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Genomic and molecular insights into thermotolerance mechanisms in cattle

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Abstract

Heat stress is a major environmental challenge impacting livestock health, particularly in tropical regions. At the molecular level, heat stress activates intricate signaling cascades and gene networks in cattle that drive cellular adaptation and survival. These include the heat shock response, oxidative stress pathways, immune regulation, and modulation of apoptotic genes. Recent transcriptomic and proteomic studies have revealed key gene families, such as heat shock proteins (HSPs), oxidative stress markers (e.g., HMOX1, BNIP3), and immune regulators (e.g., TLRs, NOS), that orchestrate these molecular defenses. Understanding these molecular responses is crucial for designing genetic, nutritional, and environmental interventions to improve thermotolerance in cattle.

Keywords: Heat shock proteins, oxidative stress, transcriptomics, hsp70, stip1, TLRS, thermotolerance, gene expression

Introduction

Heat stress is increasingly recognized as a major constraint in livestock production, especially in tropical and subtropical regions where cattle are regularly exposed to high ambient temperatures and humidity. These environmental conditions often exceed the animal's thermoneutral zone, resulting in physiological and metabolic disruptions that compromise growth, reproduction, milk production, and immune competency (West, 2003; Collier *et al.*, 2008; Debnath *et al.*, 2024) [20, 5, 14]. At the core of the bovine response to heat stress lies a series of intricate molecular mechanisms that enable cells to survive, adapt, or undergo controlled death under thermal insults.

Unlike general physiological responses, molecular mechanisms operate at the genomic, transcriptomic, proteomic, and epigenetic levels, modulating gene expression and signaling pathways in real time to defend against stress-induced damage. Molecular alterations during heat stress include protein denaturation, disruption of cell membrane integrity, oxidative injury, and inflammatory responses, which activate a broad spectrum of gene networks (Garner *et al.*, 2020; Bosco *et al.*, 2022) [6, 4].

With advances in functional genomics tools such as RNA-Seq, proteomics, and CRISPR gene editing, researchers have begun to unravel specific heat-responsive genes and their regulatory elements. Key among these are heat shock proteins (HSPs), antioxidant enzymes, inflammatory cytokines, and cell cycle regulators, which collectively orchestrate the cellular adaptation process (Bharti *et al.*, 2017; Sajjanar *et al.*, 2023) [2, 18]. Differential expression of these genes not only reflects the organism's stress status but also serves as a valuable marker for genetic selection and breeding programs.

Genetic variability in heat stress response between breeds has also been demonstrated. Indigenous and zebu breeds often show better molecular adaptability to heat compared to exotic or crossbred cattle, largely due to enhanced expression of HSPs and stress-responsive genes like HMOX1, BNIP3, and STIP1 (Zachut *et al.*, 2017; Sajjanar *et al.*, 2015) [22, 17]. Understanding these differences at the molecular level can inform targeted interventions for thermotolerance, including marker-assisted selection, transcriptomic profiling, and nutrigenomics.

Therefore, a comprehensive examination of heat-induced gene networks is not only academically important but also critical for future livestock sustainability.

This review integrates recent findings from functional genomics to provide a detailed perspective on how molecular mechanisms in cattle respond to and mitigate the detrimental effects of heat stress.

Heat Shock Protein (HSP) Gene Family

Heat shock proteins are among the earliest and most conserved molecular responders to heat stress. In cows, genes such as HSP60, HSP70, HSP90, and their co-activators (e.g., AHSA1, AHSA2) are upregulated under thermal stress (Garner *et al.*, 2020)^[6]. HSP70, in particular, plays a crucial role in folding denatured proteins, suppressing aggregation, and activating immune responses (Bharti *et al.*, 2017)^[2].

HSP genes such as DNAJB1, HSPA1A, HSP90AA1, HSPB8, and DNAJB4 have been shown to be upregulated in zebu and crossbred cattle (Sajjanar *et al.*, 2023). *in vitro*, HSP70 increases in bovine mammary epithelial cells under heat, and BAG2, a gene with pro-apoptotic properties, interacts with HSP70 to regulate stress signaling and apoptosis (Wang *et al.*, 2008; Garner *et al.*, 2023)^[8, 7].

Polymorphisms in HSP90, HSPA6, HSPB7, and HSF1 are associated with thermotolerance in cattle (Sajjanar *et al.*, 2015; Zeng *et al.*, 2019)^[17, 23], while PRL and PRLR gene variations are linked to heat-regulated hair morphology (Littlejohn *et al.*, 2014)^[13].

Oxidative Stress Response Genes

Heat stress accelerates the production of reactive oxygen species (ROS), leading to oxidative damage^[9]. Cattle respond by upregulating stress-responsive genes such as:

- BNIP3: induces apoptosis under hypoxic and energy stress (Lin *et al.*, 2013)^[12].
- HMOX1: involved in heme degradation and cytoprotection (Ryter *et al.*, 2005)^[16].
- VEGFA: regulates vascular integrity and hypoxia adaptation (Gong *et al.*, 2006)^[8].
- RHOB: provides cytoprotection by inhibiting heat-induced apoptosis (Li *et al.*, 2011)^[11].

STIP1, a co-chaperone for HSP70 and HSP90, is significantly expressed in summer and acts as a biomarker for heat stress in adipose tissue and blood (Zachut *et al.*, 2017)^[22]. In contrast, FOLH1B, a physiological antioxidant, was the most significantly downregulated gene under heat stress, indicating compromised antioxidant potential (Koyama *et al.*, 2005)^[24].

Immune-Related Gene Modulation

Heat stress suppresses immunity by downregulating genes involved in antigen presentation and cytokine signaling:

- BoLA-DRB3 expression decreases in mammary tissue, compromising antigen recognition (Yue *et al.*, 2020)^[21].
- IL-6, IL1RN, IL-10, and IL-17A show altered levels in response to heat (Park *et al.*, 2021)^[15].
- TLR2 and TLR4, key toll-like receptors, modulate short-and long-term immune responses to thermal stress (Bharti *et al.*, 2017)^[2].

Genes in the nitric oxide synthase (NOS) family, including iNOS and eNOS, play essential roles in vascular response and immune defense under heat by promoting peripheral vasodilation (Bogdan *et al.*, 2001)^[3].

Transcriptional Regulators and Cell Stress Genes

Stress-responsive transcription factors and cell cycle regulators are also modulated:

- FOSB and JUN, components of AP-1, are upregulated in response to environmental stress, regulating immune gene expression and cell proliferation (Atsaves *et al.*, 2019)^[1].
- GADD45B, a DNA damage-inducible gene, is increased during heat stress, promoting cell cycle arrest or apoptosis in stress-susceptible animals (Labonte *et al.*, 2019)^[10].

Conclusion

Molecular responses to heat stress in cattle are governed by an intricate network of gene expressions that mediate protein protection, oxidative balance, and immune function. The activation of heat shock proteins, antioxidant genes, and immune modulators reveals the depth of genomic adaptation required to counteract thermal insults. Leveraging this molecular understanding through gene selection, genome editing, or biomarker-based diagnostics can significantly enhance the heat resilience of dairy and beef cattle populations.

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