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Heat stress: an environmental challenge to immune resilience and health in dairy cows

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Increasing environmental temperatures pose significant challenges to food security and animal welfare. In dairy production systems, heat stress detrimentally affects cow health, reproductive function, and immune resilience. This review summarizes the current knowledge on the impacts of heat stress in dairy cattle, emphasizing cellular targets, physiological and molecular consequences, and implications for health and productivity. Heat stress is associated with increased disease incidence in dairy cows. Elevated temperatures can increase pathogen abundance or alter host immune function, thereby compromising overall health. Both peripheral immune responses and local tissue responses are disrupted under heat stress. These effects could be mediated by various molecular mechanisms which contribute to dysregulated immune signaling. Moreover, heat stress can impair key immune pathways leading to either insufficient or excessive inflammatory responses, both of which predispose cows to disease. Effective mitigation of heat stress requires a multifaceted approach. While no single strategy fully offsets the detrimental effects of heat stress, a combination of environmental modifications (fans, shade, sprinklers), nutritional interventions (vitamins, minerals, targeted feed additives), and genetic selection for thermotolerance offer promising avenues to support cow health, immune resilience and maintain productivity in a warming climate.

KEYWORDS

cellular response, dairy cattle health, environmental stressors, heat stress, immune resilience

1 Introduction

Optimal health is fundamental to ensure both animal welfare and productivity across all livestock species (Cooke, 2019). In intensive production systems, livestock depend on a resilient and well-coordinated immune system to withstand the diverse health challenges including a wide range of pathogens, nutritional challenges, social stress and elevated ambient temperatures (Sheldon et al., 2009; Hammon et al., 2006; Ster et al., 2012; Chebel et al., 2016; Huzzey et al., 2007; Dahl et al., 2020). This resilience depends on the competency of both innate and adaptive immunity (Vlasova and Saif, 2021). A dysregulated immune system is associated with a high susceptibility to infectious diseases (Mallard et al., 1998; Kehrli and Harp, 2001). Heat stress has emerged as a particularly critical and escalating threat, impairing both productivity and fertility (Collier et al., 2006; Hansen, 2009). Heat stress occurs when an animal fails to maintain thermal balance between heat gain and heat

loss (Lendez et al., 2021; Bertipaglia et al., 2008), leading to behavioral and physiological changes that influences health, welfare and productivity (Becker et al., 2020).

Dairy cows genetically selected for high milk production are particularly susceptible to heat stress due to elevated ambient temperatures, which reduce feed intake while increasing metabolic heat production and overall heat load (Baumgard and Rhoads, 2013; Loor et al., 2023; Bernabucci et al., 2014). This added heat load occurs due to greater energy demands for body growth and milk synthesis, making high-producing cows more prone to the negative impacts of heat stress (Collier et al., 2017; Gaulty et al., 2013). For instance, studies conducted in Germany and China reported that lactating Holstein cows exposed to heat stress produced up to 53% less milk, with a marked reduction in milk quality compared to cooled cows, as ~22% decrease was observed in the milk protein (Hou et al., 2021; Gernand et al., 2019). Global climate change is exacerbating heat stress. Average surface temperatures have risen by 0.2 °C per decade since 1970, faster than in any other 50-year period, with projections of a further 1.4 °C to 4.4 °C increase by 2100 (IPCC, 2023). Consequently, the frequency of heat stress days affecting the livestock industry has markedly increased over recent decades (Solymosi et al., 2010). Heat stress costs the United States livestock industry an estimated \$1.69–2.36 billion annually, with the dairy sector contributing the largest share, approximately \$897 million, because of reduced milk yield, impaired reproduction, and increased mortality (St-Pierre et al., 2003). These estimates exclude losses from diminished product quality such as low-quality milk (low milk protein yield and percentage, higher somatic cells count) and carcasses, meaning the true economic impact is likely even greater. Moreover, heat stress disrupts livestock production efficiency across all stages of development, affecting milk yield and composition, growth performance, reproductive efficiency, and carcass traits (Baumgard and Rhoads, 2013; Ross et al., 2017; Habimana et al., 2023) and thus represents a significant economic burden for livestock producers globally (Bagath et al., 2019). Moreover, carry-over effects of dry period heat stress on mammary gland development further compound this burden as cows that experience heat stress during the dry period produce less milk in the subsequent lactation even when cooled after calving, translating to an additional \$810 million in annual losses (Do Amaral et al., 2009, 2010, 2011; Tao et al., 2011; Fabris et al., 2020; Ferreira et al., 2016). Studies in USA have demonstrated that *in utero* exposure to maternal heat stress during gestation impairs postnatal milk production performance of offspring (Laporta et al., 2020).

Beyond its impact on productivity, heat stress compromises immune competence by impairing immune cell function and reducing immunoglobulin production (Bronzo et al., 2020; Kamwanja et al., 1994; Do Amaral et al., 2010, 2011). The specific effects of heat stress on immune cell populations and their functions will be discussed in detail in a later section of this review. However, the mechanisms underlying heat stress-induced immune dysfunction remain poorly understood, reflecting the complex interplay among metabolic, neuroendocrine, and immune pathways (Bagath et al., 2019; Dahl et al., 2020). The susceptibility of animals to heat stress and subsequent impacts on

production vary between species, breed and physiological state such as pregnancy, transition period and lactation (Baumgard and Rhoads, 2013). Maintaining immune homeostasis under heat stress is critical to prevent excessive inflammation, autoimmune disorders and potential disease susceptibility (Nathan, 2002; Grivennikov et al., 2010).

With global temperatures continuing to rise, it is increasingly pertinent to understand how heat stress disrupts immune resilience and health in livestock. Dairy cattle are particularly vulnerable to heat stress because of their high metabolic demands. Therefore, the aim of this review is to summarize the impacts of heat stress on dairy cattle, and discuss the cellular targets, physiological and molecular consequences of heat stress, and implications for dairy cow health and productivity.

A conceptual summary of the multi-level consequences of heat stress is presented in Figure 1, illustrating how elevated environmental temperatures initiate a cascade of disruptions from whole-animal health and pathogen dynamics to immune function and cellular responses. This review explores each of these levels in detail to provide a comprehensive understanding of how heat stress compromises reproductive health.

2 Impacts of heat stress on physiology, disease and immunity

Heat stress negatively affects both the productivity and health of dairy cows. In hot and humid environments, cows experience elevated body temperatures and reduced feed intake, which in turn disrupts physiological functions such as milk production (West, 2003; Bohmanova et al., 2007). One common measure of heat stress is the temperature-humidity index (THI), a single metric that combines air temperature and humidity to estimate the level of heat stress experienced by animals (West, 2003; Collier et al., 2006; Bohmanova et al., 2007).

2.1 Heat stress and milk production traits

Milk production has been shown to decline approximately 1% for each unit increase in THI above 72 (West, 2003; Bohmanova et al., 2007). The broader impact of heat stress on dairy production has also been assessed using state-level data, with estimates indicating a 1% reduction in annual milk yield due to heat stress, and even greater losses when accounting for milk quality (Gisbert-Queral et al., 2021; Hutchins et al., 2025; St-Pierre et al., 2003). Notably, farm size plays a role in moderating these effects as larger dairy farms (> 500 cows) experienced relatively modest losses (~1% of single-day milk production), while smaller farms faced more than double the impact, with losses ranging from 2.5% to 3.9%, suggesting that management practices significantly influence vulnerability to heat stress (Hutchins et al., 2025). While large-scale observational studies based on climate data have provided valuable insights into the association between heat stress and milk yield losses, they often capture the combined effects of multiple environmental and management factors. Although these studies are

Consequences of Heat Stress: From Cow to Cell

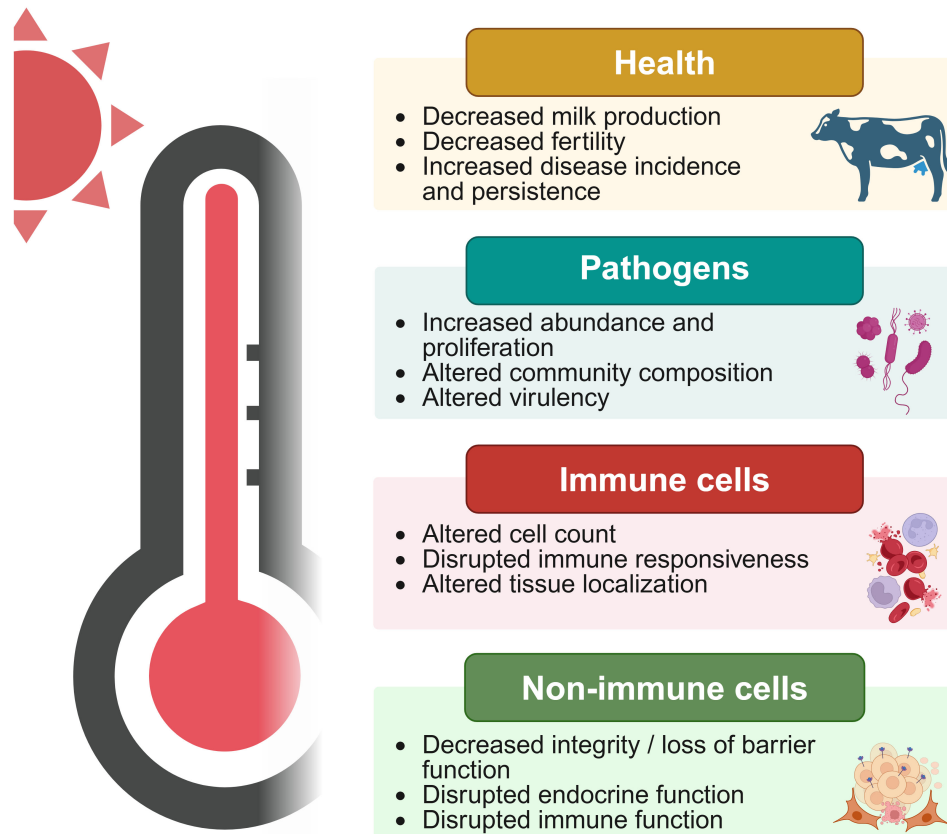


FIGURE 1

Consequences of heat stress in dairy cattle. Heat stress induces a series of disruptions across various biological systems. At the cow level, elevated environmental temperatures reduce milk production, impair fertility, and increase the incidence and persistence of disease. At the pathogen level, heat stress alters microbial community structure, increases pathogen abundance, and can enhance virulence traits. Within the host, immune cells exhibit altered abundance, impaired responsiveness, and disrupted localization, while non-immune epithelial and stromal cells experience loss of barrier integrity, altered endocrine signaling, and changes in innate immune activity. Combined, the effects of heat stress on the cow, host cells and pathogens compromise overall health and immune resilience of animals that can increase disease incidence.

critical for estimating real-world impact, they may not fully isolate the direct physiological responses to heat stress.

To complement findings from observational studies, controlled environmental chamber experiments provide valuable mechanistic insight by isolating the direct effects of heat stress. For instance, [Spiers et al. \(2004\)](#) demonstrated that cows experienced a 23% drop in milk yield just four days after abrupt exposure to elevated THI in a controlled setting. Heat stress during the dry period has been shown to impair mammary development in late gestation, ultimately reducing the milk production capacity of the cow in the subsequent lactation ([Tao et al., 2011](#); [Fabris et al., 2020](#)). In another controlled study, the use of electric blankets to induce heat stress during the dry period led to an approximate 0.2 °C increase in rectal temperature and a 6 kg/day decline in subsequent milk yield compared to unheated controls ([Casarotto et al., 2025a](#)). Such controlled studies are critical for isolating the direct effects of heat stress from other confounding environmental and management factors. Moreover, the extent to which heat stress reduces milk production is also influenced by breed or genotype, environmental

and geographical conditions, and non-genetic factors, including parity and stage of lactation ([Menéndez-Buxadera et al., 2020](#); [Leliveld et al., 2023](#)). Further research is needed to disentangle these interacting effects across production systems. The negative impact of heat stress extends beyond the dams, affecting multiple generations. For example, gestational heat stress reduces milk yield by 2.2 kg/day in daughters and 1.3 kg/day in granddaughters compared with offspring of cooled dams, highlighting the lasting, multigenerational consequences on dairy production ([Laporta et al., 2020](#)).

2.2 Heat stress and reproduction

One of the major physiological effects of heat stress in cows is reduced fertility, as it significantly impairs their ability to establish and maintain pregnancy ([Jordan, 2003](#)). Female fertility traits such as pregnancy per artificial insemination (AI) decrease with an increasing THI ([Gernand et al., 2019](#)). In Germany, only 16% of inseminations resulted in pregnancies at a THI of 80, underscoring

the profound fertility losses associated with heat stress conditions (Gernand et al., 2019). Another study reported that long-term heat stress (THI $\geq$ 73) reduced pregnancy success with frozen-thawed semen by 63%, while short-term heat stress reduced success with fresh semen by 80% (Schüller et al., 2016). Several mechanisms could explain reduced fertility under heat stress. Elevated temperatures impair follicular development (Badinga et al., 1993; Wilson et al., 1998; Roth et al., 2000), disrupt steroid hormone synthesis, and suppresses estrus behavior (Kadokawa et al., 2012; Provolo and Riva, 2009). For example, estrus expression is nearly halved under seasonal heat stress, averaging only 4.5 mounts compared to 8.6 in winter, partly due to reduced 17 β -estradiol production by the dominant follicle (Wilson et al., 1998; Nebel et al., 1997). Gestational heat stress in cows reduces uterine and umbilical blood flow by 51% and 30% respectively, resulting in a 22% decrease in fetal weight (Wolfenson et al., 1988; Dreiling et al., 1991). Furthermore, heat stress can compromise gestation success during the peri-implantation period and fetal losses. For example, a study from Spain reported pregnancy losses of 12.3% in cows conceiving during the warm period, compared with 2.1% during the cool period (García-Ispuerto et al., 2006). Abortions also represent a loss of reproductive efficiency. Hossein-Zadeh et al. (2008) reported higher odds of abortion during spring and summer compared with other seasons. Similarly, under subtropical Egyptian conditions, fetal loss increased significantly from 17.1% at low (< 70) THI to 24.9% at high (80–85) THI (El-Tarabany and El-Tarabany, 2015). While the detrimental effects of heat stress on cow reproductive physiology are well established, gaps remain in linking molecular alterations (e.g., epigenetics alterations, oocyte mitochondrial dysfunction, embryonic mortality) with observed reductions in fertility (Laporta et al., 2024; Halli et al., 2025).

Gestation length is defined as the number of days from confirmed conception to calving (Vieira-Neto et al., 2017; Pajohande et al., 2023). Several factors influence gestation length including fetal sex, age of the dam, and season (Silva et al., 1992). Notably, cows calving during the warm season have been reported to have a gestation length approximately 1.5–2.8 days shorter than those calving in the cool season (Dubois and Williams, 1980; Vieira-Neto et al., 2017). Shorter gestation lengths are associated with high summer temperatures (Mcguirk et al., 1998; Norman et al., 2009; Tomasek et al., 2017). Heat stress during late gestation triggers inflammatory responses and disrupts nutrient transport functions in the placenta of dairy cows (Casarotto et al., 2025c). Reduced nutrient transfer, increased reactive oxygen species (ROS) and oxidative stress-induced inflammation in the metabolically active placenta during late gestation can lead to premature birth (Agarwal et al., 2012; Sultana et al., 2023; Casarotto et al., 2025c). The shorter gestation lengths under heat stress may increase the risk of postpartum complications such as still birth and retained fetal membranes which are also important risk factors for uterine diseases such as metritis (Dubois and Williams, 1980; Ghavi Hossein-Zadeh and Ardalan, 2011; Norman et al., 2009; Vieira-Neto et al., 2017). Dairy cows with short gestation length have 2.5-fold greater incidence of still birth and 5-fold greater incidence of retained fetal membranes, resulting in a 2-fold increase in the incidence of uterine diseases

(Vieira-Neto et al., 2017). Retained fetal membranes in dairy cattle may result from impaired immune-mediated clearance of fetal tissues at parturition (Kimura et al., 2002; Davies et al., 2004). The combination of a weakened immune response and retained necrotic tissues likely contributes to the increased incidence of metritis.

2.3 Heat stress, immunity and health

The immune system is a central system that protects mammals against environmental stressors and maintains cellular and physiological resilience (Sonna et al., 2002). However, under heat stress conditions, this finely tuned system becomes disrupted, leading to impaired immunocompetence. As a first line of defense, the innate immune system plays a crucial role in mounting an immediate, non-specific response to pathogens and environmental immune challenges (Medzhitov, 2007). The innate immune system then primes and supports the activation of the adaptive immune system to produce pathogen-specific antibodies and cellular responses (Janeway, 1999). Dysregulation of both innate and adaptive immune functions weakens an animal's ability to mount effective defenses against pathogens, creating conditions that favor infection establishment and progression that ultimately threaten productivity and welfare (Sonna et al., 2002; Vlasova and Saif, 2021).

Heat stress influences the incidence and persistence of infectious diseases. Seasonal variation in clinical mastitis is well documented with an increased incidence of 10–40% in hotter summer months when cows experience heat stress compared to cool season months (Erskine et al., 1988; Hogan et al., 1989a, 1989). Mastitis is a primary cause of elevated somatic cell count (SCC) in milk (Pakrashi et al., 2023). The detrimental effects of heat stress on somatic cell count and the incidence of clinical mastitis have been consistently reported across dairy herds in multiple regions such as USA, Netherlands and Thailand (Rhone et al., 2008; Berry et al., 2006; Olde Riekerink et al., 2007). Heat stress increases SCC, with studies from Canada reporting higher SCC during summer months (Becker et al., 2020; Sargeant et al., 1998). During the summer, mastitis is highly associated with increased infections caused by *Streptococcus* and *Coliform* bacteria, which are the predominant pathogens isolated during this season (June to August) in confined dairy herds in the United States (Erskine et al., 1988; Hogan et al., 1989a; Makovec and Ruegg, 2003). Higher THI is also associated with increased incidence of retained placenta and puerperal disorders (Morse et al., 1988; Olde Riekerink et al., 2007; Gernand et al., 2019; Joosten et al., 1991; Labernia et al., 1998; Jingar et al., 2014). Cows calving between May and September in the Northern Hemisphere experience nearly double the incidence of retained placenta and metritis (24%) compared to those calving in the cooler months (12%) (Dubois and Williams, 1980). Notably, heat stress contributes to both a higher incidence and persistence of disease (Molinari et al., 2022). found a significant increase in both incidence and persistence of metritis in dairy cows during warmer months, despite no significant change in bacterial load in the vagina. Additionally, cows calving in the summer were seven times more likely to exhibit persistent endometritis beyond 60

days postpartum compared with those calving in autumn (Gautam et al., 2010; Pascottini et al., 2017).

The persistence of uterine diseases during heat stress may be attributed to reduced vascular perfusion of the uterus, which impairs leukocyte trafficking to the endometrium and compromises immune-mediated clearance of pathogens (Roman-Ponce et al., 1978). Seasonal variation also influences macrophage distribution within the endometrium, with macrophages primarily concentrated in the subepithelial stroma during winter, while exhibiting a more diffuse and sparse localization across the endometrial tissue in summer (Sakai et al., 2020). However, it remains unclear whether the altered localization of macrophages under heat stress directly contributes to the prolonged course of endometritis observed in summer, highlighting the need for further *in vivo* investigations. Collectively, heat stress may not only impair host susceptibility to infection and disease but also the recovery from diseases in dairy cows.

Beyond infectious diseases, heat stress has been implicated in metabolic and inflammatory disorders. For instance, the incidence of ketosis increases by 11% during summer compared with cooler seasons (Pavlicek et al., 1989), likely reflecting the combined effects of oxidative stress and negative energy balance due to high milk production, low feed intake, reduction in rumination and nutrient absorption and increased maintenance requirements under heat stress (Collier et al., 2006; Rhoads et al., 2009). Similarly, lameness and digital phlegmon (foot rot) occur more frequently in warm and humid conditions (Sanders et al., 2009; Do Amaral et al., 2011; Gernand et al., 2019). This is likely due to an increased abundance of foot rot causing pathogens, including *Fusobacterium necrophorum*, in warmer, more humid conditions (Van Metre, 2017). Prolonged exposure to moderate heat stress also promotes systemic inflammation, evidenced by increased circulating tumor necrosis factor (TNF) α , interleukin (IL)-1 β , and IL-6 in dairy cows (Min et al., 2016). Transcriptomic analysis of whole blood from Holstein bull calves exposed to heat stress for 12 hours in an environmentally controlled chamber revealed a 1.5- to 3-fold increase in the expression of immune-related genes. These included genes involved in Toll-like receptor (TLR) signaling, interferon (IFN) signaling, and interleukins such as IL-8 and IL-15 (Srikanth et al., 2017). The findings suggest systemic activation of the innate immune response under heat stress.

Heat stress has been associated with reduced immune responses following vaccination. Dry cows exposed to heat stress during the prepartum period showed reduced immunoglobulin responses to ovalbumin vaccination, although these deficits recovered post-calving when cooling was provided (Do Amaral et al., 2011). Similarly, elevated stress hormones such as cortisol and corticosterone under heat stress interfere with antigen presentation and antibody production in swine and poultry, undermining vaccination efficacy and complicating disease control efforts (Prates, 2025). Using a murine model, Hu et al. (2007) demonstrated that chronic heat stress using $38 \pm 1^\circ\text{C}$ for 2 h per day for 35 days impaired cell-mediated immune response in mice following vaccination by reducing IgG2a production, T-cell proliferation, IFN γ expression, and cytotoxic T cell activity as compared to control mice maintained at $24 \pm 18^\circ\text{C}$. This study

suggests that heat stress can result in a weaker immune response to vaccines and reduce vaccine efficacy. Beyond immediate effects on vaccine responses, genetic variation in immune responsiveness offers a promising avenue for resilience under heat stress. Holstein dairy cattle classified as high antibody and high cell-mediated immune responders show reduced disease incidence and improved vaccine responsiveness (Mallard et al., 1998; Wagter et al., 2000; Thompson-Crispi et al., 2012). Collectively these data highlight a critical gap in current vaccination programs under heat stress conditions and points to a promising research avenue for developing strategies to mitigate immune dysregulation caused by heat stress.

Evidence indicates lasting carryover effects of heat stress beyond the immediate period of heat stress. Mice exposed to chronic heat stress at $38 \pm 1^\circ\text{C}$ for 21 days prior to H5N1 influenza infection exhibited a decreased mRNA expression of *Il6* and *Ifnb1* followed by increased lung viral loads and 37% increased mortality compared to mice kept in thermoneutral conditions, indicating that prior heat stress suppresses innate immune responses that increase the virulence of disease pathogens in mice (Hu et al., 2007; Jin et al., 2011). Although rodent models highlight links between prior heat stress and impaired immunity, equivalent mechanistic studies in livestock are limited (Gernand et al., 2019). showed a linear increase in digital phlegmon and puerperal disorders with increasing THI values in the week preceding disease onset, suggesting a carry-over effect of heat stress on disease. Such findings imply that prior heat stress primes animals for higher disease susceptibility, prolonged recovery, and reduced resilience in subsequent physiological stages. Major gaps remain in mechanistic understanding of how heat stress alters long-term disease susceptibility. Few studies directly associate heat stress-induced immune cell dysfunction with disease onset in livestock (Do Amaral et al., 2010; Tao et al., 2011). Longitudinal research is needed to clarify how prior heat stress exposure alters immune response, tissue resilience, and disease persistence across lactations. Taken together, heat stress not only triggers immediate immune challenges but also may have lasting effects on immune function. Understanding these long-term impacts is an important area for future research.

While heat stress during the summer is widely recognized as a major factor impairing immunity and overall health, it remains important to recognize that other seasonal factors such as photoperiod, feed intake, pathogen load, and management changes also contribute to immune function (Pavlicek et al., 1989; Auchtung et al., 2004; Guinn et al., 2019; Bai et al., 2020; Akkose and Vural, 2025). For instance, photoperiod itself plays a role, as extended daylight during summer has been shown to impair cellular immunity in cows (Auchtung et al., 2004), highlighting how neuroendocrine-immune interactions may further exacerbate disease susceptibility during the summer season.

Not all studies demonstrate a clear association between ambient temperature and disease incidence. Some studies report weak or no associations of summer high temperatures with retained fetal membranes (Gröhn and Rajala-Schultz, 2000; Han and Kim, 2005; Pinedo et al., 2020), while others report a positive association with low seasonal temperatures during winter and higher rate of retained fetal membranes, metritis and clinal

mastitis (Bruun et al., 2002; Ghavi Hossein-Zadeh and Ardalan, 2011). These discrepancies likely reflect differences in management systems, housing (pasture vs. confinement), change of feeding regimes, duration of heat stress, adaptation to the environment and statistical approaches (Wetherill, 1965; Muller and Owens, 1974; Dubois and Williams, 1980; Benzaquen et al., 2007; Ghavi Hossein-Zadeh and Ardalan, 2011; Gisbert-Queral et al., 2021). For example, pasture access during summer has been associated with lower rates of retained placenta and metritis (Bruun et al., 2002), highlighting management as an important modifier of heat stress effects.

The preponderance of evidence suggests that heat stress, either experimentally or seasonally, alters dairy cattle physiology, diminishes productive performance, reduces fertility, alters innate and adaptive immune responses and increases the incidence of disease. Thus, the mechanism by which heat stress impacts dairy cattle health requires increased investigation to develop mitigation strategies.

3 Cellular targets of environmental stress

With the well-characterized impacts of heat stress on productive traits, much of the efforts have shifted toward understanding its cellular targets, particularly those related to immune function and host defense (Rhoads et al., 2009; Wheelock et al., 2010). In this section, we review the literature on how heat stress targets the cells (immune & non-immune) involved in host defense, and the microbiome, each of which plays a critical role in disease susceptibility, immune resilience and overall health (Bronzo et al., 2020; Molinari et al., 2022).

3.1 Classical hematopoietic immune cells

Environmental heat stress exerts profound effects on hematological and immunological profiles in livestock, though findings often vary across experimental models (Sejian et al., 2018). Hematological shifts are among the earliest indicators of systemic response to heat stress (Kim et al., 2020; Gujar et al., 2022). For example, heat-stressed Holsteins (THI $\geq$ 79) exhibited a 10% reduction in hemoglobin and 11% reduction in red blood cell (RBC) counts compared to cows with no heat stress (THI $\leq$ 68) (Zeng et al., 2023). This effect is likely due to hemodilution, as water intake can increase by 50% as the THI reaches 80 (Sejian et al., 2018). Decrease in RBC counts may also result from erythrocyte destruction, reflected in decreased hematocrit (%), mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration values (Lee et al., 1976; Ju et al., 2014).

Leukocytes are central components of the immune system that function to protect the animal against a wide range of invading pathogens (Chandra et al., 2012). These immune cells show both stimulatory and suppressive responses to heat stress (Lacetera et al., 2005). In dairy cows, confinement in an environmental chamber (40–48 °C, 70–80% humidity for 24 hours) or natural

environmental heat exposure during the summer months (THI 71.2–80.3, June–August) increase leukocyte counts by approximately 20%, particularly neutrophils and eosinophils (Wegner et al., 1976; Sejian et al., 2018). This observation may be linked to corticosteroid-driven mobilization of mature neutrophils from bone marrow. In a similar study, dairy cows exposed to seasonal heat stress (temperature: 20.4–33.6 °C; relative humidity: 45.1–97.5%) showed a 201% increase in circulating neutrophils, a 26.7% increase in eosinophils and a 5.3% increase in lymphocytes compared to cows in the intermediate season (temperature: 10.7–21.8 °C, relative humidity: 45.1–97.5%) (Lee et al., 1976). Together, these findings indicate that heat stress potentially induces a leukocytic response in dairy cows, reflecting systemic immune dysregulation.

Other experimental systems have reported decreases in leukocyte concentrations during the summer compared to winter in both cows and buffaloes (O'Connor et al., 2000; Ju et al., 2014), reflecting inconsistencies that may stem from breed, age, or methodological differences (Elvinger et al., 1991; Kamwanja et al., 1994; Lacetera et al., 2002, 2006). For example, when polymorphonuclear leukocytes (PMN) from dairy cows were exposed to heat stress *in vitro* (41 °C) for 2 h, their phagocytic activity and oxidative burst capacity decreased by 37% and 21% compared to PMN under normothermic condition (39 °C) (Lecchi et al., 2016). Several *in vitro* studies have demonstrated that short and severe heat shock (42 °C) reduces the viability and responsiveness of bovine PMN and lymphocytes to mitogen stimulation (Elvinger et al., 1991; Kamwanja et al., 1994). Similarly, murine macrophages exposed to heat shock (45 °C) for 12 min exhibited a ~60-fold reduction in *Tnf* mRNA expression following endotoxin stimulation while maintaining phagocytic capacity, highlighting a stress-adapted modulation of innate immune activity (Snyder et al., 1992). However (Do Amaral et al., 2011), reported no differences in neutrophil phagocytic activity or oxidative burst capacity when comparing dairy cows exposed to heat stress during the dry period (THI 77.6; no fans or water sprinklers) and cooled cows (THI: 77.1; with fans and water sprinklers). Interestingly, by 20 days postpartum, when all cows were maintained under the same cooling conditions, neutrophils from previously heat-stressed cows exhibited a 13% reduction in oxidative burst capacity and a 14% decline in phagocytic activity compared with cooled counterparts (Do Amaral et al., 2011). These findings highlight that the effects of heat stress on immune responses can persist beyond the period of direct exposure, suggesting long-term carryover impacts on postpartum immune competence that warrants further investigation.

Lymphocytes play a central role in immune function, including the production of immunoglobulins and the regulation of immune responses (Balakrishnan and Adams, 1995; Pearce et al., 2013a). Lymphocyte proliferation and viability are diminished following heat shock *in vitro* (Lacetera et al., 2005; Elvinger et al., 1991; Kamwanja et al., 1994), often associated with a Th1 to Th2 cytokine shift (Lacetera et al., 2005, 2006). *In vivo* results, however, remain inconclusive, with some studies reporting minimal effects of heat stress on lymphocyte proliferation in Holsteins (Elvinger et al., 1991). These discrepancies highlight the need for integrative studies

linking endocrine, metabolic, and immune pathways. These findings suggest that adaptive immunity in cows is also vulnerable to heat stress.

Heat stress alters cytokine production and receptor signaling, as evidenced by dairy cows exposed to elevated seasonal THI (80.3 ± 1.0 ; June–July) showing increased serum concentrations of TNF α and IL-10 compared with cows under low to moderate THI conditions (56.4 ± 2.5 to 73.9 ± 1.7 , May–June) (Zhang et al., 2014). Similar findings were reported in dairy cows exposed to prolonged heat stress (THI = 80 for 23 days) which increased the plasma concentrations of inflammation-related proteins, including IL-6 and TNF α , indicating that long-term heat stress may promote an inflammatory response in dairy cows (Min et al., 2016).

While studies on immune cell function demonstrate that heat stress impairs processes such as phagocytosis, oxidative burst, and cytokine secretion, molecular analyses can also provide insights into the mechanisms underlying these functional shifts. For example, transcriptomic analysis of peripheral blood mononuclear cells collected from cows subjected to heat stress for four days using controlled environmental chambers (21.3 to 32.8 °C and 35 to 88% relative humidity; THI 69–83) revealed that bradykinin receptor B1 (*BDKRB1*) was the most highly upregulated gene (5-fold), compared with the cows under thermoneutral conditions (10.2 – 15.9 °C, and 61–94% relative humidity; THI 55) (Garner et al., 2020). Even short-term heat stress (42 °C, 90% humidity for 4 h) in controlled environmental chambers has been shown to upregulate innate immune and inflammation-related genes, such as *IL17A*, which remained elevated for up to 48 h. This sustained increase indicates an accelerated inflammatory response consistent with a role for IL-17A in promoting cytokine release, immune cell recruitment, and vascular permeability (Raslan et al., 2010; Mehla et al., 2014). Heat stress also increases the expression of apoptosis related genes such as BCL2-associated athanogene 2 (*BAG2*) and oxidative stress related genes such as *STIP1* were upregulated while glucose 6-phosphate dehydrogenase (*G6PD*) was downregulated, indicating that heat challenge increases cellular vulnerability to free radical damage during oxidative stress (Garner et al., 2020).

Peripheral blood mononuclear cells from heat-stressed cows exhibit enhanced responsiveness to lipopolysaccharide (LPS) via TLR 2/4 upregulation (Ju et al., 2014; Zhou et al., 2005; Chen et al., 2018), yet paradoxically, heat shock can inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation by stabilizing the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (I κ B α)–NF- κ B complex, suppressing downstream cytokine production (Sun et al., 2005; Zhou et al., 2005; Chen et al., 2006). This may suggest that the inhibitory effects of heat shock response on LPS-induced NF- κ B activation and cytokine production may be independent of TLR4.

Neutrophil dysfunction during the dry period persists into lactation (Do Amaral et al., 2011), while peripheral blood mononuclear cells from heat-stressed cows display heightened inflammatory responses to LPS for > 21 days postpartum, even under thermoneutral conditions (Marins et al., 2021; Molinari et al., 2023). These findings suggest that immune dysregulation under heat stress extends beyond immediate exposure, likely through

epigenetic reprogramming, metabolic ‘memory’, or unresolved mechanisms.

Although bovine PMN cells play a critical role in defense against diseases, the lasting carry-over effects of elevated temperatures on their innate immune function remain underexplored. Despite extensive *in vitro* evidence for suppressed leukocyte and lymphocyte function under heat stress, *in vivo* findings are inconsistent and often confounded by nutrition, parity, and management systems. Future work should focus on (a) longitudinal field studies integrating hematological, cellular, and molecular alterations, (b) mechanistic exploration of PMN dysfunction, particularly its persistence across different physiological states including lactation and pregnancy, and (c) identification of epigenetic or metabolic ‘memory’ pathways that facilitate carry-over effects of prepartum heat stress on postpartum immunity.

3.2 Non-immune cells

In addition to classical immune cells, epithelial and stromal cells actively coordinate inflammation and support immune defense alongside their normal physiological functions (Medzhitov, 2008; Iwasaki and Medzhitov, 2015). In particular, the mucosal epithelial cells that line the gastrointestinal, reproductive and respiratory tracts form a barrier to the underlying stroma and serve as the frontline responders to microorganisms, shaping downstream immune cell activation (Yang and Yan, 2021; Zhou et al., 2025). Under heat stress, intestinal epithelial barrier integrity is compromised, which leads to translocation of luminal microorganisms and their products to the underlying tissues (Hall et al., 2001; Pearce et al., 2013b) and initiation of local and systemic inflammation (Koch et al., 2019; Song et al., 2019; Yi et al., 2020).

During the dry period, mammary gland regeneration for the next lactation relies on epithelial cell apoptosis and proliferation (Capuco et al., 1997). Heat stress impairs this remodeling by suppressing autophagic activity and cell proliferation (Tao et al., 2011; Wohlgemuth et al., 2016), resulting in fewer mammary epithelial cells and reduced milk production in subsequent lactations (Collier et al., 2006; Do Amaral et al., 2009; Fabris et al., 2020). At the molecular level, these functional impairments are reflected in altered gene expression patterns of mammary epithelial cells exposed to heat stress. Gene expression microarrays of cultured bovine mammary epithelial cells showed that heat shock (42 °C for up to 4 h) downregulated the expression of genes related to immune response (*CCL2*, *IGF2* and *S100A1*), metabolism and biosynthesis (*PFKP*, *IDH3B*, *CSN* and *HSD17B7*), and morphogenesis (*MYL6*, *CFL2* and *COL14A1*) (Collier et al., 2006; Kapila et al., 2016).

It is important to distinguish between the effects of short-term *in vitro* heat shock and the prolonged environmental heat stress experienced by whole animals on innate immune responses. For example, dairy cows exposed to seasonal heat stress (THI: 78.6 ± 4.5) for 28 days and then challenged with an intramammary LPS infusion (10 μ g in 5 ml saline) on day 30 exhibited higher milk concentrations of IL-10 and TNF α , with a tendency for increased milk haptoglobin, indicating that heat stress amplified mammary

inflammatory responses to LPS (Chen et al., 2023). Whether other tissues, such as the endometrium, display a similar heightened response to LPS after prolonged heat stress remains an important question for future investigation. Furthermore, the impact of prepartum heat stress does not dissipate with removal of the stressor, but persists as evidenced in lactating mammary glands where heat-stressed cows showed more than 200 differentially abundant proteins and phosphoproteins, affecting immune, metabolic, and stress-response pathways (Skibieli et al., 2018). These long-lasting molecular imprints suggest a need to investigate mechanisms of cellular ‘memory’ in the mammary gland (Naik and Fuchs, 2022; Silva et al., 2024) as it relates to lactation but also immune function.

The endometrium (mucosal lining of the uterus) integrates endocrine, reproductive, and immunological functions (Wira and Fahey, 2004; Mansouri-Attia et al., 2009). Heat stress disrupts bovine endometrial signaling, including prostaglandin synthesis in response to TNF α or IFN-tau (Katagiri et al., 2013; Sakai et al., 2018, 2021). In addition to its reproductive functions, the endometrium serves as a key immunological barrier, providing innate defense against ascending uterine pathogens using TLRs, antimicrobial peptides, and acute-phase proteins (Wira and Fahey, 2004). Both endometrial epithelial and stromal cells detect pathogen-associated molecular patterns via TLRs, triggering an inflammatory response marked by the secretion of inflammatory mediators such as IL-1 β , IL-6, and CXCL8 (IL-8) that mobilize and activate immune cells (Beutler, 2004; Akira et al., 2006; Turner et al., 2014). *In vitro* cultured bovine endometrial epithelial and stromal cells show opposite innate immune responses to LPS when exposed to short-term heat shock (40.5 °C for 32 h) (Sakai et al., 2020; Chotimanukul et al., 2022). For example (Sakai et al., 2020), demonstrated that bovine endometrial epithelial cells produce less IL-6 protein in response LPS (1 μ g/mL) under heat shock condition (40.5 °C) compared with epithelial cells under thermoneutral conditions (38.5 °C), whereas stromal cells produced more IL-6 and monocyte chemoattractant protein 1. These changes occurred without altering pathogen-recognition receptor expressions such as TLRs. However, a mixed population of *in vitro* cultured bovine endometrial cells, containing both epithelial and stromal cells, showed a reduced innate immune response to LPS (1 μ g/mL) under short-term heat shock (40.4 °C for 24 h) compared with thermoneutral conditions (37 °C). This was evidenced by decreased *S100A8* expression and reduced secretion of IL-8 and PGF2 α (Chotimanukul et al., 2022). In support of these findings, studies have also identified heat shock protein (HSP) 70 as a negative regulator of the inflammasome pathway controlling IL-1 β production in rodent macrophages (Martine and Rébé, 2019). A major role of epithelial cells in innate immunity is the production of chemokines such as IL8. If heat stress perturbs epithelial cell synthesis of chemokines, this could have a significant impact on innate immune responses and leukocyte inflammation (Zachariae, 1993; Brodzki et al., 2014; Turner et al., 2014; Karstrup et al., 2017; Martínez-Burgo et al., 2019).

By contrast (Molinari and Bromfield, 2023), reported exaggerated inflammatory responses in bovine endometrial epithelial cells under acute heat exposure *in vitro*, suggesting that

exacerbated inflammatory responses may predispose animals to uterine diseases. Similarly, liver transcriptome analysis of dairy cows exposed to environmental heat stress (THI: 74–82 for 14 days) revealed down regulation of protein-coding genes in mitochondria (*COX1*, *COX2*, *CYTB*, *ND1* and *ND2*) and key regulators of phosphorylation and milk fat synthesis (*ASCL1*, *KCNIP4*), while genes involved in immune response (*HAMP*, *SAA3* and *IL1B*) were upregulated compared with cows in thermoneutral conditions (THI: 68) (Li et al., 2023). These molecular adjustments may enhance basic survival mechanisms but fail to fully counteract metabolic turbulence during heat stress that contributes to immune dysregulation and reduced milk production (Li et al., 2023). Nonetheless, future research should determine whether the decline in cellular energy metabolism under heat stress results from a direct effect of heat stress on mitochondrial function or is a secondary consequence of an activated inflammatory response (Ganeshan et al., 2019).

Maternal heat stress alters placental development, reducing cotyledon number, placental mass, and vascularity in cattle and sheep, potentially compromising nutrient exchange and fetal growth (Bell et al., 1989; Early et al., 1991; Van Wettere et al., 2021; Casarotto et al., 2025c). Some studies, however, suggest compensatory hypertrophy of cotyledons to preserve fetal growth (Silva et al., 2021; Casarotto et al., 2025b). At the molecular level, heat exposure disrupts placental gene expression linked to angiogenesis, hypoxia, and oxygen metabolism, potentially impairing oxygen delivery to the fetus (Casarotto et al., 2025c). These findings highlight the placenta as a sensitive and underexplored target of maternal heat exposure, with significant implications for offspring health.

Collectively, these findings indicate distinct cellular responses in immune and non-immune cells under heat stress that require further investigation, and underscores the need to account for cell type, timing, and culture conditions. Despite insights from *in vitro* heat shock cell culture experiments, where alterations in cell function are primarily driven by the high temperature, the *in vivo* gene expression dynamics of different bovine tissues such as the endometrium remain poorly understood, with most studies limited by invasive sampling methods such as biopsies or post-mortem analysis (Pfaffl et al., 2003). Recent advances in non-invasive approaches such as endometrial cytology could improve real-time monitoring of stress-induced transcriptional changes (Rocha et al., 2022). Furthermore, changes in gene expression represent only one component of the cellular response to high ambient temperatures; a comprehensive understanding requires an integrative approach that considers not only transcriptional regulation but also the functional interactions among molecular, metabolic and physiological pathways.

3.3 Microbiome

The host microbiota is increasingly recognized as a critical regulator of health and disease (Clemente et al., 2012; O'Hara et al., 2020; Peixoto et al., 2021), to the extent that it has been described as a ‘forgotten organ’ due to its profound physiological influence on the host (O'Hara and Shanahan, 2006). Environmental stressors

including social stress (Bailey et al., 2011), weaning (Davis et al., 2016), and thermal stress (Song et al., 2014) reshape microbial communities with consequences for host health (Kim et al., 2022).

Disease development depends on the interaction between a susceptible host and the pathogen, and environmental factors that affect both the host defense and pathogen activity which may enhance pathogenic bacterial prevalence or virulence and impair host immune function, thereby increasing the risk of disease (Molinari et al., 2022). Elevated temperatures can increase pathogen proliferation and facilitate microbial dysbiosis, thereby increasing the risk of infectious disease (Altizer et al., 2006). For example, higher environmental temperatures correlate with increased bloodstream infections in humans, particularly by Gram-negative pathogens such as *Escherichia coli* and *Acinetobacter* spp (Eber et al., 2011). This highlights the influence of ambient temperature on pathogen dynamics, a pattern also relevant to livestock health. In dairy cattle, bacterial load on teat skin and bedding increases during the summer and is associated with an increased incidence of mastitis (Hogan et al., 1989a; Rowbotham and Ruegg, 2016). Seasonal peaks of *Streptococcus uberis* and *E. coli*-associated mastitis have also been reported during the summer months, particularly in August, compared to the winter season (Olde Riekerink et al., 2007). Furthermore, the increased incidence of mastitis under hot and humid conditions has been attributed to the proliferation of pathogen vectors (Das et al., 2016). Environmental heat stress (THI > 60 in Germany) has also been shown to increase the shedding of pathogens such as yeasts and *Streptococcus uberis* from intramammary-infected quarters. This effect may result from impaired immune function and elevated milk temperature, both of which favor pathogen proliferation (Hamel et al., 2021).

In ruminants, heat stress disrupts rumen fermentation by altering bacterial composition. While (Zhao et al., 2019) found that heat stress did not markedly change the overall bacterial community of the rumen, heat stress selectively increased lactate-producing bacteria and reduced acetate-producing bacteria, potentially contributing to acidosis and impaired milk fat synthesis. Other studies in dairy cows (Zhao et al., 2019; Chen et al., 2018), pigs (Xia et al., 2022), and goats (Contreras-Jodar et al., 2019) confirm heat stress-associated microbial shifts in the gut, yet the extent to which these are direct effects of temperature versus indirect effects of reduced feed intake and altered behavior remain unresolved.

Emerging evidence suggests heat stress may also foster microbial persistence and adaptation (Zhang et al., 2025). Novel findings indicate that bacteria can transiently tolerate lytic phages without acquiring resistance mutations, a survival mechanism enhanced by heat stress (Park et al., 2022; Zhang et al., 2025). Similar persistence has been described under antibiotic stress (Levin-Reisman et al., 2017, 2019), raising the possibility that heat stress inadvertently promotes microbial survival and resistance emergence. Such dynamics may contribute to the increased persistence of uterine diseases like metritis during hot seasons. However, *in vivo* studies are needed to investigate the direct and long-term effects of heat stress on uterine microbial diversity and resistance, as well as to determine whether heat stress to dairy cows

induces microbial mutations or epigenetic adaptations that lead to systemic immune dysfunction and facilitate pathogen persistence.

4 Stress-induced signaling pathways in immune modulation

4.1 Heat shock proteins and stress signaling

Heat shock proteins (HSP) represent the primary molecular chaperones induced by cellular stress, and their expression is markedly upregulated during heat stress across multiple livestock species, including genes such as *HSPA4*, *HSPA6*, *HSPA1A/HSPA1L* (HSP70), *HSP90AB1* (HSP90), *HSPH1* (HSP105), and HSP90 activators *AHSA1* (Schmidt and Abdulla, 1988; Lei et al., 2009; Hu et al., 2016; Kapila et al., 2016; Garner et al., 2020). Functionally, HSPs preserve protein homeostasis by preventing aggregation, refolding damaged proteins, and inhibiting apoptosis, thereby sustaining cell survival under stress (Garrido et al., 2001; Stetler et al., 2010; Srivastava, 2002; Mayer and Bukau, 2005).

Beyond cytoprotection HSP70 also exerts critical immunomodulatory roles, enhancing innate immunity by activating antigen-presenting cells, promoting antibody production, stimulating T-cell responses, and providing both cell protection and immune support during heat stress (Wallin et al., 2002; Zügel and Kaufmann, 1999). In the bovine endometrium, heat shock response also intersects with the innate immune response. For instance (Molinari and Bromfield, 2023), demonstrated that while heat shock (40 °C for 24 h) of endometrial epithelial cells increases the gene expression of *HSPA1A* and amplified inflammatory responses to LPS (1 or 10 µg/mL), knock down of *HSPA1A* or heat shock factor 1 (*HSF1*) exacerbated the immune response to LPS. This suggests that the heat shock response (increased HSP) functions as an intrinsic brake on excessive inflammation, highlighting that immune responses may be modulated by heat shock (Molinari and Bromfield, 2023). Heat shock protein 70 acts as a danger signal that activates antigen-presenting cells and promotes proinflammatory cytokine production (Somensi et al., 2017; Song et al., 2019). For example, human monocytes exposed to purified exogenous HSP70 (7 nM at 37 °C for 2–4 h) increased IL-1β, IL-6 and TNFα through CD14 engagement and NF-κB-mediated signaling (Asea et al., 2000). Similarly, exposure of human lung cancer cells to extracellular HSP70 induced proinflammatory gene transcription after 30 min (Somensi et al., 2017). These findings suggest that although HSP70 is primarily an intracellular chaperone, it can also elicit immune responses when released outside the cell (Mambula and Calderwood, 2006; Vega et al., 2008). Contradictory evidence also suggests that HSP70 can suppress NF-κB-mediated inflammation by interfering with TRAF6 ubiquitination (Hauser et al., 1996; Ding et al., 2001; Chen et al., 2006). These findings underscore the complexity of HSP-mediated regulation, which may vary by cell type, context, and exposure duration.

Taken together, elevated HSP expression under acute heat shock supports cytoprotection and immune modulation, yet questions remain about the long-term consequences of heat stress on HSP activity. Chronic or repeated heat stress may lead to sustained HSP overexpression, potentially diverting cellular resources, promoting persistent inflammation, or disrupting immune balance (Calderwood et al., 2016; Singh et al., 2025). This raises an important question: Could prolonged HSP induction, while protective in the short term, compromise cellular performance or predispose livestock to immune dysregulation under chronic environmental stress?

4.2 Inflammatory pathways: NF- κ B and MAPKs

Inflammation is a fundamental component of innate immune responses, crucial for maintaining immune homeostasis and initiating adaptive immunity. Inflammatory mediators activate antigen-presenting cells, which in turn amplify cytokine production (Bennouna et al., 2003). These cytokines stimulate T and B lymphocytes, thereby promoting the development of adaptive immune responses (Iwasaki and Medzhitov, 2010). The functional and transcriptional alterations to cells under heat stress are, at least in part, mediated by changes in the activity and nuclear translocation of key transcription factors. For example, Y-box factor translocates to the nucleus under heat stress where it upregulates the expression of multidrug resistance genes such as *MDR1* and *MRP1*, thereby enhancing protection against drug-induced cytotoxicity, including that caused by the anti-cancer drug Adriamycin in human colorectal carcinoma cells (Stein et al., 2001).

The NF- κ B family comprises inducible transcription factors that regulate a wide range of genes governing immune and inflammatory responses (Oeckinghaus and Ghosh, 2009). While inflammation is normally beneficial and self-limiting, dysregulated NF- κ B activity can cause prolonged tissue damage and drive acute or chronic inflammatory diseases (Liu et al., 2017). The role of heat stress and heat shock proteins in the inflammatory response is very controversial. Nuclear translocation of NF- κ B, normally induced by LPS or cytokines, is suppressed by heat shock (41–43 °C for 1 h) in murine lung epithelial cells through stabilization of the I κ B α /NF- κ B complex when followed by stimulation with a combination of IL-1 β or TNF α and IFN γ (5 ng/mL for 24 hours) (Wong et al., 1997). A similar inhibition of NF- κ B nuclear localization was observed under heat shock conditions in human respiratory epithelial cells (43 °C for 2–4 h), followed by IL-1 β or TNF α stimulation (1 U/mL for 18 hours), in rat pancreatic islet cells (42 °C for 60 min) stimulated with IL-1 β , and in human pancreatic islet cells (42 °C for 90 min) stimulated by IL-1 β and IFN γ (Scarim et al., 1998; Yoo et al., 2000). These findings underscore that heat stress modulates NF- κ B dynamics and targeted gene expression, thereby regulating inflammatory responses (Harper et al., 2018; Abdelnour et al., 2019).

As discussed earlier, the number of circulating leukocytes often increase during heat stress (Mitlöhner et al., 2002; Barnes et al., 2021) contributing to elevated systemic cytokines such as IL-1 β , IL-

6, and TNF α (Borish and Steinke, 2003; Chen et al., 2018; Min et al., 2016). Heat shock proteins, particularly extracellular HSP70, act as danger-associated molecular patterns that activate TLR2/4 signaling, leading to downstream ERK1/2 and NF- κ B activation and transcription of proinflammatory genes (Basu et al., 2000; Asea et al., 2000; Orhan et al., 2012; Liu et al., 2016; Somensi et al., 2017; Martine and Rébé, 2019). These findings are further supported by Tang et al. (2021) who demonstrated that heat stress (41 °C for 12 h) intensified intestinal inflammation by activating the TLR4–NF- κ B signaling after *E. coli* infection (Tang et al., 2021). In parallel, MAPK signaling, including p38 and JNK, is stimulated by oxidative stress under heat stress, further driving cytokine synthesis and release (Dodd et al., 2010; Chauhan et al., 2021). A transcriptomic analysis of peripheral blood mononuclear cells of heifers exposed to seasonal heat stress (THI: 82; August) revealed an increase in expression of the genes involved in MAPK signaling pathway such as *HRAS*, *MAP3K9*, and *MAP2K7* (Dutta et al., 2024).

As outlined previously, several studies also report that heat stress can suppress inflammatory transcription by blocking nuclear translocation of NF- κ B (Curry et al., 1999; Yoo et al., 2000; Ferat-Osorio et al., 2014). This occurs through inhibition of I κ B kinase (IKK) activation, stabilization of I κ B α , and prevention of its phosphorylation, ubiquitination, and degradation, thereby sequestering NF- κ B to the cytoplasm (Wong et al., 1997; Scarim et al., 1998; Curry et al., 1999; Yoo et al., 2000; Shanley et al., 2000). Some systems (*in vitro* cell culture or live mice) show heat shock-induced upregulation of I κ B α mRNA (*NFKBIA*), further stabilizing the NF- κ B/I κ B α complex (Wong et al., 1997; Pritts et al., 2000). These inhibitory mechanisms underscore the importance of NF- κ B inhibition under heat stress, as cells exposed to heat stress following proinflammatory stimulation often undergo apoptosis, highlighting a critical role of NF- κ B suppression in maintaining cell survival during stress (Buchman et al., 1993; DeMeester et al., 2001).

Together, these findings emphasize a paradoxical role of heat stress in inflammatory signaling; while acute heat shock dampens the immune response, prolonged or severe heat stress induces inflammatory responses. This suggests that the net outcome likely depends on cell type, stress duration, and the presence of concurrent immune stimuli. Importantly, most current evidence is derived from *in vitro* studies or short-term heat stress models, with limited *in vivo* data from livestock. Defining the temporal and tissue-specific dynamics of NF- κ B and TLR signaling under heat stress in dairy cows is important. Such knowledge may elucidate sensitive windows such as the dry period or early postpartum, where targeted modulation of inflammatory pathways could mitigate the detrimental effects of heat stress while preserving essential immune defense (Lim et al., 2007).

4.3 Heat stress-induced impairment of mitochondrial function

Mitochondria play a central role in health and disease (Casanova et al., 2023). Mitochondria are the main energy hubs of the cell, producing about 90% of required ATP through oxidative phosphorylation (Casanova et al., 2023). Heat stress can impair bioenergetic status of tissues and alter mitochondrial biogenesis and

functions such as oxidative phosphorylation (Singh, 2004; Marquez Acevedo et al., 2025). *In vitro* heat shock (42 °C for 3h) of fetal sheep myoblasts resulted in decreased mitochondrial biogenesis, reduced ATP production and decreased cell proliferation and increased apoptosis (Singh, 2004; Li et al., 2023; Lu et al., 2023). These findings are supported by other *in vitro* studies where bovine mammary epithelial cells were exposed to either moderate (40 °C for 1 h) or adverse heat shock (42 °C for 2 h) resulting in mitochondrial dysfunction and inhibition of cellular proliferation (Du et al., 2008; Chen et al., 2020). Heat stress (41.0 °C for 12 h) during *in vitro* maturation of bovine oocytes reduces mitochondrial membrane potential and increases ROS, indicating mitochondrial dysfunction (Payton et al., 2018). Moreover, these impairments persist in early embryogenesis (Payton et al., 2018). Such alterations in maternally derived mitochondria likely explain some of the negative impacts of heat stress on oocyte competence, embryonic development, and pregnancy outcomes (Schrock et al., 2007; Edwards et al., 2009).

Mitochondrial dysfunction also acts as a driver of inflammation as damaged mitochondria release excessive ROS and other byproducts that function as danger signals, activating innate immune pathways but simultaneously inducing low-grade, chronic inflammation (Zampino et al., 2020; Diaz-Vegas et al., 2020). In cattle, heat stress downregulates protein-coding genes in liver mitochondria that regulate electron transfer, NADH dehydrogenase, and respiratory chain complexes, thereby impairing hepatic energy production (Li et al., 2023). Immune activation itself imposes significant metabolic demands. For example, stimulation of TLR4 with LPS reduces oxygen consumption as part of an energy-conserving response, suggesting that activation of the immune system imposes an energetic trade-off, often leading to hypometabolism (Ganeshan et al., 2019). When mitochondrial capacity is compromised, these trade-offs become more pronounced, leaving insufficient energy to sustain robust immune responses (Bird, 2019).

Additionally, heat stress suppresses the expression of transporters such as *SLC38A10* (amino acid transport) and *SLC2A1/GLUT1* (glucose transport), while repressing PPAR γ -mediated metabolic pathways in dairy cows, further limiting cellular fuel availability, weakening mitochondrial integrity, and imposing energetic constraints on immunity (Wheelock et al., 2010; Gao et al., 2019). This raises critical questions: To what extent do mitochondrial defects directly impair immune cell function, and can targeted metabolic interventions restore immunocompetence under thermal stress? Furthermore, current evidence on heat stress and mitochondrial function is mostly from *in vitro* studies on muscle or mammary epithelial cells, with little known about heat stress impact on endometrial epithelial cells. Addressing these gaps will be essential to improve thermotolerance and postpartum health in dairy cows.

4.4 Oxidative stress pathways

Heat stress provokes oxidative stress by enhancing ROS production across multiple tissues, disrupting redox homeostasis and impairing cellular metabolism (Bernabucci et al., 2002;

Chauhan et al., 2014; Flanagan et al., 1998). Concurrently, oxidative stress promotes cytokine synthesis and release (Dodd et al., 2010; Chauhan et al., 2021). In response, animals activate antioxidant defense systems, including enzymatic antioxidants (superoxide dismutase, glutathione peroxidase, catalase), non-enzymatic compounds (melatonin, L-cysteine, albumin), and low-molecular-weight antioxidants (ascorbic acid, glutathione, α -tocopherol, β -carotene) to mitigate ROS toxicity. These antioxidant responses are often upregulated in response to heat stress to mitigate the damaging effects of ROS. Oxidative stress, caused by excessive production of free radicals and ROS or a decline in antioxidant defenses, results in cellular damage and promotes tissue inflammation (Khor et al., 2011; Weismann et al., 2011). Evidence in dairy cattle shows elevated oxidative stress markers, such as catalase, superoxide dismutase, glutathione reductase, and malondialdehyde, particularly during hot months, confirming systemic redox imbalance under heat stress (Bernabucci et al., 2002). Oxidative stress has been directly implicated in immune dysfunction by impairing leukocyte activity, weakening responses to inflammatory stimuli, and predisposing animals to infectious and metabolic diseases (Bochniarz et al., 2024). Elevated ROS generation under heat stress conditions inhibited DNA synthesis and suppressed *IL2* gene expression in murine T cells (Pahlavani and Harris, 1998).

Crosstalk between oxidative stress and immune regulation occurs through activation of NF- κ B, which amplifies proinflammatory cytokine production, and through NRF2 which orchestrates antioxidant gene transcription (Gehrig et al., 2012; Morris et al., 2022). Acute heat stress stimulates mitochondrial superoxide production in skeletal muscle of poultry, leading to oxidative damage of mitochondrial lipid and protein synthesis (Mujahid et al., 2005). Heat shock proteins such as HSP72 further modulate this balance by limiting the propagation of inflammatory mediators, suggesting a protective but insufficient adaptation during chronic heat stress. While numerous studies have quantified oxidative stress biomarkers in livestock, the precise mechanisms linking ROS signaling with immune dysfunction remain poorly defined *in vivo*.

4.5 Hypothalamic–pituitary–adrenal axis and glucocorticoid signaling under heat stress

During heat stress, the hypothalamic–pituitary–adrenal (HPA) axis is activated to maintain homeostasis in response to stress stimuli (Sejian et al., 2018). Activation of the HPA axis represents a central mechanism by which environmental stress alters immune function in dairy cows (Grandin, 1997). Under heat or other stressors, hypothalamic secretion of corticotropin-releasing hormone stimulates the anterior pituitary to release adrenocorticotrophic hormone, which in turn drives glucocorticoid (primarily cortisol) production from the adrenal cortex (Hicks et al., 1998). Cortisol, known as the stress hormone, modulates immune function by regulating genes that encode cytokines, chemokines, inflammatory mediators, and their receptors (Cruz-Topete and Cidlowski, 2015; Aleri et al., 2016). Increased cortisol due to heat

stress binds with DNA, inhibiting the expression of genes involved in immune cell activation and cytokine production (Elenkov and Chrousos, 1999; Webster et al., 2002; Sgorlon et al., 2012; Caroprese et al., 2013). Cortisol also engages in crosstalk with STAT pathways, altering cytokine signaling, and inducing MAPK phosphatase-1, which inhibits p38 MAPK activity, thereby broadly downregulating inflammatory gene expression (Wu et al., 2005). Glucocorticoids act via the glucocorticoid receptor to reshape immune gene expression and their receptors (Busillo and Cidlowski, 2013; Cruz-Topete and Cidlowski, 2015). The glucocorticoid receptor directly interferes with proinflammatory transcription factors, such as NF- κ B and AP-1, suppressing transcription of cytokines, chemokines, and their receptors (Liberman et al., 2007; Busillo and Cidlowski, 2013). Acutely, glucocorticoids inhibit vasodilation and vascular permeability following inflammation and reduce leukocyte extravasation into inflamed sites (Mcewen et al., 1997; Perretti and Ahluwalia, 2000).

Heat stress increases cortisol secretion, but levels plateau and eventually decline with prolonged exposure, suggesting adaptation of the HPA axis (Mishra, 2021). Cortisol secretion is accompanied by the release of catecholamines and other hormones, as heat stress also activates the sympathetic-adrenal-medullary axis (Mishra, 2021). Catecholamines further stimulate cortisol secretion and act directly on immune cell functions (Carroll and Forsberg, 2007). Heat stress has been associated with elevated cortisol concentrations in both blood and milk of cattle (Chen et al., 2018). In contrast, as noted earlier, heat stress has been shown to induce proinflammatory responses in dairy cows (Chen et al., 2018). Because cortisol concentrations fluctuate widely depending on the duration of heat stress exposure, they may be insufficient to elicit a sustained anti-inflammatory effect. In such cases, inflammation may emerge despite elevated cortisol (Min et al., 2016; Most and Yates, 2021). Supporting this concept (Cruz-Topete and Cidlowski, 2015), demonstrated that glucocorticoids can also trigger inflammation in humans, depending on exposure duration and the basal immune state. In cows, high cortisol levels have been associated with greater occurrence of retained fetal membranes, which is further associated with metritis (Kaczmarowski et al., 2006). The effects of heat stress on cortisol levels (Mishra, 2021) may help explain the increased incidence of metritis with heat stress (Mishra, 2021; Molinari et al., 2022).

4.6 Heat stress-induced epigenetic modifications

Conrad Hal Waddington first coined the term “epigenetic” to describe the dynamic interaction between an organism’s genetic makeup and its environment in shaping observable traits (Waddington, 1956). His classic experiments with *Drosophila* demonstrated that environmental stress could induce epigenetic changes; for instance, larvae exposed to heat stress developed adults with abnormal wings. These abnormalities represented phenocopies of phenotypic changes driven by environmental influences rather than genetic mutations (Waddington, 1957). Epigenetic mechanisms including microRNAs (miRNA), long non-coding

RNAs, histone modifications, and DNA methylation play a central role in regulating gene expression and shaping cellular function (Gibney and Nolan, 2010; Allis and Jenuwein, 2016). Among these, DNA methylation is the most extensively studied, typically occurring at cytosine residues within CpG dinucleotides in gene promoter regions, where methylation can interfere with transcription factor binding and consequently suppress gene transcription (Greenberg and Bourc’his, 2019), and influencing phenotypic variation and adaptive responses to environmental stressors such as heat stress (Law and Holland, 2019). Evidence from chickens, sheep, goats, and cattle demonstrates that elevated temperatures induce differential DNA methylation across genes involved in metabolism, immune function, inflammatory signaling, and cellular stress responses (Vinoth et al., 2018; Denoyelle et al., 2021; Del Corvo et al., 2021; Livernois et al., 2021; Sajjanar et al., 2024).

Genome-wide DNA methylation analysis of blood from bulls exposed to seasonal heat stress (THI: 75–85; 56 days) revealed differentially methylated genes associated with cellular and metabolic processes, stress responses, and, importantly, immune and inflammatory pathways (Del Corvo et al., 2021). In cattle, cytosine methylation differences between indicine and taurine subspecies of cattle have been linked to variation in thermal resilience (Capra et al., 2023). Evidence from multiple species, including birds, fish, and insects, suggests that variable methylation in adaptive genomic regions may contribute to evolutionary processes (Gore et al., 2018; Alvarado et al., 2015). Recent work in taurine and indicine cattle further supports the role of DNA methylation in linking genotypes to phenotypes, underscoring its potential as a marker for climate adaptability (Chen et al., 2023).

Emerging evidence indicates that environmental stressors can induce transgenerational effects in cattle (Skibieli et al., 2018; Larsen and Laporta, 2024). It has been reported that granddaughters (F2) of heat-stressed granddams have impaired epithelial microstructure and stunted cellular turnover: the balance between cell growth and cell loss (Larsen and Laporta, 2024). In Italian Simmental cows, the season of the great-granddam’s pregnancy (F0) was linked to the performance of great-granddaughters (F3), with winter and spring gestations associated with favorable estimated breeding values for milk and protein yields, while summer and autumn gestations had detrimental effects (Macciotta et al., 2023). These trends were consistent with THI values (< 69, 69–73, 73–75, > 75) recorded during different stages of F0 pregnancy, highlighting the role of maternal heat stress in shaping production traits across generations. Although these results were based on estimated breeding values, validation using raw phenotypic records will be essential to strengthen the evidence for heat stress-mediated epigenetic inheritance in dairy cattle (Macciotta et al., 2023). Importantly, shared differentially methylated promoter regions in both dams and calves strengthen the possibility that certain epigenetic marks induced by heat stress may persist and influence immune responsiveness later in life (Kipp et al., 2021; Halli et al., 2025).

Cellular stress also reshapes post-transcriptional regulation through altered miRNA expression, which fine-tunes the specificity, timing, and magnitude of gene expression (Bartel,

2004; Baskerville and Bartel, 2005; Harfe, 2005; Mckenna et al., 2010). For instance, heat exposure induces differential expression of miRNAs in bovine peripheral blood mononuclear cells, suggesting a role in coordinating adaptive cellular responses (Sengar et al., 2018). Collectively, these findings establish epigenetic modifications as pivotal mediators of cellular responses to heat stress, enabling both dynamic adaptation and heritable changes in gene expression without altering the underlying DNA sequence (Wang and Ibeagha-Awemu, 2020). Future research should integrate epigenomic, transcriptomic, and phenotypic datasets to uncover regulatory nodes that may serve as biomarkers or intervention targets to enhance thermotolerance in livestock.

5 Mitigation strategies for heat stress in dairy cows

5.1 Managemental strategies

The dairy cattle industry has invested in efforts to mitigate heat stress through adjustments in daily management practices, cooling infrastructure, and strategic modifications to breeding schedules. Studies conducted in the United States have shown that providing heat-abatement measures, such as fans and water sprinklers, significantly improves milk production. Cows with access to these cooling systems produced about 34 kg of milk per day, whereas cows without heat abatement produced only 27.7 kg per day (Tao et al., 2012). Moreover, simulation models suggest that optimal heat abatement strategies could reduce livestock industry-wide losses from heat stress by approximately \$700 million (St-Pierre et al., 2003). Nevertheless, despite technological advances, no single intervention can fully safeguard the cattle industry against heat stress. Evidence from extreme heat stress conditions indicate that even well-managed large-scale herds sustain significant losses, highlighting the inherent limitations of current technologies and management practices (Hutchins et al., 2025). Dairy producers invest in infrastructure such as shade structures, fans, and sprinkler systems to provide cooling during periods of elevated heat stress. The decline in milk production and reproductive efficiency due to heat stress can be mitigated by implementing cooling strategies (Armstrong, 1994). Investments in cooling infrastructure, including sprinklers and fans, can lessen yield losses under mild to moderate heat stress and may partly explain the lower losses observed in larger operations compared with smaller operations (Hutchins et al., 2025). However, the effectiveness of these cooling systems diminishes under high relative humidity, when evaporative cooling capacity is greatly reduced (Bohmanova et al., 2007). Shading systems provide an economical strategy to reduce heat load in livestock by limiting direct solar radiation, thereby helping to maintain body temperature and alleviate the adverse effects of heat stress (Fournel et al., 2017). Furthermore, heat abatement during the dry period enhances immune function in dairy cows. Studies show that cooled cows exhibit greater IgG secretion and stronger neutrophil oxidative burst compared with heat-stressed cows,

highlighting improvements in both humoral and innate immunity (Do Amaral et al., 2010, 2011).

Another cost-effective approach to reducing the impact of heat stress involves adjusting management decisions such as the timing of calving. Peripartum cows are especially susceptible to heat stress, as environmental challenges during this period can intensify production losses (Do Amaral et al., 2009; Tao et al., 2011; Ferreira et al., 2016; Fabris et al., 2020). Adjusting calving schedules to avoid the spring and summer months may help mitigate these effects in warmer regions. However, shifting calving into cooler seasons introduces additional challenges, including higher risks of calf mortality and increased production losses in colder climates (Litherland et al., 2014; Hulbert and Moisé, 2016).

5.2 Feed supplements and immune modulators

Nutritional interventions and immune-modulating strategies can serve as valuable complements to environmental management, particularly during periods of prolonged heat stress. However, strong evidence for substantive interventional strategies that limit or reduce the negative impacts of heat stress on cow production are limited at best. Historically dietary interventions to overcome the impacts of heat stress have included diet formulation to account for reduced feed intake, enhanced nutrient requirements during heat stress, dietary heat increment and avoiding nutrient excess in diets. During heat stress, altering diet composition has been shown to stimulate feed intake, partially compensating for reduced consumption (Renaudeau et al., 2012). Modulation of post absorptive metabolism and metabolic heat production could serve as effective strategies to reduce heat stress effects, while enhanced water consumption may have even greater positive effects at alleviating heat stress effects on production than dietary manipulation. Dietary manipulations to overcome the production effects of heat stress have been extensively reviewed in the literature (West, 2003, 1999; Golder and Lean, 2024; Burhans et al., 2022; Plaizier et al., 2022).

In terms of health and immunity, supplementation with antioxidants and electrolytes to the animals under heat stress can potentially strengthen immunity and alleviate oxidative stress associated with heat stress. In buffaloes, vitamin C and electrolytes have been shown to reduce oxidative damage during heat stress, while provision of dietary ascorbic acid improves immunity, growth, semen quality, fertility, and oxidative balance in poultry under heat stress (Panda et al., 2008; Kumar et al., 2010). Vitamin A supplementation has been shown to enhance immune function in dairy cattle by increasing pro-inflammatory cytokines such as IL-1 and TNF α , along with immunoglobulins IgM, IgG, and IgA and their transport proteins (Tjoelker et al., 1990; Jin et al., 2014). Similarly, supplementation with vitamin E and selenium has demonstrated beneficial effects in postpartum buffalo affected by dystocia by mitigating oxidative stress and enhancing neutrophil function by improving chemotaxis (Sathya et al., 2007).

Rumen-protected methionine improves liver function, oxidative balance, and inflammation during the transition period (Osorio et al., 2013; Zhou et al., 2017; Batistel et al., 2018), though

data under heat stress are limited. Supplementing methionine and arginine during heat stress has been shown to enhance mammary cell function and metabolism in dairy cows (Salama et al., 2019). Appropriate insulin action is essential for survival and adaptation under heat stress. Studies have shown that enhancing insulin sensitivity through supplementation with insulin-sensitizing additives such as chromium, thiazolidinediones, or lipoic acid can improve animal performance during heat stress (Ranganathan et al., 2006; Diesel et al., 2007; Rhoads et al., 2013). As mentioned earlier, the gastrointestinal tract is highly susceptible to heat stress due to reduced blood flow and hypoxia (Johnson et al., 2016b, 2016). Nutritional interventions can help preserve intestinal integrity and function. L-glutamine, a primary fuel for enterocytes and lymphocytes, supports barrier function, suppresses pro-inflammatory cytokines, and improves productivity, including milk yield in dairy cows and growth in pigs (Reeds and Burrin, 2000; Jiang et al., 2009; Caroprese et al., 2013; Johnson and Lay, 2017). Under heat stress, adding chromium to the diet helped strengthen the primary immune response by boosting IgM and IgG production in poultry and improved ruminal fermentation and metabolism in Holstein dairy cows (Vivier et al., 2008; Zhang et al., 2014; Wo et al., 2023). Zinc contributes to gut health by enhancing tight junction proteins and providing antioxidant protection via metallothionein induction (Zhang and Guo, 2009; Wang et al., 2013, 2014), while betaine acts as an osmotic regulator and methyl donor, improving thermoregulation, immunity, and production outcomes under heat stress (Singh et al., 2022; Hassan et al., 2011).

Dietary supplementation with yeasts, plant extracts, and probiotics can support heat-stressed animals by improving rumen metabolism, regulating body temperature, and strengthening intestinal barriers. Combined prebiotics and probiotics further enhance immunity by promoting phagocytosis, cytokine production (TNF α , IFN γ), and vaccine-induced antibody responses (Salehimanesh et al., 2016). While these nutrients offer promising protective effects against heat stress, they should be viewed as complementary, rather than replacements for environmental management strategies.

5.3 Genetic selection for heat tolerance in dairy cows

Genetic adaptation offers long-term solutions to mitigate heat stress in livestock. Genetic selection for thermotolerance has been pursued using both quantitative and genomic approaches, revealing a low to moderate heritable component that is often negatively correlated with production traits in dairy animals (Ravagnolo and Misztal, 2002; Dikmen et al., 2012; Bernabucci et al., 2014; Dikmen et al., 2015; Nguyen et al., 2016). A recent genome-wide association study introduced a principal component-based measure of heat tolerance, derived from milk yield, fat and protein percentages, and somatic cell score across THI classes (Macciotta et al., 2017). This approach captured both the baseline level of performance and the slope of decline under heat stress, revealing that these components are genetically uncorrelated and heritable. Significant loci near genes such as *HSF1* and *MCAT* highlight the involvement of classical heat-shock response and metabolic pathways, offering

new insights into the complex biology of thermotolerance and providing novel targets for genetic selection (Macciotta et al., 2017). Furthermore, the Australian Heat Tolerance Breeding Value enables the selection of cows that maintain lower body temperatures under heat stress (Nguyen et al., 2016, 2017). However, its effectiveness in distinguishing heat-stress responses in lactating Holstein cows remains under investigation (Jensen et al., 2022).

Although several thermotolerance-related genes have been identified, the inheritance of heat stress tolerance is further complicated by epigenetic regulation, underscoring the need for integrative genetic and epigenetic strategies to improve resilience in dairy cattle (Dikmen et al., 2015; Macciotta et al., 2017; Ghaffari, 2022). Cattle inheriting the *PRLR* slick mutation exhibit enhanced thermotolerance, characterized by improved regulation of body temperature during heat stress (Dikmen et al., 2008; Landaeta-Hernández et al., 2021; Carmickle et al., 2022). This mutation shortens and thins the hair coat, facilitating more efficient heat dissipation and reducing susceptibility to heat stress (Olson et al., 2003; Dikmen et al., 2008). As a result, slick-haired cattle maintain lower rectal temperatures, higher sweating rates, and improved reproductive and productive performance under hot environmental conditions (Dikmen et al., 2008, 2014; Eisemann et al., 2020).

At the molecular level, heat shock proteins are key regulators of cellular defense. Single nucleotide polymorphisms in genes such as *HSP90AB1*, *HSP70A1A*, *HSF1*, and *HSBP1* have been associated with thermotolerance in various cattle breeds (Liu et al., 2011; Charoensook et al., 2012; Wang et al., 2013; Deb et al., 2014). Non-heat shock protein genes, including *ATP1A1* and *ATP1B2*, have also been implicated in thermotolerance (Liu et al., 2011; Wang et al., 2011; Das et al., 2016). These markers can be applied in genomic selection programs, along with the use of thermotolerant sires accelerating the development of heat-adapted offspring without compromising productivity.

6 Conclusion and future directions

Heat stress, driven by rising ambient temperatures under global warming and climate change, is a major challenge to dairy production, particularly in warmer regions. Heat stress reduces milk yield and quality including protein content and somatic cell count, compromises reproductive performance, weakens immunity, and collectively contributes to billions of dollars in annual economic losses to global animal agriculture. At the farm level, mitigation of heat stress relies on environmental modifications (e.g., shade, shelter, cooling systems) and nutritional interventions, which have helped buffer some effects of climate variability. Indeed, the sensitivity of milk yield to thermal extremes has declined over time, suggesting that genetic selection and advances in management practices, such as improved cooling, housing, and diet formulation, are already having a positive impact (Gisbert-Queral et al., 2021). However, the cost of climate adaptation efforts alone has been estimated to reduce productive growth in dairy systems by 0.31% per year (Njuki et al., 2020). As summarized in

Figure 1, the collective evidence demonstrates that heat stress acts across multiple biological levels, affecting whole-animal physiology, microbial ecology, immune responsiveness, and cellular function, resulting in compromised health and immune resilience in dairy cattle. Nevertheless, the underlying mechanisms by which heat stress increases disease susceptibility and disrupts immune function remain incompletely understood.

Genetic strategies offer promising avenues for long-term resilience. Modeling cow performance against continuous THI values has proven useful for identifying animals that combine high yield with reduced thermal sensitivity. Furthermore, polymorphisms in immune-related genes may serve as predictive markers for thermotolerance and could be integrated into breeding programs to enhance resilience. However, inheritance of heat tolerance is complex, shaped not only by genetic variation but also by epigenetic regulation.

Future research should therefore focus on unraveling the cellular and molecular pathways through which heat stress alters immune function, including detailed analysis of signaling cascades involved in immunity and disease resistance. Refinements in breeding strategies will be crucial for developing heat stress-resilient cattle capable of sustaining productivity and immune competence under higher THI conditions. Integration of genomics, epigenomics, and proteomics with conventional and advanced breeding approaches holds particular promise. These tools can improve the precision and predictability of selection programs while offering deeper insight into gene function and regulation. Such integrative strategies will be essential to accelerate genetic improvement and ensure sustainable livestock production in the face of global climate challenges.

Author contributions

AT: Conceptualization, Writing – original draft, Writing – review & editing. JB: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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