined with APACHEII for prognosis of severe heatstroke. *Heliyon*. (2023) 9:e20346. doi: 10.1016/j.heliyon.2023.e20346
102. Stefanska B, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Impact of heat stress during close-up dry period on performance, fertility and immunometabolic blood indices of dairy cows: prospective cohort study. *Sci Rep*. (2024) 14:21211. doi: 10.1038/s41598-024-72294-2
103. Kozlowski HM, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Fever-range hyperthermia promotes macrophage polarization towards regulatory phenotype M2b. *Int J Mol Sci*. (2023) 24:17574. doi: 10.3390/ijms242417574
104. Velayudhan SM, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. Molecular, physiological and hematological responses of crossbred dairy cattle in a tropical savanna climate. *Biol (Basel)*. (2022) 12:26. doi: 10.3390/biology12010026
105. Jang PG, Lee J, Kim S, Park M, Choi Y, Jung H, et al. NF- κ B activation in hypothalamic pro-opiomelanocortin neurons is essential in illness- and leptin-induced anorexia. *J Biol Chem*. (2010) 285:9706–15. doi: 10.1074/jbc.M109.070706
106. Lin W, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Functional role of skeletal muscle-derived interleukin-6 and its effects on lipid metabolism. *Front Physiol*. (2023) 14:1110926. doi: 10.3389/fphys.2023.1110926
107. Alhendi A, Naser SA. The dual role of interleukin-6 in Crohn's disease pathophysiology. *Front Immunol*. (2023) 14:1295230. doi: 10.3389/fimmu.2023.1295230
108. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. (1999) 340:448–54. doi: 10.1056/NEJM199902113400607
109. Iwaniec J, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Acute phase response to exertional heat stroke in mice. *Exp Physiol*. (2021) 106:222–32. doi: 10.1113/EP088501
110. Syafiq NN, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. Physiological, haematological and electroencephalographic responses to heat stress in Katjang and Boer goats. *Saudi J Biol Sci*. (2023) 30:103836. doi: 10.1016/j.sjbs.2023.103836
111. Jain S, Gautam V, Naseem S. Acute-phase proteins: As diagnostic tool. *J Pharm Bioallied Sci*. (2011) 3:118–27. doi: 10.4103/0975-7406.76489
112. Ćukić A, et al. Influence of heat stress on body temperatures measured by infrared thermography, blood metabolic parameters and its correlation in sheep. *Metabolites*. (2023) 13:957. doi: 10.3390/metabo13080957
113. Lemal P, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Invited review: From heat stress to disease-Immune response and candidate genes involved in cattle thermotolerance. *J Dairy Sci*. (2023) 106:4471–88. doi: 10.3168/jds.2022-22727
114. Shi L, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Effects of heat stress on antioxidant status and immune function and expression of related genes in lambs. *Int J Biometeorol*. (2020) 64:2093–104. doi: 10.1007/s00484-020-02000-0
115. Monteiro AP, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Effect of heat stress during late gestation on immune function and growth performance of calves: isolation of altered colostrum and calf factors. *J Dairy Sci*. (2014) 97:6426–39. doi: 10.3168/jds.2013-7891
116. Cartwright SL, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Effect of *In-vivo* heat challenge on physiological parameters and function of peripheral blood mononuclear cells in immune phenotyped dairy cattle. *Vet Immunol Immunopathol*. (2022) 246:110405. doi: 10.1016/j.vetimm.2022.110405
117. Demers-Mathieu V, Lee J, Kim S, Park M, Choi Y, Jung H, et al. Differences in Maternal Immunoglobulins within Mother's Own Breast Milk and Donor Breast Milk and across Digestion in Preterm Infants. *Nutrients*. (2019) 11:920. doi: 10.3390/nu11040920
118. Skibić AL, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Effects of feeding an immunomodulatory supplement to heat-stressed or actively cooled cows during late gestation on postnatal immunity, health, and growth of calves. *J Dairy Sci*. (2017) 100:7659–68. doi: 10.3168/jds.2017-12619
119. Li P, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. MicroRNA-155 promotes heat stress-induced inflammation via targeting liver X receptor α in microglia. *Front Cell Neurosci*. (2019) 13:12. doi: 10.3389/fncel.2019.00012
120. Bhol NK, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. The interplay between cytokines, inflammation, and antioxidants: mechanistic insights and therapeutic potentials of various antioxidants and anti-cytokine compounds. *BioMed Pharmacother*. (2024) 178:117177. doi: 10.1016/j.biopha.2024.117177
121. Dahl GE, Tao S, Laporta J. TRIENNIAL LACTATION SYMPOSIUM/BOLFA: Late gestation heat stress of dairy cattle programs dam and daughter milk production. *J Anim Sci*. (2017) 95:5701–10. doi: 10.2527/jas2017.2006
122. Verhasselt V, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Antibodies in breast milk: Pro-bodies designed for healthy newborn development. *Immunol Rev*. (2024) 328:192–204. doi: 10.1111/imr.13411
123. Nardone A, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Composition of colostrum from dairy heifers exposed to high air temperatures during late pregnancy and the early postpartum period. *J Dairy Sci*. (1997) 80:838–44. doi: 10.3168/jds.S0022-0302(97)76005-3
124. Halli K, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Heat stress during late pregnancy and postpartum influences genetic parameter estimates for birth weight and weight gain in dual-purpose cattle offspring generations. *J Anim Sci*. (2021) 99:skab106. doi: 10.1093/jas/skab106
125. Rollins-Smith LA, Le Sage EH. Heat stress and amphibian immunity in a time of climate change. *Philos Trans R Soc Lond B Biol Sci*. (2023) 378:20220132. doi: 10.1098/rstb.2022.0132
126. Knezevic E, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. *Cells*. (2023) 12:2726. doi: 10.3390/cells12232726
127. Yin T, Halli K, König S. Direct genetic effects, maternal genetic effects, and maternal genetic sensitivity on prenatal heat stress for calf diseases and corresponding genomic loci in German Holsteins. *J Dairy Sci*. (2022) 105:6795–808. doi: 10.3168/jds.2022-21804
128. Pockley AG, Henderson B. Extracellular cell stress (heat shock) proteins-immune responses and disease: an overview. *Philos Trans R Soc Lond B Biol Sci*. (2018) 373:20160522. doi: 10.1098/rstb.2016.0522
129. Tao S, Su H, Zhang Y, Wang Z, Zhao J, Chen L, et al. Effect of late-gestation maternal heat stress on growth and immune function of dairy calves. *J Dairy Sci*. (2012) 95:7128–36. doi: 10.3168/jds.2012-5697
130. Cattaneo L, Laporta J, Dahl GE. Programming effects of late gestation heat stress in dairy cattle. *Reprod Fertil Dev*. (2022) 35:106–17. doi: 10.1071/RD22209

131. acetera N, Silva M, Costa J, Ferreira L, Gomes A. Lymphocyte functions in dairy cows in hot environment. *Int J Biometeorol.* (2005) 50:105–10. doi: 10.1007/s00484-005-0273-3
132. Ghaffari MH. Developmental programming: prenatal and postnatal consequences of hyperthermia in dairy cows and calves. *Domest Anim Endocrinol.* (2022) 80:106723. doi: 10.1016/j.domaniend.2022.106723
133. Paape MJ, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. The bovine neutrophil: Structure and function in blood and milk. *Vet Res.* (2003) 34:597–627. doi: 10.1051/vetres:2003024
134. Mishra SR. Behavioural, physiological, neuro-endocrine and molecular responses of cattle against heat stress: an updated review. *Trop Anim Health Prod.* (2021) 53:400. doi: 10.1007/s11250-021-02790-4
135. Vitali A, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Heat load increases the risk of clinical mastitis in dairy cattle. *J Dairy Sci.* (2020) 103:8378–87. doi: 10.3168/jds.2019-17748
136. Ma FT, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Effect of *Lonicera japonica* extract on lactation performance, antioxidant status, and endocrine and immune function in heat-stressed mid-lactation dairy cows. *J Dairy Sci.* (2020) 103:10074–82. doi: 10.3168/jds.2020-18504
137. Alberghina D, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Impact of heat stress on the balance between oxidative markers and the antioxidant defence system in the plasma of mid-lactating modicana dairy cows. *Anim (Basel).* (2024) 14:2034. doi: 10.3390/ani14142034
138. Hirayama D, Iida T, Nakase H. The phagocytic function of macrophage-enforcing innate immunity and tissue homeostasis. *Int J Mol Sci.* (2017) 19:92. doi: 10.3390/ijms19010092
139. Hammon DS, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Neutrophil function and energy status in Holstein cows with uterine health disorders. *Vet Immunol Immunopathol.* (2006) 113:21–9. doi: 10.1016/j.vetimm.2006.03.022
140. Fabris TF, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. Effect of heat stress during the early and late dry period on mammary gland development of Holstein dairy cattle. *J Dairy Sci.* (2020) 103:8576–86. doi: 10.3168/jds.2019-17911
141. Sajjanar B, Lee J, Kim S, Park M, Choi Y, Jung H, et al. Identification of SNP in HSP90AB1 and its association with the relative thermotolerance and milk production traits in Indian dairy cattle. *Anim Biotechnol.* (2015) 26:45–50. doi: 10.1080/10495398.2014.882846
142. Kaushik R, Goel A, Rout PK. Differential expression and regulation of HSP70 gene during growth phase in ruminants in response to heat stress. *Sci Rep.* (2022) 12:18310. doi: 10.1038/s41598-022-22728-6
143. Boonkum W, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Impact of heat stress on milk yield, milk fat-to-protein ratio, and conception rate in Thai-Holstein dairy cattle: A phenotypic and genetic perspective. *Anim (Basel).* (2024) 14:3026. doi: 10.3390/ani14203026
144. Vargas N, Marino F. Heat stress, gastrointestinal permeability and interleukin-6 signaling - Implications for exercise performance and fatigue. *Temperature (Austin).* (2016) 3:240–51. doi: 10.1080/23328940.2016.1179380
145. Delalat S, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Dysregulated inflammation, oxidative stress, and protein quality control in diabetic HFpEF: unraveling mechanisms and therapeutic targets. *Cardiovasc Diabetol.* (2025) 24:211. doi: 10.1186/s12933-025-02734-4
146. Laporta J, Khatib H, Zachut M. Review: Phenotypic and molecular evidence of inter- and trans-generational effects of heat stress in livestock mammals and humans. *Animal.* (2024) 18 Suppl 2:101121. doi: 10.1016/j.animal.2024.101121
147. do Amaral BC, Wang Y, Li H, Zhang Z, Zhao J, Chen L, et al. Heat stress abatement during the dry period influences metabolic gene expression and improves immune status in the transition period of dairy cows. *J Dairy Sci.* (2011) 94:86–96. doi: 10.3168/jds.2009-3004
148. Garner JB, Li J, Zhang Y, Wang Z, Zhao J, Chen L, et al. Gene expression of the heat stress response in bovine peripheral white blood cells and milk somatic cells *in vivo*. *Sci Rep.* (2020) 10:19181. doi: 10.1038/s41598-020-75438-2
149. Alhussien MN, Hussien J, De Matteis G. Editorial: Heat stress and immune responses in livestock: current challenges and intervention strategies. *Front Vet Sci.* (2024) 11:1366274. doi: 10.3389/fvets.2024.1366274
150. Bernardo G, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. The emerging role of the microbiota in breast cancer progression. *Cells.* (2023) 12:1945. doi: 10.3390/cells12151945
151. Fisher DT, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Fine-tuning immune surveillance by fever-range thermal stress. *Immunol Res.* (2010) 46:177–88. doi: 10.1007/s12026-009-8122-9
152. Laborda-Illanes A, Sharma R, Singh A, Kumar V, Joshi R, Pandey A, et al. Breast and gut microbiota action mechanisms in breast cancer pathogenesis and treatment. *Cancers (Basel).* (2020) 12:2465. doi: 10.3390/cancers12092465
153. Jiang DF, Lee J, Kim S, Park M, Choi Y, Jung H, et al. Differential expression of lipid metabolism genes in the liver and adipose tissue of mice treated with evodiamine. *Genet Mol Res.* (2013) 12:1501–10. doi: 10.4238/2013.January.4.13
154. Derakhshani H, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Invited review: Microbiota of the bovine udder: Contributing factors and potential implications for udder health and mastitis susceptibility. *J Dairy Sci.* (2018) 101:10605–25. doi: 10.3168/jds.2018-14860
155. Rascon-Cruz Q, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Antioxidant potential of lactoferrin and its protective effect on health: an overview. *Int J Mol Sci.* (2024) 26:555. doi: 10.3390/ijms26010055
156. Huang Q, Xiao Y, Sun P. Rumen-mammary gland axis and bacterial extracellular vesicles: Exploring a new perspective on heat stress in dairy cows. *Anim Nutr.* (2024) 19:70–5. doi: 10.1016/j.aninu.2024.08.003
157. Dahl GE. Impact and mitigation of heat stress for mastitis control. *Vet Clin North Am Food Anim Pract.* (2018) 34:473–8. doi: 10.1016/j.cvfa.2018.07.002
158. Summer A, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Impact of heat stress on milk and meat production. *Anim Front.* (2019) 9:39–46. doi: 10.1093/af/vfy026
159. Lecchi C, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. *In vitro* assessment of the effects of temperature on phagocytosis, reactive oxygen species production and apoptosis in bovine polymorphonuclear cells. *Vet Immunol Immunopathol.* (2016) 182:89–94. doi: 10.1016/j.vetimm.2016.10.007
160. Mishra A, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Influence of induced heat stress on HSP70 in buffalo lymphocytes. *J Anim Physiol Anim Nutr (Berl).* (2011) 95:540–4. doi: 10.1111/j.1439-0396.2010.01082.x
161. Grinter LN, Mazon G, Costa JHC. Voluntary heat stress abatement system for dairy cows: Does it mitigate the effects of heat stress on physiology and behavior? *J Dairy Sci.* (2023) 106:519–33. doi: 10.3168/jds.2022-21802
162. Ogola H, Shitandi A, Nanua J. Effect of mastitis on raw milk compositional quality. *J Vet Sci.* (2007) 8:237–42. doi: 10.4142/jvs.2007.8.3.237
163. Leandro MA, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Is heat stress a growing problem for dairy cattle husbandry in the temperate regions? A case study of Baden-Württemberg in Germany. *J Anim Sci.* (2024) 102:skae287. doi: 10.1093/jas/skae287
164. Zhao S, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Effect of heat stress on bacterial composition and metabolism in the rumen of lactating dairy cows. *Anim (Basel).* (2019) 9:925. doi: 10.3390/ani9110925
165. Cartwright SL, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Effect of *in-vitro* heat stress challenge on the function of blood mononuclear cells from dairy cattle ranked as high, average and low immune responders. *BMC Vet Res.* (2021) 17:233. doi: 10.1186/s12917-021-02940-8
166. Martinez de Toda I, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. The role of immune cells in oxi-inflamm-aging. *Cells.* (2021) 10:2974. doi: 10.3390/cells10112974
167. Pizzino G, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev.* (2017) 2017:8416763. doi: 10.1155/2017/8416763
168. Yang Z, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Hydroxy-selenomethionine helps cows to overcome heat stress by enhancing antioxidant capacity and alleviating blood-milk barrier damage. *Anim Nutr.* (2025) 20:171–81. doi: 10.1016/j.aninu.2024.10.003
169. Dokladny K, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Cellular and molecular mechanisms of heat stress-induced up-regulation of occludin protein expression: regulatory role of heat shock factor-1. *Am J Pathol.* (2008) 172:659–70. doi: 10.2353/ajpath.2008.070522
170. Siddiqui SH, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Chronic heat stress regulates the relation between heat shock protein and immunity in broiler small intestine. *Sci Rep.* (2020) 10:18872. doi: 10.1038/s41598-020-75885-x
171. Venkataramani S, Truntzer J, Coleman DR. Thermal stability of high concentration lysozyme across varying pH: A Fourier Transform Infrared study. *J Pharm Bioallied Sci.* (2013) 5:148–53. doi: 10.4103/0975-7406.111821
172. Bochniarz M, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Cytokine inflammatory response in dairy cows with mastitis caused by *Streptococcus agalactiae*. *J Vet Res.* (2024) 68:115–21. doi: 10.2478/jvetres-2024-0002
173. Vitenberga-Verza Z, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Identification of inflammatory and regulatory cytokines IL-1 α -, IL-4-, IL-6-, IL-12-, IL-13-, IL-17A-, TNF- α -, and IFN- γ -producing cells in the milk of dairy cows with subclinical and clinical mastitis. *Pathogens.* (2022) 11:372. doi: 10.3390/pathogens11030372
174. Kelley DW, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Effects of chronic heat and cold stressors on plasma immunoglobulin and mitogen-induced blastogenesis in calves. *J Dairy Sci.* (1982) 65:1514–28. doi: 10.3168/jds.S0022-0302(82)82376-X
175. Cui Y, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Chronic heat stress induces immune response, oxidative stress response, and apoptosis of finishing pig liver: A proteomic approach. *Int J Mol Sci.* (2016) 17:393. doi: 10.3390/ijms17050393
176. Morrow-Tesch JL, McGlone JJ, Salak-Johnson JL. Heat and social stress effects on pig immune measures. *J Anim Sci.* (1994) 72:2599–609. doi: 10.2527/1994.72102599x
177. Wheelock JB, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Effects of heat stress on energetic metabolism in lactating Holstein cows. *J Dairy Sci.* (2010) 93:644–55. doi: 10.3168/jds.2009-2295

178. Santschi DE, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Incidence of metabolic disorders and reproductive performance following a short (35-d) or conventional (60-d) dry period management in commercial Holstein herds. *J Dairy Sci.* (2011) 94:3322–30. doi: 10.3168/jds.2010-3595
179. Wankhade PR, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Metabolic and immunological changes in transition dairy cows: A review. *Vet World.* (2017) 10:1367–77. doi: 10.14202/vetworld.2017.1367-1377
180. Zachut M, Tam J, Contreras GA. Modulating immunometabolism in transition dairy cows: the role of inflammatory lipid mediators. *Anim Front.* (2022) 12:37–45. doi: 10.1093/af/vfac062
181. Yang Z, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. T-cell metabolism in autoimmune disease. *Arthritis Res Ther.* (2015) 17:29. doi: 10.1186/s13075-015-0542-4
182. Hu C, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Immune cell metabolism and metabolic reprogramming. *Mol Biol Rep.* (2022) 49:9783–95. doi: 10.1007/s11033-022-07474-2
183. Sun H, Li X. Metabolic reprogramming in resting and activated immune cells. *Metabolomics (Los Angel).* (2017) 7.
184. Alhussien MN, Dang AK, Bu D. Editorial: Strategies for mitigating the transition period stress in dairy cattle. *Front Vet Sci.* (2023) 10:1157526. doi: 10.3389/fvets.2023.1157526
185. Cheng Z, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Hepatic global transcriptomic profiles of Holstein cows according to parity reveal age-related changes in early lactation. *Int J Mol Sci.* (2023) 24:9906. doi: 10.3390/ijms24129906
186. Contreras GA, Sordillo LM. Lipid mobilization and inflammatory responses during the transition period of dairy cows. *Comp Immunol Microbiol Infect Dis.* (2011) 34:281–9. doi: 10.1016/j.cimid.2011.01.004
187. Habel J, Sundrum A. Mismatch of glucose allocation between different life functions in the transition period of dairy cows. *Anim (Basel).* (2020) 10:1028. doi: 10.3390/ani10061028
188. Baez-Magaña M, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Lipid-Rich Extract from Mexican Avocado Seed (*Persea americana* var. *drymifolia*) Reduces *Staphylococcus aureus* Internalization and Regulates Innate Immune Response in Bovine Mammary Epithelial Cells. *J Immunol Res.* (2019) 2019:7083491. doi: 10.1155/2019/7083491
189. Zhang H, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Transcriptomics and iTRAQ-Proteomics Analyses of Bovine Mammary Tissue with *Streptococcus agalactiae*-Induced Mastitis. *J Agric Food Chem.* (2018) 66:11188–96. doi: 10.1021/acs.jafc.8b02386
190. Campos B, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Diversity and pathogenesis of *Staphylococcus aureus* from bovine mastitis: current understanding and future perspectives. *BMC Vet Res.* (2022) 18:115. doi: 10.1186/s12917-022-03197-5
191. Esposito G, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Interactions between negative energy balance, metabolic diseases, uterine health and immune response in transition dairy cows. *Anim Reprod Sci.* (2014) 144:60–71. doi: 10.1016/j.anireprosci.2013.11.007
192. Trevisi E, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Metabolic stress and inflammatory response in high-yielding, periparturient dairy cows. *Res Vet Sci.* (2012) 93:695–704. doi: 10.1016/j.rvsc.2011.11.008
193. Lukasova M, et al. Nicotinic acid inhibits progression of atherosclerosis in mice through its receptor GPR109A expressed by immune cells. *J Clin Invest.* (2011) 121:1163–73. doi: 10.1172/JCI41651
194. Wanders D, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Niacin increases adiponectin and decreases adipose tissue inflammation in high fat diet-fed mice. *PLoS One.* (2013) 8:e71285. doi: 10.1371/journal.pone.0071285
195. Si Y, Zhang Y, Zhao J, Guo S, Zhai L, Yao S, et al. Niacin inhibits vascular inflammation via downregulating nuclear transcription factor- κ B signaling pathway. *Mediators Inflammation.* (2014) 2014:263786. doi: 10.1155/2014/263786
196. Zhou E, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Niacin attenuates the production of pro-inflammatory cytokines in LPS-induced mouse alveolar macrophages by HCA2 dependent mechanisms. *Int Immunopharmacol.* (2014) 23:121–6. doi: 10.1016/j.intimp.2014.07.006
197. To EE, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Spatial properties of reactive oxygen species govern pathogen-specific immune system responses. *Antioxid Redox Signal.* (2020) 32:982–92. doi: 10.1089/ars.2020.8027
198. Chandimali N, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Free radicals and their impact on health and antioxidant defenses: a review. *Cell Death Discov.* (2025) 11:19. doi: 10.1038/s41420-024-02278-8
199. Shan CH, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Effects of fermented Chinese herbal medicines on milk performance and immune function in late-lactation cows under heat stress conditions. *J Anim Sci.* (2018) 96:4444–57. doi: 10.1093/jas/sky270
200. Abbas Z, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Glucose metabolism and dynamics of facilitative glucose transporters (GLUTs) under the influence of heat stress in dairy cattle. *Metabolites.* (2020) 10:312. doi: 10.3390/metabo10080312
201. Sun Y, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Protective effects of zymosan on heat stress-induced immunosuppression and apoptosis in dairy cows and peripheral blood mononuclear cells. *Cell Stress Chaperones.* (2018) 23:1069–78. doi: 10.1007/s12192-018-0916-z
202. Wang LI, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Effect of acute heat stress on adrenocorticotropic hormone, cortisol, interleukin-2, interleukin-12 and apoptosis gene expression in rats. *BioMed Rep.* (2015) 3:425–9. doi: 10.3892/br.2015.445
203. Chen AL, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Activation of the hypothalamic-pituitary-adrenal (HPA) axis contributes to the immunosuppression of mice infected with *Angiostrongylus cantonensis*. *J Neuroinflamm.* (2016) 13:266. doi: 10.1186/s12974-016-0743-z
204. Merlot E, Quesnel H, Prunier A. Prenatal stress, immunity and neonatal health in farm animal species. *Animal.* (2013) 7:2016–25. doi: 10.1017/S175173111300147X
205. Shan Q, et al. Physiological functions of heat shock proteins. *Curr Protein Pept Sci.* (2020) 21:751–60. doi: 10.2174/138920372066619111113726
206. Konits PH, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Serum thyroid hormone changes during whole body hyperthermia. *Cancer.* (1984) 54:2432–5. doi: 10.1002/1097-0142(19841201)54:11<2432::AID-CNCR2820541120>3.0.CO;2-W
207. Jiang Q, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Impact of a *Saccharomyces cerevisiae* fermentation product during an intestinal barrier challenge in lactating Holstein cows on ileal microbiota and markers of tissue structure and immunity. *J Anim Sci.* (2023) 101.
208. Wen C, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Heat stress alters the intestinal microbiota and metabolomic profiles in mice. *Front Microbiol.* (2021) 12:706772. doi: 10.3389/fmicb.2021.706772
209. Lambert J, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Fructose: A dietary sugar in crosstalk with microbiota contributing to the development and progression of non-alcoholic liver disease. *Front Immunol.* (2017) 8:1159. doi: 10.3389/fimmu.2017.01159
210. Harwood JL. Polyunsaturated fatty acids: conversion to lipid mediators, roles in inflammatory diseases and dietary sources. *Int J Mol Sci.* (2023) 24:8838. doi: 10.3390/ijms24108838
211. Liu S, Silva M, Costa J, Ferreira L, Gomes A, Santos P, et al. Alteration of gut microbiota after heat acclimation may reduce organ damage by regulating immune factors during heat stress. *Front Microbiol.* (2023) 14:1114233. doi: 10.3389/fmicb.2023.1114233
212. Li M, Dubois M, Leroy P, Petit C, Lambert J, Moreau F, et al. Effects of acute and chronic heat stress on the rumen microbiome in dairy goats. *Anim Biosci.* (2024) 37:2081–90. doi: 10.5713/ab.24.0120
213. Roy S, Smith A, Jones B, Brown C, Davis D, Wilson E, et al. Aging and climate change-induced heat stress synergistically increase susceptibility to *Vibrio vulnificus* infection via an altered gut microbiome-immune axis. *Sci Total Environ.* (2025) 989:179881. doi: 10.1016/j.scitotenv.2025.179881