Review Article

Stress Proteins and Immune Response – A Review

Shilpa R*
Saveetha Dental College, Saveetha University, Chennai, Tamil Nadu, India.
*Corresponding author's E-mail: itsfins@gmail.com

Received: 18-07-2017; **Revised:** 26-08-2017; **Accepted:** 16-09-2017.

ABSTRACT

This article is a review of stress proteins, produced by our body and its immune response. Heat shock proteins (HSPs) are present in all living organisms, from bacteria to humans under normal conditions, immunological functions are conserved. Heat shock proteins are an evolutionary conserved family of proteins whose expression increases in response to a variety of different metabolic insults. In addition, heat shock proteins have been shown to participate in protein assembly, secretion, trafficking, protein degradation, and the regulation of transcription factors and protein kinases. Heat shock proteins (hsps) are among the most abundant intracellular proteins. Their synthesis is rapidly up-regulated by various 'stressors' including temperature, glucose deprivation, infection and cancer.

Keywords: Heat shock proteins, immune response, proteins, stress.

INTRODUCTION

Heat shock proteins was accidentally observed by FM Ritosa in 1960when the Incubation temperature of Drosophilia was accidentally increased and when he examined the chromosomes, he found "puffing pattern" which indicated the elevated gene transcription of an unknown protein [1] the stress induced in the drosophilia cell was accident heat and thereby it got the name "Heat Shock Proteins" (HSPs).[2]The main function of these proteins is to make sure that the cellular proteins are functioning properly. HSPs are expressed more in wide range of human cancers and are implicated in tumour cell proliferation, differentiation, invasion, metastasis, death and recognition by the immune system.

Types of Heat Shock proteins

Heat shock proteins are classified based on their molecular weight into various classes namely, HSP27, HSP60, HSP70, HSP90, HSP100 and the small heat-shock proteins (sHSPs).[3]

HSP 27

HSP27 is well expressed in several organs and tissues like eye, nervous system, heart, blood and blood vessels, lung, bladder, colon, stomach as well as in oestrogen responsive organs such as uterus, vagina, cervix and placenta. HSP27 levels are elevated in different tumours like breast cancer, prostate cancer, gastric tumours, head and neck cancers, uterine and ovarian cancers as well as cancers in urinary system and the nervous system (meningiomas, astrocytomas and neuroblastomas).HSP27 interacts with actin and intermediate filaments and protects actin filaments from fragmentation.[4] It is also involved in process of celldifferentiation.[5]

HSP 60

HSP60 can activate the monocytes, macrophages and dendritic cells and also increases the secretion of a wide range of cytokines.[6] The cytoplasmic HSP60 forms a complex with proteins responsible for apoptosis and regulates the activity of these proteins thereby preventing apoptosis. It also plays role in a "danger signal cascade" immune response.[6, 7] Bacterial HSP60 play a role in autoimmunity causing the immune system to create anti-chaperonin antibodies. These new antibodies then recognize and attack human HSP60 which causes an autoimmune disease.

HSP70

It is mainly localized in the cytosol, mitochondria and endoplasmic reticulum and exhibit constitutive and inducible regulation. It is expressed at high levels in stress conditions and not during normal times. Under stressful conditions, elevated HSP70 levels allow cells to cope with increased concentrations of unfolded or denatured proteins.[8] It also inhibits apoptosis.[9] It is seen to be over expressed in conditions like malignant melanoma[10]and is under expressed in renal cell cancer.[11]

HSP90

HSP90 is one of the most abundant proteins expressed in cells.[12]In unstressed cells, it helps in folding, intracellular transport, maintenance and degradation of proteins as well as facilitating cell signalling. It acts as a general protective chaperone.[13] In oncogenesis it participates in processes such as self-sufficiency in growth signals, stabilization of mutant proteins, angiogenesis and metastasis.[14, 15]

HSPS and Immune response

Hsps are immune dominant molecules, and a significant element of the immune response to pathogenic microorganisms which is directed toward hsp-derived peptides.[16]The proposition that immunologic recognition of cross-reactive hsp epitopes might provide a link between infection and autoimmunity[17]has been supported by studies implicating immunity to hsps in arthritis,[18]multiple sclerosis,[19]and diabetes[20] Evidently, due to their high conservation among various microbial pathogens, hsp are major antigens. They are known to induce very strong humoral and cellular immune responses in numerous infections.

HSPS as inducers of vascular diseases

Hsp gene transcription in response to stress is regulated by the interaction of heat shock factor (HSF) transcription factors (mainly HSF1)with heat shock elements in the hsp gene promoter regions.[21]The stress response is only transient, because of a prolonged and inappropriate presence of protein-binding. They may be involved in the initiation of atherosclerosis via nonspecific inflammatory events or its progression via the induction of adaptive immunity either to themselves or to homologous molecules derived from infective organisms. Serum hsp60 levels increases with the presence of early atherosclerosis, [22] and levels of hsp70 are raised in patients with peripheral and renal vascular disease.[23] Risk factors for atherosclerosis such as hyperlipidemia, diabetes, smoking and hypertension cause oxidative stress, and oxidative stress leads to the induction of hsp expression in vascular smooth muscle cells which says it all.[24]

Role of Heat Shock Proteins in protection from pathogenesis of infectious diseases

Both host cells and microbes are confronted with dramatic alterations in their living conditions during infection. With these changing conditions, induction of hsp synthesis is vital for pathogen survival. Subsequently, increased pathogen hsp levels in cells lead to rapid degradation of hsp by the host processing machinery. Pathogen-derived determinants may then be efficiently presented by host cells and promote recognition of infected cells by the immune system. Although the exact role of hsp in immunity to microbial infection is incompletely understood, hsp apparently serve as important antigens in defense against infectious agents.[25]Immune responses to hsp have been observed in infectious diseases caused by bacteria, protozoa, fungi, and nematodes, as well asin various experimental infection models.[26] At least two factors contribute to the fact that hsp represent major antigens in a wide spectrum of infections: first, these proteins are abundant in the pathogen, especially under stress conditions; and second, immunologic memory for cross-reactive determinants of conserved hsp is generated during life based on frequent restimulation by subsequent encounters with microbes of with different degrees of virulence.[27] Under these conditions, infection of an individual with a virulent pathogen would enable the already prepared immune system to react quickly before the immune response to more pathogen-specific antigens develops. An immune response to conserved determinants of hsp shared by different microbes may, furthermore, prevent colonization of the host by microbial pathogens. Increased antibody levels to hsp70, for example, have been identified in sera of patients suffering from malaria, leishmaniasis, schistosomiasis, filiariasis, and candidiasis.[28] The hsp90-specificantibodies contributed directly in the protection against *Candida albicans* infection. [29]

Relation with autoimmune diseases

In healthy individuals, there exists a well balanced network of potentially self-reactive antibodies and T cells that have evaded deletion processes. In this situation, the immune system responds to its own hsp in a manner that could promote the recognition and elimination of aberrant cells. However, when hsp expression and hsp-specific immune responses are regulated inappropriately, autoimmune reactions may follow. Tolerance to self antigens in particular may become distorted by the frequent encounter of the immune system with foreign (e.g., microbial) antigens with high similarity to self. [30] Infact, molecular mimicry is widely discussed as one mechanism responsible for the induction of autoimmune disease.[31] Immune responses to conserved regions shared by pathogen and self hsp in individuals during active infection were not unexpected. Hence, in several infectious diseases, increased titers of antibodies reactive for conserved regions of hsp shared by the pathogen and host have been identified. For example, increased levels of antibodies against self hsp60 have been found in sera of patients with Lyme disease, suggesting an association between self-reactive antibodies and infection with *Borrelia burgdorferi*. [32] Involvement of hsp in autoimmune responses depends on two criteria: first, hsp need to be expressed by cells of the target organ in a different way from at other tissue sites to allow organ-specific recognition by T cells and antibodies; and second, control of natural regulatory mechanisms for organ-specific inflammation must be disturbed.

Extracellular Heat shock proteins: Alarmins for host immune system:

Several properties would suggest that extracellular HSPs are biologically plausible and likely candidates to serve as alarmins. First, collectively, the HSPs are the most abundant intracellular proteins. Second, several of the HSPs are markedly induced in response to a diverse range of cellular insults, including increased temperature, oxidative stress, glucose deprivation, chemical exposure, I/R injury, ultraviolet radiation, and infectious agents such as LPS. Third, HSPs are ancient, highly conserved molecules that have been identified in virtually every organism, both prokaryotic and eukaryotic, that have

been examined to date. Fourth, HSPs are highly immunomodulatory and have the capacity to mediate the induction of peptide-specific immunity. For example, as molecular chaperones, HSPs bind to many peptides derived from the cells from which they are isolated. HSP-peptide complexes elicit potent T cell responses against the chaperoned peptide as well as the cell type from which the chaperoned peptide is derived, including tumors and viruses, and vaccination with HSP-tumor peptide complexes as an immunotherapy for cancer is an active area of investigation. [33, 34]Similarly, HSP-pathogen derived peptide complexes have the capacity to elicit a pathogen-specific immune response. [33] Finally, HSPs themselves, especially members of the Hsp70 (HSPA) andHsp60 (HSPD) families, have the capacity to activate the host innate immune response, resulting in dendritic cell activation and maturation, activation of complement, and release of proinflammatory cytokines.[35, 36, 37]

Stressed apoptotic tumour cells express heat shock proteins and elicits tumour – specific immunity:

The mechanism by which a cell dies determines whether an immune response will be generated. [38, 39]Recent studies have documented that apoptotic tumor cells have low immunogenicity in vivo, whereas those that die by necrosis can generate an antitumor response. [40] This may be due in part to the high expression of inducible heat shock protein (HSP) 70 found in necrotic but not apoptotic cells.[40] Because apoptotic tumor cells apparently do not increase the expression of HSPs during their demise, we hypothesized that stressing the cells before apoptosis may recreate the danger signal to which antigen-presenting cells (APCs) are primed to respond. Stressed apoptotic tumor cells express HSP72 and HSP60 on their cell surface, and these cells elicit an antitumor response.

Microbial Heath shock proteins

Bacterial hsp are examples of bacterial Ags that are immunologically dominant, despite a high degree of homology with their host self counterparts. It has been suggested that the immune system may have a vested interest in setting a focus on the recognition of some of these conserved bacterial Ags. [41] Evidence is mounting that hsp are critical Ags in the regulation of certain chronic inflammatory diseases, and are important both in disease induction and in protection from disease. [42] However, it is unknown whether or not such effects of immune regulation would be restricted to hsp or that, alternatively, all conserved and immunogenic bacterial Ags would share these properties.

CONCLUSION

This review has attempted to summarize evidence for a functional role of hsp and its immune response. And have been proved with evidences and references that the HSP plays very important role in protecting as well as affecting our health. It is also responsible in a way for cardiovascular diseases and also auto immune disorders. The chaperone which is the word used to describe the biological function of HSPs also acts as an antigen in infections and in autoimmune disorders.

REFERENCES

1. Ritossa F, A new puffing pattern induced by temperature shock and DNP in drosophila, Cellular and Molecular Life Sciences (CMLS), 18(12), 1962, 571–573.
2. Ritossa F, Discovery of the heat shock response, Cell Stress Chaperones, 1(2), 1996, 97–8.
3. Schlesinger MJ, Heat shock proteins, The Journal of Biological Chemistry, 265(21), 1990, 12111–12114.
4. Sarto C, Binz PA, Mocarelli P, Heat shock proteinsin human cancer, Electrophoresis, 21(6), 2000, 1218-26.
5. Arrigo AP, In search of the molecular mechanism bywhich small stress proteins counteract apoptosis during cellular differentiation, J Cell Biochem, 94(2), 2005, 241-6.
6. Hansen JJ, Bross P, Westergaard M, et al., Genomic structure of the human mitochondrial chaperoningenes: HSP60 and HSP10 are localised head to headon chromosome 2 separated by a bidirectional promoter, Hum. Genet, 112 (1), 2003, 71–7.
7. Itoh H, Komatsuda A, Ohtani H, et al., MammalianHSP60 is quickly sorted into the mitochondria under conditions of dehydration, Eur. J. Biochem, 269(23), 2002, 5931–8.
8. Panjwani N, Akbari O, Garcia S, Brazil M,Stockinger B, The HSC73 molecular chaperone: involvement in MHC class II antigen presentation, JImmunol,163, 1999, 1936-1942.
9. Beere HM, Wolf BB, Cain K, Mosser DD,Mahboubi A, Kuwana T, Tailor P, Morimoto RI,Cohen GM, Green DR, Heat-shock protein 70inhibits apoptosis by preventing recruitment ofprocaspase-9 to the Apaf-1 apoptosome, Nat. CellBiol., 2(8), 2000, 469–75.
10. Ricaniadis N, Kataki A, Agnantis N, Androulakis G,Karakousis CP, Long-term prognostic significance of HSP-70, c-myc and HLA-DR expression inpatients with malignant melanoma, Eur J SurgOncol, 27 (1), 2001, 88–93.
11. U, Mahotka C, Heikaus S, Shibata T, Grimm MO, Willers R, Gabbert HE, Expression of heat shock protein 70 in renal cell carcinoma and its relation to tumor progression and prognosis, Histol. Histopathol. 22(10), 2007, 1099–107.
12. Csermely P, Schnaider T, Soti C, Prohászka Z, Nardai G, The 90-kDa molecular chaperone family: structure, function, and clinical applications. A comprehensive review, Pharmacol. Ther. 79(2), 1998, 129–68.
13. Wiech H, Buchner J, Zimmermann R, Jakob U,HSP90 chaperones protein folding in vitro, Nature,358 (6382),1992, 169–70.
14. Calderwood SK, Khaleque MA, Sawyer DB, CioccaDR, Heat shock proteins in cancer: chaperones oftumorigenesis, Trends Biochem. Sci., 31(3), 2006,164–72.
15. Eustace BK, Sakurai T, Stewart JK, Yimlamai D,Unger C, Zehetmeier C, Lain B, Torella C, HenningSW, Beste G, Scroggins BT, Neckers L, Ilag LL, JayDG, Functional proteomic screens reveal an essential extracellular role for HSP90 alpha incancer cell invasiveness, Nat. Cell Biol., 6(6), 2004, 507–14.

16. Kaufmann SHE. Heat shock proteins and the immune response. Immunol Today. 11, 1990, 129–136.

17. Lamb JR, Bal V, Mendez-Samperio A, et al. Stress proteins may providea link between the immune response to infection and autoimmunity. IntImmunol. 1, 1989, 191–196.

18. De Graeff-Meeder ER, van der Zee R, Rijkers GT, et al. Recognition of human 60 kD heat shock protein by mononuclear cells from patients with juvenile chronic arthritis. Lancet. 337, 1991, 1368–1372.

19. Stinissen P, Vandevyver C, Medaer R, et al. Increased frequency of __T cells in cerebrospinal fluid and peripheral blood of patients with multiple sclerosis: reactivity, cytotoxicity, and T cell receptor V genere arrangements. J Immunol. 154, 1995, 4883–4894.

20. Tun RYM, Smith MD, Lo SSM, et al. Antibodies to heat shock protein65 kD in type 1 diabetes mellitus. Diabetic Med. 11, 1994, 66–70.

21. Voellmy R. Transduction of the stress signal and mechanisms of transcription alregulation of heat shock/stress protein gene expression in higher eukaryotes. Crit Rev Eukaryotic Gene Expression. 4, 1994, 357–401.

22. Xu Q, Schett G, Perschinka H, et al. Serum soluble heat shock protein60 is elevated in subjects with atherosclerosis in a general population. Circulation. 102, 2000, 14–20.

23. Wright BH, Corton J, El-Nahas AM, et al. Elevated levels of circulating heat shock protein 70 (Hsp70) in peripheral and renal vascular disease. Heart Vessels. 15, 2000, 18–22.

24. Liao D-F, Jin Z-G, Baas AS, et al. Purification and identification of secreted oxidative stress-induced factors from vascular smooth musclecells. J Biol Chem. 275, 2000, 189–196.

25. Kaufmann, S. H. E. 1991. Heat shock proteins and pathogenesis of bacterial infections. Springer Semin. Immunopathol. 13, 25–36.

26. Kaufmann, S. H. E., and B. Schoel. 1994. Heat shock proteins as antigensin immunity against infection and self, p. 495–531.

27. Kaufmann, S. H. E., and B. Schoel. 1994. Heat shock proteins as antigensin immunity against infection and self, p. 495–531. In R. I. Morimoto, A. Tissieres, and C. Georgopoulos (ed.), The biology of heat shock proteins and molecular chaperones. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.

28. Shinnick, T. M. 1991. Heat shock proteins as antigens of bacterial and parasitic pathogens. Curr. Top. Microbiol. Immunol. 167, 145–160.

29. Matthews, R., and J. Burnie. 1992. The role of hsp90 in fungal infection. Immunol. Today 133, 345–348.

30. Mougdil, K. D., and E. Sercarz. 1994. The T cell repertoire against self determinants and its involvement in autoimmunity and cancer. Clin. Immunol. Immunopathol. 73, 283–289.

31. Theofilopoulos, A. N. 1995. The basis of autoimmunity. I. Mechanisms of abberant self-recognition. Immunol. Today 16, 90–98.

32. Shanafelt, M. C., P. Hindersson, C. Soderberg, N. Mensi, C. W. Turck, D. Webb, H. Yssel, and G. Peltz. 1991. T cell and antibody reactivity with the Borrelia burgdorferi 60-kDa heat shock protein in lyme arthritis. J. Immunol.146, 3985–3992.

33. Pockley AG. Heat shock proteins as regulators of the immune response. Lancet. 362, 2003, 469-76.

34. Tamura Y, Peng P, Liu K, Daou M, Srivastava PK. Immuno therapy of tumors with autologous tumor-derived heat shock protein preparations. Science 278, 1997, 117-20.

35. Panjwani NN, Popova L, Srivastava PK. Heat shock proteins gp96and hsp70 activate the release of nitric oxide by APCs. J Immunol 168, 2002, 2997-3003.

36. Prohaszka Z, Singh M, Nagy K, et al. Heat shock protein 70 is apotent activator of the human complement system. Cell Stress Chaperones. 7, 2002, 17-22.

37. Feng H, Zeng Y, Graner MW, Katsanis E. Stressed apoptotic tumorcells stimulate dendritic cells and induce specific cytotoxic T cells.Blood 100, 2002, 4108-15.

38. Forsdyke DR. Heat shock proteins as mediatorsof aggregation-induced 'danger' signals: implicationsof the slow evolutionary fine-tuning of sequencesfor the antigenicity of cancer cells. CellStress Chaperones. 4, 1999, 205-210.

39. Matzinger P. Tolerance, danger, and the extendedfamily. Annu Rev Immunol. 12, 1994, 991-1045.

40. Melcher A, Todryk S, Hardwick N, Ford M, JacobsonM, Vile RG. Tumor immunogenicity is determined by the mechanism of cell death via induction of heat shock protein expression. Nat Med. 4, 1998, 581-587.

41. Cohen, I. R., and D. B. Young. 1991. Autoimmunity, microbial immunity and the immunological homunculus. Immunol. Today 12, 105.

42. Van Eden, W., R. van der Zee, L. S. Taams, A. B. J. Prakken, J. A. G. van Roon and M. H. M. Wauben. 1998. Heat-shock protein T cell epitopes trigger a spreading regulatory control in a diversified arthritogenic T cell response. Immunol. Rev. 164, 169.

Source of Support: Nil, **Conflict of Interest:** None.