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Heat Shock Proteins In Oral Health And Disease: Structure, Function, And Therapeutic Implications

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Abstract

Heat shock proteins (HSPs) are a conserved family of molecular chaperones that maintain protein homeostasis under physiological and stress conditions. In the oral environment, HSPs such as HSP27, HSP60, HSP70, and HSP90 are constitutively expressed in mucosa, salivary glands, and dental pulp, and their expression is upregulated by thermal, oxidative, or microbial stress. Beyond their canonical roles in protein folding and degradation, HSPs act as danger-associated molecular patterns (DAMPs) to modulate innate and adaptive immunity, participate in wound healing, and preserve tissue integrity. In oral pathology, aberrant HSP expression has been implicated in infections (e.g., Candida, Streptococcus), inflammatory conditions (periodontitis, peri-implantitis, pulpitis), and odontogenic lesions (keratocysts, ameloblastomas). In potentially malignant disorders such as leukoplakia and lichen planus, elevated HSP27 and HSP70 levels correlate with dysplastic severity, while in oral squamous cell carcinoma (OSCC), overexpression of HSP27, HSP70, and HSP90 promotes tumor cell survival, invasion, and chemoresistance. These findings underscore the diagnostic and prognostic potential of HSPs as biomarkers. Moreover, pharmacologic modulation of HSP activity—via HSP90 inhibitors (e.g., geldanamycin analogs), HSP70 ATPase blockers, or HSF-1 antagonists—offers novel therapeutic avenues. However, monotherapy may induce compensatory chaperone upregulation; thus, combination strategies targeting multiple HSPs or integrating conventional therapies may be required. Continued investigation into HSP localization, post-translational regulation, and interplay with oral microenvironmental cues will advance our understanding and enable translation into clinical practice.

Keywords : Heat Shock Proteins, Oral Pathology,HSP70,HSP90 Inhibitors, Oral Squamous Cell Carcinoma, Protein Homeostasis,Molecular,Chaperones,Diagnostic Biomarkers.

INTRODUCTION

Heat shock proteins (HSPs) are highly conserved molecular chaperones that facilitate the proper folding, stabilization, and degradation of cellular proteins, particularly under stress conditions such as heat, hypoxia, and toxin exposure. These proteins are ubiquitously expressed across various domains of life including archaea, fungi, and eukaryotes, and they participate in critical physiological processes like protein homeostasis, cell proliferation, apoptosis, and immune response regulation [1]. Based on their molecular weights, mammalian HSPs are categorized into families including HSP27, HSP40, HSP60, HSP70, HSP90, and large HSPs such as HSP110 and GRP170 [2].

Among these, HSP70 and HSP90 have been extensively studied for their role in supporting the stability and function of oncogenic proteins, thus contributing to all six hallmarks of cancer [3]. In response to environmental stresses, HSP expression is upregulated via the heat shock response (HSR), which is predominantly regulated by the heat shock factor (HSF), particularly HSF-1, a transcription factor that binds heat shock elements (HSEs) to drive HSP gene expression [4]. Importantly, HSPs also act as immunomodulatory molecules, functioning as danger-associated molecular patterns (DAMPs) that stimulate innate immune responses via Toll-like receptors and facilitate antigen cross-presentation. These roles position HSPs at the intersection of inflammation, immunity, and cancer.

HSPs are often overexpressed in tumor microenvironments characterized by hypoxia, acidosis, and nutrient deprivation, aiding in the survival, metastasis, and drug resistance of cancer cells [5]. Notably, their interaction with oncogenic signaling pathways and anti-apoptotic proteins makes them prime candidates for cancer diagnosis, prognosis, and therapeutic targeting [6]. Studies have demonstrated that HSP27 expression correlates with tumor aggressiveness and poor prognosis in breast and prostate cancers [7], while HSP70 has been identified as a diagnostic biomarker for hepatocellular carcinoma [8]. Hence, the therapeutic potential of targeting HSPs through inhibitors or immunotherapies is being increasingly explored in oncology research [9].

HSP – STRUCTURE, ACTIVATION AND INHIBITION

Heat shock proteins (HSPs) are a conserved family of molecular chaperones that play a vital role in protein folding, stabilization, and quality control. Based on their molecular weight, mammalian HSPs are categorized into small HSPs such as HSP27, HSP40, HSP60 (a mitochondrial chaperonin), HSP70, HSP90, and large HSPs including HSP110 and GRP170 (10–13). These proteins are typically inactive under normal conditions but become rapidly upregulated in response to cellular stresses like hyperthermia, hypoxia, toxins, and radiation, a protective response termed the heat shock response (HSR) (14,15).

The HSR is orchestrated by heat shock factor 1 (HSF-1), a transcription factor that, upon activation, trimerizes and translocates into the nucleus where it binds to heat shock elements (HSEs) in the promoters of HSP genes and triggers their expression (16). Overexpression of HSPs and hyperactivation of HSF-1 are frequently observed in cancer cells, driven by the hypoxic, acidic, and nutrient-deprived tumor microenvironment (17,18). It is worth noting that recent evidence supports that post-translational modifications of HSF-1, such as phosphorylation at serine 326, are crucial for its full transcriptional activation and are associated with aggressive tumor phenotypes.Elevated levels of HSF-1 have been shown to correlate with poor prognosis in several malignancies including prostate, breast, endometrial, liver, esophageal, oral, and ovarian cancers (19).

Functionally, HSPs support tumor progression by maintaining oncogenic protein function. HSP90 interacts with key signalling molecules such as PI3K, AKT, HIF-1α, and c-Myc, preventing their degradation and thus promoting proliferation, metabolic rewiring, angiogenesis, and epithelial-mesenchymal transition (20). TRAP1, a mitochondrial isoform of HSP90, modulates metabolic enzymes like succinate dehydrogenase (SDH) to support mitochondrial bioenergetics and tumor cell adaptation. Similarly, HSP70 promotes tumorigenesis by inhibiting apoptosis, regulating glycolysis, and modulating AKT signaling (21). HSP60, on the other hand, exhibits dual roles—it may promote tumor growth by stabilizing mitochondrial function, or inhibit it by interacting with apoptosis-related proteins like caspase-3 and Bax (22).

Due to their central role in cancer, HSPs have emerged as therapeutic targets. HSP90 inhibitors such as geldanamycin (GA), 17-AAG, and 17-DMAG bind to its ATP-binding domain, disrupting client protein folding and leading to cell death. However, drugs like GA were limited by hepatotoxicity, leading to the development of

safer analogs like ganetespib, PU-H71, and NVP-AUY922, which have shown promise in preclinical and clinical settings (23). Recent clinical trials involving PU-H71 and NVP-AUY922 in breast and head and neck cancers have shown encouraging results in terms of tumor regression and reduced recurrence risk, warranting further investigation.

PU-H71, for example, induces apoptosis by destabilizing BCR kinases in chronic lymphocytic leukemia (24). Similarly, inhibitors targeting HSF-1, such as dorsomorphin, fisetin, vitexin, and schizandrin A, reduce HSP transcription by preventing HSF-1 activation or nuclear translocation (25).

HSP70 inhibitors like MKT-077, artesunate, pifithrin-μ (PES), and apoptozole function by blocking ATPase activity or enhancing apoptosis through death receptor pathways. Among them, MKT-077 has entered phase I clinical trials but was suspended due to nephrotoxicity (26).
HSP27 inhibition strategies include ivermectin (which interferes with phosphorylation), RP101 (which showed survival benefits in pancreatic cancer), and quercetin, all showing potent chemosensitizing effects (27). In the case of HSP60, sinularin, a marine-derived compound, reduces HSP60 expression and activates caspase-mediated apoptosis in melanoma cells .
It is essential to acknowledge that monotherapies targeting HSPs may lead to compensatory expression of other chaperones or resistance pathways, such as increased expression of co-chaperones like HOP and BAG family proteins. Combination approaches or sequential therapies may help overcome this resistance.
Combination therapies targeting multiple HSPs or integrating HSP inhibition with chemotherapy have demonstrated enhanced efficacy. For example, dual inhibition of HSP90 and HSP70 increased sensitivity to chemotherapeutics in bladder cancer models (28). Altogether, HSPs remain at the forefront of research as biomarkers and therapeutic targets, providing multiple avenues for improving cancer diagnostics and treatment outcomes .

HSP LOCALIZATION AND FUNCTIONS

Heat Shock Factor 1 (HSF-1) is a master transcriptional regulator that activates the heat shock response by binding to heat shock elements (HSEs) and upregulating HSP gene expression. It is commonly overexpressed in various cancer types, including prostate, breast, endometrial, hepatocellular carcinoma, and esophageal cancers . HSF-1 contributes to tumor growth by enhancing cancer cell survival, migration, invasion, and metastasis. Notably, its nuclear expression correlates with poor prognosis and tumor aggressiveness in ER-positive breast cancers and endometrial carcinoma [29].

HSP27 (HSPB1) is a small heat shock protein mainly localized in the cytoplasm but can translocate to the nucleus under stress. It is strongly expressed in various tumors such as prostate, lung, ovarian, cervical, and esophageal cancers . HSP27 plays a role in cytoskeletal stabilization, apoptosis inhibition, and metastasis. Its phosphorylated form (p-HSP27) is considered a more specific biomarker in hepatocellular carcinoma and osteosarcoma [30]. High expression is often associated with increased chemoresistance and poor clinical outcomes .

HSP60 is a mitochondrial chaperonin involved in protein folding and maintenance of mitochondrial function. However, it can also be found in the cytoplasm of cancer cells. It plays dual roles—either promoting or inhibiting apoptosis—depending on the context [31]. HSP60 expression has been reported in cancers such as ovarian, prostate, bladder, and clear cell renal carcinoma . Its overexpression is associated with poor prognosis in bladder and prostate cancers, but paradoxically indicates better survival in lung adenocarcinoma and ccRCC, reflecting its complex biological role .

HSP70 family proteins are located in the cytosol, mitochondria, and endoplasmic reticulum. They regulate protein folding, protect cells from stress-induced apoptosis, and interact with p53 and other key signaling proteins. HSP70 is overexpressed in many cancers including lung, breast, gastric, colorectal, and glioblastoma . It also exists extracellularly in soluble, exosomal, or peptide-bound forms, which makes it a promising diagnostic marker . Mortalin (HSPA9), a mitochondrial variant, binds p53 and interferes with its tumor suppressor function, contributing to cancer cell survival [32].

HSP90 is a cytosolic chaperone essential for the stability and function of many oncogenic proteins. It is ubiquitously overexpressed in malignancies such as breast, lung, melanoma, leukemia, and pediatric brain tumors . HSP90 promotes tumor progression by regulating angiogenesis, apoptosis, and metastasis through its interactions with HIF-1α, AKT, and PI3K pathways [33]. Additionally, its isoform TRAP1 located in mitochondria is linked to metabolic adaptation in tumors, helping them resist stress and therapy .

Role of Heat Shock Proteins (HSPs) in Oral Health

1. Cellular Protection & Homeostasis

Heat shock proteins (HSPs), notably HSP70, function as essential molecular chaperones in oral tissues, safeguarding nascent and stress denatured proteins from misfolding and aggregation. Under physiological conditions, HSPs are constitutively expressed in the oral mucosa, salivary glands, and dental pulp cells, maintaining proteome integrity. When cells encounter thermal, oxidative, or bacterial stress, upregulation of HSP70 ensures continued protein folding fidelity, prevents the accumulation of cytotoxic aggregates, and directs irreversibly damaged proteins toward proteasomal degradation thereby preserving cellular homeostasis and viability [34].

2. Salivary Defense Mechanism

Saliva is more than a digestive lubricant; it serves as a frontline immunological barrier enriched with HSP70 and related chaperones. Secreted by salivary gland acinar cells, gingival crevicular fluid, and shed mucosal epithelium, these extracellular HSPs bind to microbial surface proteins and to salivary antimicrobial peptides, stabilizing their structure and enhancing pathogen neutralization. By maintaining a stable oral microbiome and reinforcing mucosal integrity, salivary HSPs help prevent opportunistic infections and contribute to both innate and adaptive immune defenses [35].

3. Immune Modulation

Beyond their chaperoning role, HSPs act as potent immunomodulators in the oral environment. Extracellular HSP70 engages Toll-like receptors on monocytes and macrophages, triggering the release of pro-inflammatory cytokines such as IL-6 and TNF-α, which orchestrate acute immune responses to invading pathogens. HSPs also facilitate antigen presentation by dendritic cells, bridge innate and adaptive immunity, and activate cytotoxic T lymphocytes and natural killer cells—thus enhancing oral immune surveillance and pathogen clearance while modulating inflammatory tone [36].

4. Wound Healing & Tissue Repair

HSPs are upregulated in response to oral mucosal injury—from ulceration to surgical incisions—where they accelerate the healing cascade. By activating epidermal growth factor receptor (EGFR) signaling, HSP70 promotes epithelial cell proliferation and migration across wound beds. Concurrently, HSPs enhance macrophage phagocytic activity to clear debris, stimulate fibroblast–endothelial interactions for granulation tissue formation, and support extracellular matrix remodeling. Collectively, these actions shorten healing time and restore mucosal integrity after trauma [34].

5. Periodontal and Mucosal Health

In the periodontium and oral mucosa, a baseline expression of HSPs provides continuous “molecular sentinel” functions. During microbial challenge or mechanical stress, transient increases in HSP levels act as danger signals, alerting immune cells to potential threats. This rapid HSP-mediated signaling prevents excessive bacterial colonization, preserves tight junction integrity between epithelial cells, and mitigates tissue breakdown in gingivitis and early periodontitis helping to maintain long term periodontal stability [37].

6. Dental Pulp & Odontoblast Function

Within the dental pulp, HSPs play dual roles in defense and regeneration. Odontoblasts and pulp fibroblasts upregulate HSP27 and HSP70 following carious insults or cavity preparation, where these chaperones guide differentiation of progenitor cells into reparative odontoblast-like cells. HSP-mediated signaling supports the formation of tertiary dentin, reinforces pulp vitality, and shields against bacterial invasion. By orchestrating both cytoprotection and tissue regeneration, HSPs ensure pulp resilience after injury [38].

HEAT SHOCK PROTEINS IN ORAL DISEASES:

Heat shock proteins (HSPs) play pivotal roles across a spectrum of oral pathologies—from microbial colonization to cystic and neoplastic transformations, and from inflammation of the periodontium to malignant progression.

1. Oral Infections and Microbial Pathogenesis

Host–Microbe Interplay

Pathogens such as Candida albicans and Streptococcus sanguis exploit or induce host HSPs to bolster their survival and subvert mucosal defenses. In C. albicans, small HSPs (Hsp21) facilitate adaptation to temperature and oxidative stresses, support morphogenetic transitions, and help the fungus evade immune clearance during oral candidiasis [39].

Viral Co-option of Chaperones

Viruses including HBV, polyomavirus, and HIV hijack HSP60, HSP70, and HSP90 within oral mucosal and salivary gland cells to assist genome uncoating, reverse transcription, polymerase activation, and capsid assembly. Elevated salivary levels of HSP90/GRP94 also co correlate with chronic viral infection and may serve as noninvasive biomarkers of disease [34].

2. Periodontal, Periapical, and Pulpal Inflammation

Periodontitis

In chronic periodontitis, elevated levels of HSP60 and HSP70 have been observed in gingival tissues. These heat shock proteins serve as molecular chaperones but also act as danger signals, stimulating pro-inflammatory immune responses. Their levels correlate with inflammatory severity and may play a role in chronic periodontal breakdown [40].

Peri-implantitis

In peri-implant diseases, HSP27 and HSP70 are upregulated in inflamed tissues. This expression may reflect cellular stress due to microbial invasion and implant-associated inflammation. HSPs here could contribute to tissue damage or potentially serve as local protective factors during early breakdown [41].

Pulpal Inflammation

In inflamed dental pulp, odontoblasts and pulp fibroblasts show increased expression of HSP70 and HSP27. These stress proteins may protect the pulp from thermal or bacterial insults, helping maintain cell viability and supporting healing responses [42].

3. Odontogenic cysts and tumours

Heat shock proteins regulate key steps in odontogenesis and odontogenic lesion biology by balancing proliferation, differentiation, and apoptosis.

Odontogenic Keratocysts (OKCs)

The basal epithelium of OKCs shows marked HSP70 overexpression, which correlates with local inflammation and likely enhances epithelial proliferation and survival under stress [43].

Radicular Cysts:

Cytoplasmic HSP27 localizes to proliferating epithelial rests—regardless of inflammatory infiltrate—where it may drive rest cell migration and bolster resistance to necrosis and apoptosis, contributing to cyst persistence [43,44].

Odontogenic Tumors :

Heat shock proteins (Hsps), particularly Hsp27, Hsp70, and Hsp90, play crucial roles in the development and progression of odontogenic tumors. These molecular chaperones are involved in regulating tumor cell survival, differentiation, and resistance to cellular stress.

Hsp27 is prominently expressed in ameloblastomas, with strong cytoplasmic localization in stellate-shaped tumor cells and those undergoing squamous metaplasia. Its expression is limited to tumor cells and is absent in stromal components such as fibroblasts and vascular endothelial cells. This suggests a tumor-specific role in promoting cellular transformation and aiding in the differentiation of columnar and cuboidal tumor cells into squamous cells.

Hsp70 expression is associated with the aggressive biological behavior of ameloblastomas. High levels of Hsp70 have been detected in more invasive variants and are linked to increased resistance to apoptosis, contributing to tumor persistence and recurrence.

Granular cell ameloblastomas, in particular, show elevated expression of both Hsp70 and Hsp90. These proteins are associated with enhanced tumor cell survival, local tissue invasion, and a greater likelihood of recurrence, indicating a potential role in supporting the aggressive nature of these tumors [43,45].

4. Salivary gland neoplasms:

Heat shock proteins (HSPs) play a crucial role in cellular stress responses and have been implicated in the pathogenesis of both benign and malignant salivary gland tumors. Elevated expression of HSP60 and HSP70 has been observed in these tumors, with significantly higher levels in malignant compared to benign lesions. HSP70 is particularly associated with aggressive tumor behavior, including neural invasion, metastasis, and site-specific occurrence. In contrast, HSP27, although upregulated in both benign and malignant tumors, shows lower expression in malignant tumors and is negatively correlated with factors such as patient age, tumor size, and metastasis. Furthermore, the proliferation index in malignant tumors, marked by PCNA, aligns with the heightened expression of HSP70, while HSP27 displays an inverse relationship. Notably, some studies report reduced expression of HSP27 and HSP110 in malignant cells compared to benign counterparts, suggesting that the loss or downregulation of these proteins may serve as a marker of malignant transformation. Collectively, the distinct expression profiles of HSPs in salivary gland tumors highlight their potential diagnostic and prognostic value, particularly in distinguishing benign from malignant phenotypes and in assessing tumor aggressiveness. [46, 47].

5. Potentially malignat disorders and Malignancy

Heat Shock Proteins (Hsps) function as cytoprotective chaperones and play crucial roles in cellular stress response, particularly in oral pathological conditions. Their overexpression is a hallmark of several oral potentially malignant disorders (OPMDs) and oral cancers. Hsps contribute to DNA repair, inhibit apoptosis, modulate immune responses, and facilitate malignant transformation and progression by stabilizing mutated or overactive proteins.

1. Oral Premalignant Lesions

Oral Leukoplakia

Hsp27 and Hsp70 are significantly upregulated in oral leukoplakia, with their expression levels rising in correlation with the severity of epithelial dysplasia. These proteins help dysplastic cells evade apoptosis and support their survival, thereby increasing the risk of malignant transformation [48].

Oral Lichen Planus (OLP)

In OLP, keratinocytes show elevated expression of Hsp60 and Hsp70, triggered by cytokine-mediated inflammation. These chaperones are believed to protect the oral epithelium from immune-mediated damage. Immunomodulatory treatments like tacrolimus reduce their expression, suggesting a pathogenic role for these proteins in OLP [49].

Other Dysplastic Conditions

Hsp70 is also overexpressed in other premalignant oral lesions such as oral verrucous carcinoma, oral verrucous hyperplasia, and oral lichen planus. Hsp60 expression has been observed in both leukoplakia and oral squamous cell carcinoma (OSCC), often correlating with histopathological severity [48,49].

Oral Squamous Cell Carcinoma (OSCC)

Heat shock proteins (HSPs), including Hsp27, Hsp70, and Hsp90, are markedly overexpressed in oral squamous cell carcinoma (OSCC), where they facilitate tumor progression, increased invasiveness, and resistance to therapy. Hsp27 plays a critical role in inhibiting mitochondrial-mediated apoptosis by preventing the activation of cytochrome c and procaspases. Its elevated expression also enhances tumor cell survival by increasing oxidative stress tolerance through free radical regulation. Notably, significant differences in Hsp27 expression between normal oral mucosa and well-differentiated OSCC underline its potential as a prognostic indicator [50].

Hsp70 facilitates immune evasion by interfering with antigen presentation mechanisms, thereby protecting tumor cells from immune-mediated destruction. It also contributes to tumor survival under stress and has been associated with increased resistance to cytotoxic agents. Elevated Hsp70 expression in oral epithelial dysplasia has been proposed as a predictive marker for malignant transformation, emphasizing its role in early carcinogenesis [51].

Hsp90, a critical molecular chaperone, supports oral squamous cell carcinoma (OSCC) progression by stabilizing oncogenic proteins and signaling pathways involved in cell proliferation, invasion, and metastasis. Heat shock factor 1 (HSF1), the master regulator of heat shock proteins, is overexpressed in both tumor cells and cancer-associated fibroblasts (CAFs) in OSCC and correlates with poor prognosis. HSF1 in CAFs promotes epithelial-mesenchymal transition (EMT), tumor cell proliferation, migration, and invasion, whereas its knockdown reduces these malignant traits and tumor growth. These findings establish HSF1 as a central driver of OSCC malignancy and a potential prognostic and therapeutic target [52,53].

Collectively, the upregulation of Hsp27, Hsp70, and Hsp90 underscores their pivotal involvement in oral carcinogenesis and highlights their potential utility as diagnostic biomarkers and therapeutic targets in the management of OSCC

Conclusion

Heat shock proteins serve as pivotal regulators of proteostasis, immunity, and cellular stress responses within the oral cavity. Their spatial and temporal expression patterns across oral tissues underpin fundamental processes including wound healing, microbial defense, and maintenance of epithelial integrity. In pathological contexts, dysregulated HSP expression contributes to the pathogenesis and progression of infections, inflammatory diseases, odontogenic lesions, and malignant transformations. The prognostic association of HSP27, HSP70, and HSP90 with disease severity in premalignant and malignant oral lesions highlights their value as biomarkers for early detection and risk stratification. Therapeutically, targeting HSPs or their master regulator HSF-1 holds promise for sensitizing tumor cells to apoptosis and overcoming resistance mechanisms. Nevertheless, the redundancy and compensatory networks within the chaperone system necessitate combinatorial or sequential intervention strategies. Future research should focus on elucidating HSP interactomes in diverse oral microenvironments, optimizing inhibitor specificity, and integrating HSP modulation with immunotherapeutic and conventional modalities. Ultimately, harnessing the multifaceted roles of HSPs will foster innovative diagnostic and treatment paradigms, improving outcomes for patients with oral diseases.

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Figure 1a. Heat Shock Response (HSR) Pathway

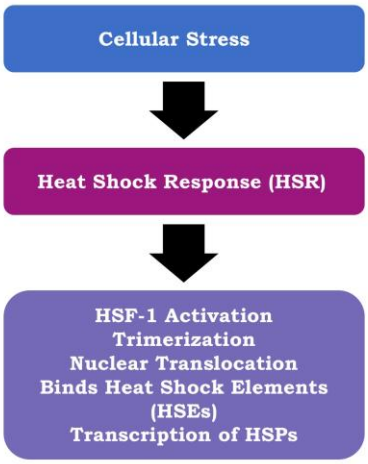

Figure 1b. Multifunctional Roles of Heat Shock Proteins