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GENETIC EXPRESSION MARKERS FOR ASSESSING CELLULAR RESPIRATION STATUS UNDER HEAT STRESS IN CATTLE: A REVIEW

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Abstract: *Thermal stress significantly affects the metabolic efficiency and health of cattle, with cellular bioenergetics and mitochondrial function being key targets. The regulation of oxidative metabolism and thermotolerance is largely governed by specific genetic markers that reflect adaptive responses to heat exposure. This review discusses genes involved in mitochondrial respiration and stress response mechanisms, such as those encoding components of the electron transport chain (ND1–ND5, COX1–COX3, CYCS), heat shock proteins (HSP70, HSP90), and antioxidant enzymes (SOD1, NRF2, PGC-1α). Alterations in the expression of these genes provide valuable insights into mitochondrial efficiency and cellular adaptation to elevated temperatures, reflecting the dynamic processes that allow cattle to cope with heat stress. Furthermore, disruptions in these pathways may contribute to metabolic inefficiencies, negatively impacting overall health and productivity. Additionally, this review explores the potential of integrating transcriptomic, proteomic, and genomic data to identify molecular markers associated with heat tolerance. Such approaches provide valuable insights into the mechanisms underlying thermal resilience, which can guide genetic selection strategies aimed at improving cattle health and productivity in extreme temperature conditions.*

• Introduction

Cellular respiration is vital for energy metabolism in cattle, particularly during lactation when mitochondrial oxygen demand rises significantly [Baumgard and Rhoads, 2013; Collier et al., 2017]. Heat stress, increasingly common due to climate change, disrupts mitochondrial function by reducing electron transport chain activity, lowering ATP production, and increasing reactive oxygen species (ROS), which impair essential processes like milk synthesis and immune responses [Wheelock et al., 2010; Lacetera, 2019; Sejian et al., 2018]. Complex I and IV are especially vulnerable, with notable declines in ND4 and COX1 expression in Holsteins under heat stress [Deb et al., 2014], unlike resilient Bos indicus breeds that maintain mitochondrial function via HSP90 and SOD1 upregulation [Kishore et al., 2014]. Excessive endogenous heat from lactation, combined with environmental heat, overwhelms thermoregulation, leading to metabolic inefficiency and systemic strain [Kadzere et al., 2002]. Genomic advances reveal that differential expression of mitochondrial, heat shock, and antioxidant genes under stress conditions can serve as early indicators of dysfunction [Dikmen et al., 2014; Garner et al., 2016].

This review explores these genetic markers and the utility of multi-omics approaches to improve thermotolerance in dairy cattle through targeted breeding and adaptive management.

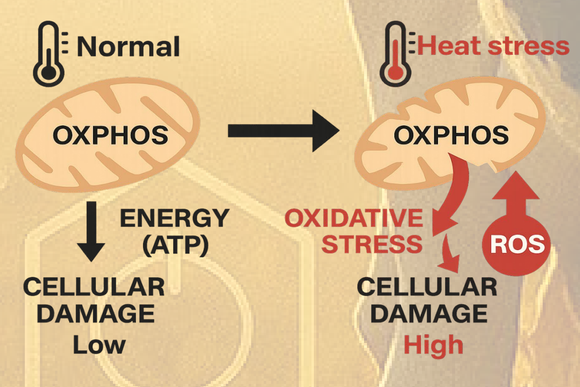

Figure 1. Impact of heat stress on mitochondrial bioenergetics in cattle.

• Material and method

To investigate genetic markers linked to mitochondrial function and heat stress in cattle, this review employed databases like PubMed, Scopus, Web of Science, and Google Scholar, using Boolean search strategies enhanced by AI tools such as OpenAI (GPT-4o-mini) and DeepSeek. Key terms included "bovine heat stress," "mitochondrial genes," and "HSP70," yielding focused results on gene expression and thermotolerance. AI platforms also facilitated semantic analysis and image generation (via Sora) to support data visualization. Data extraction prioritized findings on differential expression and phenotypic correlations for genes like ND4, CYCS, HSP90, and PGC-1α. Only peer-reviewed articles with detailed methods and relevance to cattle under heat stress were included, while non-English, paywalled, or poorly detailed studies were excluded. Zotero and Excel supported a structured methodological workflow, enabling clear data organization and cross-study comparisons. All AI-assisted results were manually validated for accuracy, ensuring data integrity and consistency throughout the review process.

• Theoretical basis

HSP90 and HSP70 are central heat shock proteins mediating thermotolerance in cattle, with HSP90AA1 and HSP90AB1 playing protective roles by stabilizing regulatory proteins and maintaining proteostasis during prolonged thermal stress, while HSP70 acts as a rapid-response chaperone preventing protein aggregation and modulating immune signaling during acute heat exposure. PGC-1α, a master regulator of mitochondrial biogenesis and oxidative metabolism, coordinates energy balance and antioxidant defense under heat stress, directly influencing HSP expression through interaction with HSF1. NRF2, another key transcription factor, enhances cellular antioxidant defenses by activating genes like HO-1, NQO1, and SOD1, preserving mitochondrial function under oxidative and thermal stress and serving as a potential biomarker for heat resilience. SOD1, in particular, is critical for detoxifying superoxide radicals and mitigating apoptosis; its genetic polymorphisms correlate with enhanced thermotolerance in cattle. Mitochondrial genes ND1, ND2, ND4, and ND5—components of Complex I—are essential for ATP production and are differentially expressed across bovine tissues based on metabolic demand, making them sensitive indicators of bioenergetic strain during heat stress. Similarly, COX1, COX2, and COX3, core catalytic subunits of Complex IV, are vital for oxidative phosphorylation and are stabilized by HSPs under stress conditions, preventing ROS overproduction and energy collapse. Finally, cytochrome c (CYCS) serves a dual role in energy metabolism and apoptosis regulation; its stress-induced release signifies mitochondrial dysfunction and potential cell death. Together, these genes form a tightly regulated network underlying cellular thermotolerance and are promising targets for selection and management strategies in heat-resilient cattle.

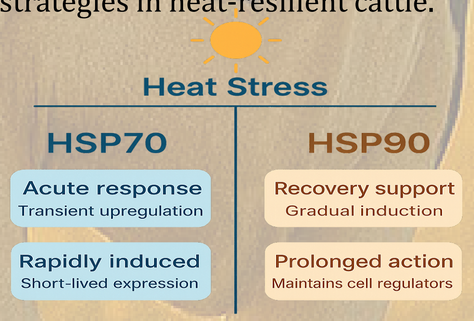

Figure 2. Comparative Roles of HSP70 and HSP90 in the Cellular Response to Heat Stress.

• Final remarks and conclusions

This review highlights the central role of mitochondrial genes—especially those encoding Complex I (ND1, ND2, ND4, ND5) and Complex IV (COX1, COX2, COX3) subunits—in shaping the heat stress response in dairy cattle, as elevated temperatures impair their expression and function, leading to disrupted electron transport, reduced ATP production, and heightened oxidative stress. Concurrently, genes like HSP70, HSP90, NRF2, SOD1, and CYCS are critical for preserving mitochondrial integrity, mediating antioxidant defenses, and preventing apoptosis under thermal stress. The integration of multi-omics approaches (genomics, transcriptomics, proteomics) allows for in-depth characterization of these biological systems, revealing gene expression patterns, mitochondrial DNA variants, and protein abundance profiles that serve as molecular signatures of thermotolerance. This systems-level insight lays the groundwork for identifying candidate markers for genetic selection. Advancing precision breeding and adaptive management strategies based on these findings is essential to improve heat resilience, ensure animal welfare, and maintain dairy productivity amid the growing challenges posed by climate change.