

Role Of Heat Shock Proteins in Various Diseases with Special Emphasis on Periodontal Inflammation - A Review.

Ahmed Elhassan ¹, Karthikeyan Ramalingam ^{2*}, Syed Wali Peeran ³, Rajendran Ganesh ⁴, Khalid Awidat Abdalla ⁵.

¹Associate Professor, Libyan Authority of Scientifics Research, Tripoli, Libya. Email: elhassan1929@yahoo.com

²Professor and Associate Dean, Department of Oral and Maxillofacial Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India, E-mail: karthikeyanr.sdc@saveetha.com

³Department of Preventive Dental Sciences, Jazan University, Jazan, KSA. Email: doctorsyedwali@yahoo.in

⁴Assistant Professor of Pediatric Dentistry, Department of Preventive Dental sciences, Faculty of Dentistry, Al Baha University, Al Baha, KSA. Email: rrajendran@bu.edu.sa

⁵Department of Oral Biology and Orthodontics, Faculty of Dentistry, Sebha University, Sebha, Libya. Email: awidat@hotmail.com

Abstract

Heat shock proteins (HSPs) behave as molecular chaperones of cell protection, immediately after exposure to external shock/stress. It is responsible for cellular homeostasis and repair. Various forms of HSPs are correlated with inflammation and neoplasia. HSP70 is a key molecule that is shown to increase in gingivitis and periodontitis. It is also expressed in gingival crevicular fluids and could be a potential marker for severity of periodontal disease.

Keywords: Heat-Shock proteins, Chronic diseases, Stress proteins, Periodontitis, HSP

DOI: 10.47750/pnr.2022.13.S04.110

INTRODUCTION

The heat-shock response or stress proteins were first observed in the fruit fly *Drosophila melanogaster*. When isolated tissues or whole flies were heat-shocked, new proteins were produced that were not detectable in unshocked cells. Moreover, after a heat shock, other particular proteins present in cells not subjected to stress were produced in considerably higher concentrations. Hence, heat-shock proteins (HSP) encompassed both of these types of proteins. They have evolved as living organisms' primary pro-survival biochemical response mechanism of cells to cope with heat stress. HSPs are universal phenomena that have been observed in all plant and animal species studied, including humans. Various Prokaryotic cells, such as bacteria, also produce HSPs. This large family of a conserved set of heat shock proteins (HSP) are expressed upregulated during stressful situations and are stimulated to extremely high levels. HSPs have a pivotal role in protein homeostasis. They act as chaperones and play roles in protein maturation, aid in conformational folding and assembly of newly synthesized proteins, refolding of denatured proteins and assist in the degradation of irreparable proteins and toxins and protect against their accumulation. Therefore their overexpression before an injury has protective effects (1-16).

Heat-Shock Protein: Structure and Functions

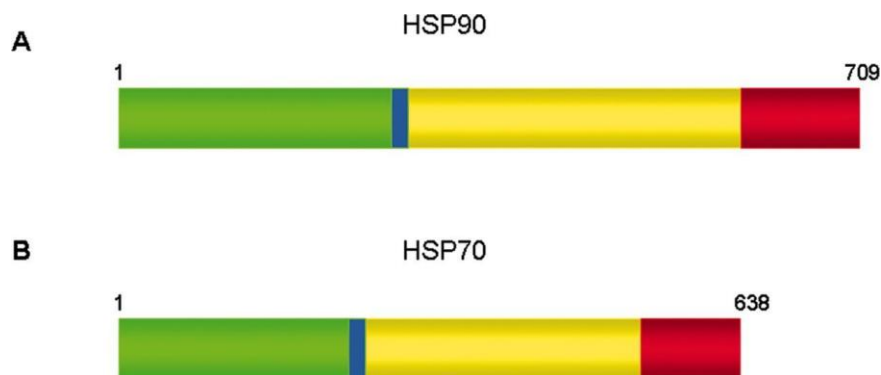


Figure 1: Schematic of the domain structures of yeast HSP90 (A) and E. coli HSP70 (B) as determined by structural and limited proteolysis studies. 21

HSP90 has three structural domains: 1) an N-terminal nucleotide-binding domain (NBD) that also binds HSP90 inhibitors and may bind peptides, 2) a middle segment that interacts with client proteins; and 3) the C terminus, which is implicated in homodimerization.

HSP70 has two domains: an NBD and a substrate-binding domain (SBD). The 44-kDa N-terminal NBD has ATPase activity and associates with the HSP70 co chaperone. The 27-kDa C terminus is composed of the SBD and a “lid” region. These two domains are connected by a conserved linker, recently shown to be critical for interdomain communication.

HSP90 has an N-terminal NBD (green) that may also contain a peptide-binding element. The middle segment (yellow) interacts with client proteins and also contributes a loop that catalyzes ATP hydrolysis. The C-terminal domain (red) is implicated in homodimerization. HSP70 has two major domains: a 44-kDa N-terminal NBD (green) and a 27-kDa C-terminal substrate-binding domain (yellow and red). This region comprises the main substrate-binding domain (yellow; 18 kDa) that consists of two times four antiparallel β -strands and four connecting loops and makes contact with the bound substrate, as well as an α -helical lid region (red; 10kDa). Both molecules have a linker region (blue) that is thought to mediate communication between the major subdomains. (16,21)

HSP plays an important role in many physiological processes, inflammatory responses, diseases and neoplasia. Its clinical implications are summarized in Table 1 and 2.

Table 1 summarizing HSP and its implications in oral diseases

HSP and its associations	Clinical Implications	Source
HSP and periodontal disease	HSPs are implicated in human periodontal disease.	Ando et al 19955
HSP and periodontal disease	HSP47 and HSP70 are expressed in PDL fibroblasts on the pressure side damaged by application of mechanical stress and contribute to the repair of collagen tissue by activating PDL fibroblasts, supporting recovery from cell damage	Muraoka et al 2018 17
HSP and periodontal disease	HSP levels increase with periodontal disease. Its levels are low in healthy controls.	Furose et al 2020 18
HSP and periodontal disease	HSP27 levels varied between aggressive periodontitis and chronic periodontitis	Kaiser et al 2018 22
HSP and oral epithelial dysplasia	HSP70 and HSP 27 has been assessed as a marker for oral leukoplakia.	Seoane et al 2006
HSP: a double-edged sword linking periodontal and cardiovascular diseases	There may be cross-reactivity of the immune response to bacterial HSPs, termed GroEL, with HSPs expressed by stressed vascular endothelial cells	Leishman et al 20177 Yamamoto and Eguchi 20208

HSP, Periodontal disease and Coronary heart disease	TLR-4 was recognized by HSP60 and HSP65 in periodontal disease patients. However cross-reaction of HSP60 was associated with immune response to coronary heart disease.	Hasan et al 2005 23
HSP, Periodontal disease and peripheral blood mononuclear cells	Mean responses of peripheral blood mononuclear cells to human and mycobacterial HSP60 and HSP70 were lower in periodontitis patients.	Petit et al 1999 24
HSP and Periodontal disease	Salivary levels of HSP70 were higher in patients with chronic periodontitis than healthy controls.	Motahari et al 2021 25

Table 2: Role of HSP in systemic diseases

HSP and cardiovascular diseases	Antibodies to HSP60 have been associated with carotid stiffness, hypertension and atherosclerosis	Zhu et al 20016
HSP and acute conditions	Several studies have observed a decrease in intracellular HSP 70 and HSP 90 levels in monocytes and polymorphonuclear cells, along with a pattern of early extracellular induction in acute conditions like sepsis	Kaiser et al 2018 22
HSP and Rheumatoid Arthritis (RA)	HSP 96 is Elevated in RA Elevated HSP levels are noted in the synovium of smokers with RA.	Huang et al 20099 Furose et al 2020 18
HSP and Pregnancy	HSPs have been found to be associated with decidualization, implantation and placentation, with their dysregulation associated with implantation failure, pregnancy loss and other fetomaternal complications	Jee et al 202110
HSP in diabetes and wound healing	The numerous defects in the function of HSPs associated with diabetes could contribute to the commonly observed complications and delayed wound healing in diabetics	Atalay et al 200911
HSP and liver regeneration	HSP70 is required for optimal liver regeneration	Wolf et al 201412
HSP and cancer	HSP are overexpressed in a wide range of human cancers and are implicated in tumor cell proliferation, differentiation, invasion and metastasis. HSP27 and HSP70 are implicated in resistance to chemotherapy in breast cancer, HSP27 predicts a poor response to chemotherapy in leukemia patients, whereas HSP70 expression predicts a better response to chemotherapy in osteosarcomas. HSP could be targeted as pharmacological modification of HSP expression or molecular chaperone activity and using the immunological role of HSPs as anticancer vaccines. HSP70 is associated with poor differentiation, lymph node metastasis, increased cell proliferation, block of	Ciocca and Calderwood 200513

	apoptosis, and higher clinical stage, which are markers of poor clinical outcome.	
Host HSP 90 and Human coronavirus	HSP90 inhibitors can be repurposed as a potent and broad-spectrum antiviral against human coronaviruses	Li et al 202014
HSP and renal ischemia-reperfusion injury	The concept that HSPs are cytoprotective after IRI	Zhang et al 200815

Heat-Shock Proteins in Periodontal inflammation

Periodontal disease is a chronic inflammatory disease initiated by microbial infections that leads to a host response resulting in inflammatory breakdown of tooth-supporting osseous and soft tissues. (20) There are three basic types of periodontitis: chronic, aggressive, and as a symptom of another disease. Periodontitis is an inflammatory condition that causes the resorption of connective tissue and alveolar bone as a result of mononuclear cells invading the gingival tissue. Although periodontal bacteria are the cause of periodontitis, the human immune system controls the disease's progression and severity. It is still unclear how precisely periodontal tissue is destroyed. The basal layer of periodontal pockets exhibits positive expression of (HSPs). Increased infiltration of mononuclear inflammatory cells in periodontal pockets beneath the basal layer. As a result, periodontal bacteria induce the development of HSPs in the periodontal cells, which in turn triggers the production of pro-inflammatory cytokines by macrophages and other inflammatory cells. (25)

In order to maintain homeostasis, the periodontal tissue reacts to various stimuli, such as mechanical stress and inflammation, and expresses a variety of proteins to cause dynamic remodeling of the periodontium. Traumatic occlusal stress led to modification of the periodontal connective tissue. Heat-shock proteins (HSPs) are known to be the primary protein exhibited by numerous systems and organizations. HSPs respond to mechanical stress. Inflammation, physical stress, chemical stress, and a pathological alteration in heat shock all contribute to HSP. But it's still unknown what each HSP does. HSP plays a key role in cellular defense and remodeling of periodontium (17)

Both bacterial and host HSPs are hypothesized to contribute to pathogenesis of periodontal disease. Limited studies have investigated the potential role of circulating levels of HSPs in periodontitis. HSP regulate the intercellular signaling activities with properties similar to both pro- or anti-inflammatory cytokines. (22)

Conclusion

HSP are implicated in periodontal disease. Future research should be directed to estimate the levels of HSP in health and in periodontal disease. Once the base levels are established, HSP levels could be estimated to assess the response to periodontal therapy. HSP targeted therapy could reduce the overall inflammatory load in the oral cavity, which is also implicated in oral carcinogenesis.

Conflict of interest

None

Funding

This research did not receive any specific grant from funding agencies in public, commercial or not-for-profit sectors.

REFERENCES

1. Dukay B, Csoboz B, Tóth ME. Heat-Shock Proteins in Neuroinflammation. *Front Pharmacol.* 2019;10:920.
2. Miller DJ, Fort PE. Heat Shock Proteins Regulatory Role in Neurodevelopment. *Front Neurosci.* 2018;12:821.
3. Candido EPM. Heat Shock Proteins. In: *Encyclopedia of Genetics.* Elsevier; 2001:914-915.
4. Rizal MI, Soeroso Y, Sulijaya B, Assiddiq BF, Bachtiar EW, Bachtiar BM. Proteomics approach for biomarkers and diagnosis of periodontitis: systematic review. *Heliyon.* 2020;6(6):e04022.
5. Ando T, Kato T, Ishihara K, Ogiuchi H, Okuda K. Heat shock proteins in the human periodontal disease process. *Microbiol Immunol.* 1995;39(5):321-327.

6. Zhu J, Quyyumi AA, Rott D, et al. Antibodies to human heat-shock protein 60 are associated with the presence and severity of coronary artery disease: evidence for an autoimmune component of atherogenesis. *Circulation*. 2001;103(8):1071-1075.
7. Leishman SJ, Ford PJ, West MJ, Cullinan MP, Seymour GJ. Heat shock proteins: a double-edged sword linking periodontal and cardiovascular diseases. *Future Cardiol*. 2017;13(6):515-519.
8. Yamamoto T, Eguchi T. Heat Shock Proteins and Periodontitis – Cross-Reaction Between Bacterial and Human HSP in Periodontal Infection Linking with Cardiovascular Diseases. *Heat Shock Proteins*. Published online 2020. doi:10.1007/7515_2020_24
9. Huang QQ, Sobkoviak R, Jockheck-Clark AR, et al. Heat shock protein 96 is elevated in rheumatoid arthritis and activates macrophages primarily via TLR2 signaling. *J Immunol*. 2009;182(8):4965-4973.
10. Jee B, Dhar R, Singh S, Karmakar S. Heat Shock Proteins and Their Role in Pregnancy: Redefining the Function of “Old Rum in a New Bottle.” *Frontiers in Cell and Developmental Biology*. 2021;9. doi:10.3389/fcell.2021.648463
11. Atalay M, Oksala N, Lappalainen J, Laaksonen DE, Sen CK, Roy S. Heat shock proteins in diabetes and wound healing. *Curr Protein Pept Sci*. 2009;10(1):85-95.
12. Wolf JH, Bhatti TR, Fouraschen S, et al. Heat shock protein 70 is required for optimal liver regeneration after partial hepatectomy in mice. *Liver Transpl*. 2014;20(3):376-385.
13. Ciocca DR, Calderwood SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. *Cell Stress Chaperones*. 2005;10(2):86-103.
14. Li C, Chu H, Liu X, et al. Human coronavirus dependency on host heat shock protein 90 reveals an antiviral target. *Emerg Microbes Infect*. 2020;9(1):2663-2672.
15. Zhang PL, Lun M, Schworer CM, et al. Heat shock protein expression is highly sensitive to ischemia-reperfusion injury in rat kidneys. *Ann Clin Lab Sci*. 2008;38(1):57-64.
16. Javid B, MacAry PA, Lehner PJ. Structure and Function: Heat Shock Proteins and Adaptive Immunity. *The Journal of Immunology*. 2007;179(4):2035-2040. doi:10.4049/jimmunol.179.4.2035
17. Muraoka, R., Nakano, K., Tsujigiwa, H., Hitoshi Nagatsuka, H., Matsuda, H., Tomida, M., Okafuji, N., Yamada, K., Kawakami, T. . Involvement of Heat-Shock Proteins During Periodontal Ligament Remodeling. In: Manakil, J., editor. *Periodontology and Dental Implantology* [Internet]. London: IntechOpen; 2018 [cited 2022 Sep 25]. Available from: <https://www.intechopen.com/chapters/62770> doi: 10.5772/intechopen.79200
18. Furuse N, Takai H, Ogata Y. Effects of Initial Periodontal Therapy on Heat Shock Protein 70 Levels in Gingival Crevicular Fluid from Periodontitis Patients. *J Clin Med*. 2020 Sep 24;9(10):3072. doi: 10.3390/jcm9103072. PMID: 32987652; PMCID: PMC7598651.
19. Seoane J.M., Varela-Centelles P.L., Ramirez J.R., Cameselle-Teijeiro J., Romero M.A., Aguirre J.M. Heat shock proteins (HSP70 and HSP27) as markers of epithelial dysplasia in oral leukoplakia. *Am. J. Dermatopathol*. 2006;28:417–422. doi: 10.1097/01.dad.0000211509.44865.bb.
20. Kumar PA, Kripal K, Chandrasekaran K, Bhavanam SR. Estimation of YKL-40 Levels in Serum and Gingival Crevicular Fluid in Chronic Periodontitis and Type 2 Diabetes Patients among South Indian Population: A Clinical Study. *Contemp Clin Dent*. 2019 Apr-Jun;10(2):304-310. doi: 10.4103/ccd.ccd_629_18. PMID: 32308295; PMCID: PMC7145233.
21. Babak Javid, Paul A. MacAry, Paul J. Lehner Structure and Function: Heat Shock Proteins and Adaptive Immunity. *The Journal of Immunology* August 15, 2007, 179 (4) 2035-2040; DOI: 10.4049/jimmunol.179.4.2035
22. Kaiser F, Donos N, Henderson B, Alagarwamy R, Pelekos G, Boniface D, Nibali L. Association between circulating levels of heat-shock protein 27 and aggressive periodontitis. *Cell Stress Chaperones*. 2018 Sep;23(5):847-856. doi: 10.1007/s12192-018-0891-4. Epub 2018 May 15. PMID: 29766408; PMCID: PMC6111086.
23. Hasan A, Sadoh D, Palmer R, Foo M, Marber M, Lehner T. The immune responses to human and microbial heat shock proteins in periodontal disease with and without coronary heart disease. *Clin Exp Immunol*. 2005 Dec;142(3):585-94. doi: 10.1111/j.1365-2249.2005.02953.x. PMID: 16297172; PMCID: PMC1809534.
24. Petit MDA, Wassenaar A, van der Velden U, van Eden W, Loos BG. Depressed Responsiveness of Peripheral Blood Mononuclear Cells to Heat-shock Proteins in Periodontitis Patients. *Journal of Dental Research*. 1999;78(8):1393-1400. doi:10.1177/00220345990780080401
25. Motahari P, Pourzare Mehrbani S, Jabbarvand H. Evaluation of Salivary Level of Heat Shock Protein 70 in Patients with Chronic Periodontitis. *J Dent (Shiraz)*. 2021 Sep;22(3):175-179. doi: 10.30476/DENTJODS.2020.87080.1228. PMID: 34514064; PMCID: PMC8417541.