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Heat shock proteins in bovine hemoparasitic infections: Molecular mechanisms, host-pathogen interactions, and translational opportunities: A comprehensive review

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Abstract

Heat shock proteins (HSPs) are highly conserved molecular chaperones that play a crucial role in maintaining cellular protein homeostasis during stress. In bovine hemoparasitic infections caused by *Theileria*, *Babesia*, *Anaplasma*, *Trypanosoma*, and *Ehrlichia*, HSPs are not only essential for parasite survival but also actively influence host immune responses. This review summarizes current molecular insights into the expression and functions of major HSP families (HSP27, HSP60, HSP70, and HSP90). These proteins are deeply involved in parasite virulence, intracellular persistence, antigenic variation, and modulation of host signaling pathways. Comparative observations indicate a conserved reliance on the HSP70-HSP90 axis in protozoan parasites, whereas HSP60 plays a dominant immunogenic role in rickettsial pathogens. We also explored the translational potential of HSPs as diagnostic biomarkers, therapeutic targets, and vaccine candidates. Finally, key knowledge gaps are highlighted, emphasizing the importance of integrative multi-omics approaches to better understand host-parasite chaperone interactions.

Keywords: Heat shock proteins, bovine hemoparasites, HSP70, HSP90, GroEL, host-pathogen interaction, proteostasis

1. Introduction

Heat shock proteins (HSPs) are a group of highly conserved proteins that are induced in response to physiological stress such as heat, oxidative stress, hypoxia, and infection. They are classified based on molecular weight into families including HSP27 (small HSPs), HSP60 (chaperonins), HSP70, and HSP90. These proteins perform a wide range of functions, including protein folding and refolding (HSP70, HSP90), prevention of protein aggregation (HSP27), mitochondrial protein assembly (HSP60), and regulation of apoptosis and signaling pathways, along with roles in antigen presentation and immune modulation (Taipale *et al.*, 2010; Calderwood *et al.*, 2016) [22, 3]. Heat shock proteins (HSPs) are evolutionarily conserved molecular chaperones essential for maintaining cellular proteostasis under both physiological and pathological conditions. Their functions extend beyond protein folding to include regulation of apoptosis, immune signaling, and intracellular trafficking (Mayer and Bukau, 2005; Lubkowska *et al.*, 2021) [12, 10].

In infectious diseases, HSPs are expressed by both the host and the pathogen. During bovine hemoparasitic infections, parasites are exposed to a hostile environment characterized by oxidative stress, immune pressure, and temperature fluctuations. To survive under these conditions, parasites utilize HSP networks, while host cells simultaneously upregulate their own HSPs as part of the stress and immune response.

2. Heat Shock Proteins in Theileria Infection

Theileria parva and *Theileria annulata* infect leukocytes and induce transformation-like changes characterized by uncontrolled cellular proliferation (Dobbelaere and Heussler, 1999) [8]. This process begins with parasite entry into leukocytes and formation of schizonts. Subsequently, there is constitutive activation of signaling pathways such as NF-κB, AP-1, and JNK, leading to increased expression of HSP70 and HSP90 during the schizont stage

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(Cheeseman and Weitzman, 2012)^[4]. Host cells also exhibit upregulation of HSP27 and HSP70 in response to oncogenic stress (Clift *et al.*, 2019)^[6].

HSP90 plays a critical role in stabilizing parasite kinases involved in host cell transformation (Shahzad *et al.*, 2013)^[19], while HSP70 facilitates protein folding during rapid parasite replication. Additionally, host HSPs contribute to NF- κ B activation and anti-apoptotic signaling, with HSP27 suppressing caspase-mediated apoptosis (Mohammed *et al.*, 2013)^[14].

Key findings indicated that HSP90 inhibitors (e.g., geldanamycin) significantly reduce proliferation of *Theileria*-infected cells (Shahzad *et al.*, 2013)^[19]. Furthermore, transcriptomic studies have demonstrated co-regulation of parasite and host chaperone systems (Tretina *et al.*, 2015)^[23].

3. Heat Shock Proteins in Babesia Infection

Babesia bovis and *Babesia bigemina* infect erythrocytes, resulting in hemolysis and oxidative stress. During intraerythrocytic stages, there is significant upregulation of parasite-derived HSP70 and HSP90 (Suarez *et al.*, 2019)^[21]. Due to the lack of a nucleus in erythrocytes, host stress responses are limited, although HSP70-like responses may still occur.

Functionally, HSP70 and HSP90 protect parasite proteins from oxidative damage and support survival, differentiation, and virulence through mechanisms such as cytoadherence (Yamasaki *et al.*, 2007; Yamasaki *et al.*, 2016; Tsutsumi *et al.*, 2023)^[27, 28, 24]. Proteomic studies have identified HSP70 as a major immunogenic protein (Yokoyama *et al.*, 2016)^[29], and RNA-seq analyses show increased HSP expression during stress conditions such as febrile episodes (Ueti *et al.*, 2018)^[25].

4. Heat Shock Proteins in Anaplasma Infection

Anaplasma marginale infects erythrocytes, whereas *A. phagocytophilum* targets leukocytes. Both organisms show strong expression of GroEL (HSP60 homolog) and HSP70 (Rikihisa, 2015)^[18]. Host cells also exhibit increased HSP expression in response to oxidative stress (Pruneau *et al.*, 2014)^[17].

GroEL (HSP60) functions as a major immunodominant antigen and plays a key role in protein folding and immune activation (Singh *et al.*, 2024)^[20]. HSP70 contributes to intracellular survival by modulating apoptosis. Importantly, immune responses targeting GroEL are associated with protective immunity (Palmer *et al.*, 2012)^[16]. HSPs are also implicated in antigenic variation mechanisms of *Anaplasma*. Studies in ticks have demonstrated that HSP70 expression is closely linked to infection dynamics and stress adaptation (Villar *et al.*, 2010; de la Fuente *et al.*, 2011; Busby *et al.*, 2011)^[26, 2, 7].

5. Heat Shock Proteins in Trypanosoma Infection

Trypanosoma evansi and *T. vivax* are extracellular parasites that evade host immunity through antigenic variation mediated by variant surface glycoproteins (VSGs). These parasites express high levels of HSP70, HSP83 (a homolog of HSP90), and small HSPs (Meyer *et al.*, 2018; Clayton, 2019)^[13, 5].

HSP70 supports rapid turnover of VSGs, while HSP90 (HSP83) regulates cell cycle progression and differentiation. Additionally, HSP90 contributes to immune evasion and

thermotolerance, enabling parasite survival in both host and vector environments (Jamabo *et al.*, 2022)^[9].

6. Heat Shock Proteins in Ehrlichia Infection

Ehrlichia ruminantium infects endothelial cells and monocytes, with prominent expression of GroEL (HSP60) and HSP70 (Allsopp, 2015)^[11]. GroEL is highly immunogenic and plays an important role in facilitating intracellular survival. HSP70 provides protection against host-induced stress.

GroEL has also been identified as a promising vaccine antigen (Marcelino *et al.*, 2015)^[11]. Host HSP responses are closely associated with inflammatory signaling pathways during infection (Moumene and Meyer, 2015)^[15].

7. Comparative Analysis of HSP Expression Across Pathogens

Key comparative observations include:

- HSP70 is universally conserved and essential across all pathogens
- HSP90 is more prominent in proliferative parasites such as *Theileria* and *Trypanosoma*
- HSP60 (GroEL) is highly immunogenic in bacterial pathogens such as *Anaplasma* and *Ehrlichia*

These patterns reflect both shared survival mechanisms and pathogen-specific adaptations.

8. Diagnostic, Therapeutic, and Vaccine Implications

HSPs, particularly HSP70 and GroEL, have significant potential as diagnostic biomarkers and can be used for early detection through ELISA and proteomic approaches. HSP90 inhibitors (e.g., geldanamycin analogs) represent promising therapeutic agents by disrupting parasite survival mechanisms.

HSP-based vaccines are also being explored due to their strong immunogenicity and potential for cross-protection. However, their high level of conservation raises concerns regarding possible autoimmunity and antigenic similarity with host proteins.

9. Knowledge Gaps and Future Directions

Despite advances, several limitations remain:

- Limited *in vivo* validation of HSP-targeted therapies
- Incomplete understanding of host-parasite HSP interactions
- Need for single-cell omics and structural biology studies
- Lack of research on co-infections and epigenetic regulation of HSP expression

Addressing these gaps will be essential for advancing translational applications.

10. Conclusion

Heat shock proteins are central to the survival, virulence, and immune interactions of bovine hemoparasites. While HSP70 and HSP90 dominate in protozoan infections, HSP60 plays a key role in rickettsial pathogens.

Their dual role as facilitators of pathogen survival and modulators of host immunity makes them promising yet complex targets for diagnostics, therapeutics, and vaccines. Future research integrating molecular biology, immunology,

and omics technologies will be critical to fully harness their potential.

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