Role of heat shock proteins in oral squamous cell carcinoma: A systematic review

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Background. Environmental and patho-physiologic stresses stimulate synthesis of heat shock proteins (HSPs) which enable the cell to survive and recover from stressful conditions, by as yet incompletely understood mechanisms. Heat shock proteins show an increased expression in a wide range of human cancers and have been associated with tumor cell proliferation, differentiation, invasion, metastasis, death, and recognition by the immune system. Yet the role of heat shock proteins in oral cancer is ambiguous. The objective of this review was to systematically assess the data available on the role of HSP expression in oral cancer with special reference to its role in diagnosis, prognosis and treatment.
Methods and Results. A systematic review of studies that investigated the HSP expression in oral squamous cell carcinoma using Scopus, Medline, Embase and Google scholar databases from their inceptions to 2013, without language restrictions was conducted. We selected 24 studies from which data extraction and validations were performed.
Conclusion. The literature search revealed differential expression of HSPs during oral tumorigenesis with implications for the specific role of HSPs in the pathogenesis of oral cancer. HSP expression has been regarded as an independent prognostic factor for oral squamous cell carcinoma patients and HSPs are being explored as potent vehicles for delivery of preventive and treatment vaccines in cancer and other diseases.

Key words: heat shock proteins, oral cancer, oral squamous cell carcinoma, molecular chaperones

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INTRODUCTION

Heat shock proteins are a group of highly conserved proteins which first came to fame as gene products whose expression is induced by heat and other stresses[1,2]. More recently the focus of research has shifted to understanding the roles of HSPs as molecular chaperones[3-5]. They are now known to play diverse roles, even in unstressed cells, in successful folding, assembly, intracellular localization, secretion, regulation, and degradation of other proteins[6]. Failure of these activities is thought to underlie numerous serious human diseases[7]. Heat shock proteins appear to play dual and contradictory roles in cancer pathogenesis. On the one hand, they endow tumor cells with stress resistance and also promote growth and survival of tumor cells by engaging misfolded or aggregated proteins involved in cell proliferation. However they can also promote tumor immunity by stimulating the innate immunity mechanisms and enhancing cross presentation of tumor antigens to lymphocytes[8].

In this article we have systematically reviewed the data available on the role of heat shock proteins (HSPs) expression in oral squamous cell carcinoma (OSCC) with special emphasis to their role in diagnosis, prognosis and treatment of the disease.

MATERIALS AND METHODS

The scheme used in the literature review was to identify all reports of investigations that had been undertaken to assess the role of Heat Shock Proteins in Oral Squamous Cell Carcinoma. A structured search was done of diverse subject-unique databases. The literature searches were done using short-string Boolean-based methodologies. Different Boolean search phrases were applied. These are denoted within < > brackets. The search phrase "operators" are presented in capital letters (e.g., < heat shock proteins AND cancer>). Various search terms were incorporated in the searches (e.g., "oral cancer", "oral squamous cancer", "heat shock proteins","chaperones" and "molecular chaperones"). All searches were free of bias and were unrestricted (i.e., excluded limits); thus, the explorations included all (a) fields (e.g., author and title), (b) languages, (c) dates, (d) subjects (e.g., humans and animals), and (e) database subject subsets (e.g., cancer and heat shock protein). The literature search, done using PubMed, Pub med central, Scopus, Medline, Embase and Google scholar databases identified articles published from 1995 to 2013.

The literature searches were extended by using the "Related Articles" link to articles recovered with PubMed. Thereafter, a search was done of the literature references cited in these articles to identify additional writings that reported the results of research defining the role of heat shock proteins in oral squamous cell carcinoma. At this

juncture, all articles were assembled and arranged in reverse chronological order. The articles were read, and off topic articles were excluded. By way of example, rejected articles included those that reported research on oral cancer other than heat shock proteins. Likewise, reports of investigations of heat shock proteins that were not associated with oral squamous cell carcinoma (e.g. oesophageal cancer) or had a more diverse group (e.g. head and neck cancer) were excluded.

RESULTS

A selection of 24 research articles was included for systematic review. Of these 17 research articles had used the immunohistochemical expression of HSPs in oral squamous cell carcinoma biopsy tissue, with 11 studies evaluating the concomitant HSP expression in dysplastic tissue and normal oral epithelium. The studies were read and on the basis of the role of heat shock proteins they were categorized under the following subheads: Implications in

Table 1. Implications in diagnosis of oral cancer.

HSP	Author	Tissue/Site	Findings
HSP70	Sugerman PB et al.[15]	Oral squamous cell carcinoma, dysplastic oral epithelium, benign oral mucosal lesions & normal mucosa	HSP 70 expression is not a definitive marker of oral malignancy
HSP 70	Kaur J et al.[16]	Normal, premalignant and malignant oral mucosa	Increasing levels with carcinogenesis, in poorly differentiated OSCC, > clinical stage The median transition time (premalignancy to malignancy) was significantly shorter in HSP70 over expressing cases
HSP 70	Kaur J et al.[14]	Oral dysplasia and cancer	p53-HSP70 complex formation may be one of the mechanisms of stabilisation of p53 protein resulting in its increased levels in potentially malignant and malignant oral lesions and may be implicated in oral carcinogenesis.
HSP27, 60, 70, 90&p53	Ito et al.[17]	TONGUE, normal epithelium, dysplasia and carcinoma	HSP27, 90: 1 in dysplastic lesions: no correlation with clinical stage; p53
HSP 70	Kaur J et al.[18]	Human oral squamous carcinoma cells (HSC-2 cell line)	HSP70 is required for proliferation and survival of oral tumor cells.
HSP 27	Leonardi R et al.[19]	Fetal, normal and inflammed oral mucosal epithelium, oral premalignant lesions & OSCC	HSP27 immunolabelling was down-regulated in poorly differentiated areas and up-regulated in highly differentiated ones.
HSP 27	Mese H et al.[20]	OSCC	no correlation between HSP27 expression and clinical stage, lymph node metastasis and histological grade
HSP 27	Lo Muzio L et al.[21]	OSCC & normal	no significant correlation between HSP27 expression, sex and tm size
HSP 70	Lee SS et al.[22]	OSCC & normal	high HSP70 expression was found in poorly differentiated tumor groups
HSP 70	Markopoulos AK et al.[23]	OSCC, Lekoplakia with dysplasia & normal oral tissue	Intensely expressed in OSCC, positive in dysplastic lesions negative in normal oral tissue Increased HSP70 immunoexpression could be a marker for the presence of epithelial dysplasia or epithelial malignant transformation.
HSP 27	Wang A et al.[24]	Tongue, normal, dysplastic and OSCC	A significant inverse correlation was observed between HSP27 expression and grading
HSP 27, 60 and 70	Tekkesin et al.[25]	OSCC	HSP 70 &27 showed increased expression during tumorigenesis in OSCC
HSP 70	Thubashini et al.[26]	OSCC, OSMF	Increase in HSP70 expression from OSMF to OSCC Inc HSP exp >50yrs in OSCC pts No association with gender , habits and duration of habits

diagnosis (Table 1), Implications in prognosis (Table 2) and Therapeutics implications (Table 3). It was noted that most studies in Table 1 and 2 were retrospective studies using immunostaining techniques. Whereas the studies on therapeutic implications were done on oral squamous cell carcinoma cell lines using flowcytometry or other methods such as RNA transfection.

DISCUSSION

HSPs are now also more generally known as stress proteins because they are induced in response to a wide variety of physiological and environmental insults[9]. The HSPs are categorized as molecular chaperones, proteins, which have in common the property of modifying the structures and interactions of other proteins[10]. Mammalian HSPs have been classified into 5 families according to their molecular weight: HSP110, HSP90, HSP70, HSP60 and the family of small HSPs (ref.[9]). Among the different HSPs, the ATP-dependent chaperone families HSP70 and HSP90 are the most studied by their involvement in cancer[9]. In our review we found that amongst all the HSPs the role of HSP70 in oral cancer had been explored the most, followed by HSP 27, HSP 90 and HSP 60.

HSP expression is tailored for induction by the stress response, and the proximal signal for HSP induction is apparently the accumulation of denatured proteins[11]. The molecular mechanisms responsible for over expression of heat-shock proteins in cancer cells are yet to be understood but may be tumor specific[12]. Suggested hypothesis is that the physiopathological features of the tumor microenvironment (low glucose, pH, and oxygen) tend toward HSP induction[13]. Another proposed mechanism states that oncoproteins may appear during carcinogenesis (e.g., mutated p53), and these mutated conformationally altered proteins may elicit an HSP response. Kaur J et al.[14] (1996) proposed that p53-HSP70 complex formation may be one of the mechanisms of stabilisation of p53 protein resulting in its increased levels in potentially malignant and malignant oral lesions and may be implicated in oral carcinogenesis.

DIAGNOSTIC IMPLICATIONS OF HSP IN ORAL CANCER

HSP expression was analyzed in relation to the histopathological characteristics of the tumor tissues (e.g. grade of differentiation), with the expression of other molecules (e.g. mutated p53), and with patient parameters like sex and age. In addition, HSP expression has been evaluated in the spectrum of normal, premalignancy to malignancy. Table 1 summarizes the work done in context with the diagnostic implications of the HSPs in cancer.

The following inferences were derived by analyzing the available data. (a) HSP expression levels can help indicate the presence of abnormal changes during the

Table 2. Implications in prognosis of oral cancer.

HSP	Author	Tissue/Site	Findings
HSP 70	Kaur J et al.[1]	Normal, premalignant and malignant oral mucosa	Elevated levels of HSP70 showed decreased median disease-free survival time (no recurrence/metastasis)
HSP27, 60, 70, 90&p53	Ito T et al.[2]	TONGUE, normal epithelium, dysplasia and carcinoma	No correlation with survival
HSP 27	Mese H et al.[26]	OSCC	Expression of HSP27 correlated inversely with survival period. Considered an independent prognostic factor
HSP 27	Lo Muzio L et al.[27]	OSCC & normal	reduced HSP27 expression had poorer survival
HSP 27	Lo Muzio L et al.[28]	OSCC	HSP27 reduced expression is an early marker of poor prognosis, useful in identifying aggressive biological behaviour in OSCC cases
HSP 70	Lee SS et al.[29]	OSCC & normal	low HSP70 expression was associated with lymph node metastasis
HSP 27	Wang A et al.[30]	Tongue, normal, dysplastic and OSCC	reduced expression of HSP27 is correlated with poor overall survival
HSP70	Fourati et al.[31]	OSCC tongue	None of the markers p53, HSP70, Ki67, and CD34 demonstrated prognostic significance for 5-year survival
HSP 90, GRP78	Huang TT[32]	OSCC cell lines (OC2 and OCSL)	Decreased GRP78 protein expression was significantly correlated with advance tumor stage and neck lymph node metastasis
HSP 70	Tavassol F et al.[33]	OSCC	T1 &T2 tumors of OSCC with low expression of HSP70 require more radical treatment

process of carcinogenesis. For example, HSP70 is intensely expressed in OSCC, shows increased expression in premalignant lesions and is not expressed in normal oral mucosa[23].

(b) HSP expression correlates with the degree of differentiation in oral cancer. Most studies show an increased HSP70 expression in poorly differentiated oral squamous cell carcinoma. Most studies on HSP 27 in oral squamous cell carcinoma revealed a strong association with decreased expression of HSP27 being linked to poor tumor differentiation[24,25] although some studies showed no correlation between HSP27 expression and histological grade[20].

HSP70 has been involved not only with poor tumor differentiation but also with higher clinical stage[15] and advanced age[26].

(c) HSPs are co-expressed in cancer tissues. In addition, certain HSPs can be significantly associated with other molecules. For example, co-immunoprecipitation of p53 and HSP70 in potentially malignant lesions (dysplasia) and oral squamous cell carcinomas (SCCs). This co-expression is suggestive of a physical association, resulting in p53-HSP70 complex formation[14].

(d) HSPs are not particularly useful in diagnostic immunopathology since they are expressed in a wide range of malignant cells and tissues[13].

PROGNOSTIC IMPLICATIONS OF HSP IN ORAL CANCER

Heat shock proteins have been shown to be necessary for survival and proliferation of oral tumor cells[18] and their association with oral carcinogenesis and differentiation of tumor cells is also well established. Therefore, it was logical to study the prognostic implications of HSPs in order to establish their role as markers which can be used to predict treatment outcomes and survival rates of the patient.

On evaluating the available literature (Table 2) we found that most studies associated poor prognosis of oral cancer patients with decreased expression of HSPs (ref.[21,22,24]). Although some authors correlated HSP expression inversely with survival time[16,21]. A few other studies demonstrated to prognostic correlation with HSP expression[17]. These variable results may be accountable for the fact that Heat shock proteins till date are not in the list of useful prognostic markers in oral cancer.

THERAPEUTIC IMPLICATIONS

Intracellular HSPs have a protective role in allowing cells to survive potentially lethal conditions largely attributable to their anti-apoptotic properties. HSP 27, HSP70 and HSP90 can directly interact with different proteins of the tightly regulated programmed cell death machinery and thereby block the apoptotic process at distinct key points[9]. In cancer cells, the remarkably increased HSP

Table 3. Implications in therapuetics of oral cancer.

HSP	Author	Tissue/Site	Findings
HSP 70	Kaur J et al.[34]	Human oral squamous carcinoma cells (HSC-2 cell line)	HSP70 is required for proliferation and survival of oral tumor cells
HSP 27	Yonekura et al.[35]	OSCC cells	HSP27 plays a significant role in the IFN-gamma-induced sensitization of oral SCC cells to anticancer drugs.
HSP60 and 70	Atre et al.[36]	Oral cancer patients	HSP60 and 70 stimulation induces NO formation and apoptosis of γδT lymphocytes.
HSP 70	Lee SS et al.[37]	OSCC & normal	HSP70 expression is significantly upregulated in areca quid chewing-associated OSCC and arecoline-induced HSP70 expression was downregulated by NAC, curcumin, PD98059, and staurosporine.
HSP 90	Kim et al.[38]	HOK-Bmi-1/E6 Immortalized cell population	Physical interaction between HSP90 and the hTERT promoter occurs in telomerase-positive cells but not in normal human cells.
HSP 27	Lee SS et al.[39]	OSCC & normal	HSP 27 expression is significantly elevated in areca quid chewing-associated OSCCS. HSP27 expression was downregulated by EGCG, NS398, NAC, quercetin, PD98059, and SB203580
HSP 27	Kim J[40]	Human OSCC KB cell cultures	Down regulation of HSP27 inhibits apoptotic pathway

expression has been accounted for rendering cancer cells resistance to chemotherapy.

In contrast to intracellular HSPs, extracellularly located or membrane-bound HSPs mediate immunological functions. They can elicit an immune response providing a link between innate and adaptive immune systems[9].

In context to oral cancer therapeutics it was found that most research was done on OSCC cell lines and focussed on the extracellular HSPs exploiting their carrier function for immunogenic peptides. The following inferences were drawn from the studies (Table 3). HSPs are vital to survival and proliferation of oral tumor cells. Studies by yonekura et al. showed HSPs 27 over expression in oral squamous cell carcinoma cell lines and resistance to apoptotic stimuli conferring a poorer prognosis. IFN-gamma downregulates HSP 27 expression and therefore promotes cells to a proapoptotic state and / aborted apoptosis. The authors suggest combining INF gamma with other anticancer drugs and propose that HSP 27 may be a useful marker of sensitivity to anticancer drugs in OSCC.

Studies carried out by Atre et al. demonstrated a novel strategy adapted by oral tumor cells to escape immune recognition. They explained the paradoxical role of HSPs in immune recognition by activated γδT lymphocytes of tumor cells and also subsequent apoptosis induced cell death of these γδT lymphocytes. Kim et al suggested that HSP 27 might contribute to regulating photodynamic therapy induced apoptosis in the photodynamic therapy resistant oral tumor cells. They recommended targeting HSP 27 as an adjunctive therapy to photodynamic therapy.

CONCLUSION

Our analysis of heat shock proteins in oral cancer indicated an immense role for HSP in many aspects of tumor progression and response to therapy. Although at the diagnostic level HSPs did not seem very relevant, they were found to be helpful biomarkers for carcinogenesis in oral cancer tissues and point towards their degree of differentiation and aggressiveness.

The established anti-apoptotic function of HSPs 27, 70 and 90 explains their increased expression in cancer cells. Yet the surface and extracellular HSPs constitute an important arm of adaptive and innate immune responses against cancer cells. This dual role of HSPs depending on their intracellular or extracellular location may be a big challenge in cancer therapy.

The comprehension of the role of HSPs in oral squamous cell carcinomas is still in an early stage, and little tangible information is available on how HSP affects the molecular events involved with tumor proliferation and invasiveness. More research will be necessary in order to correctly construe the role of HSPs in oral cancer and targeting HSPs in oral cancer therapy.

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REFERENCES

1. Ritossa F. Discovery of the heat shock response. Cell Stress Chaperones1996;1:97-8.
2. Lindquist S. The heat-shock response. Annu Rev Biochem 1986;55:1151-91.
3. Gething MJ, ed. Guidebook to Molecular Chaperones and Protein-Folding Catalysts. Oxford, UK: Oxford Univ. Press; 1997.
4. Thomas PJ, Qu BH, Pedersen PL. Defective protein folding as a basis of human disease. Trends Biochem Sci 1995;20:456-9.
5. Bonorino C, Souza AP. HSP70 in Tumors: Friend or Foe? Heat Shock Proteins in Cancer. Volume 2, Springer Netherlands; 2007. p.191-208.
6. Joly AL, Wettstein G, Mignot G, Ghiringhelli F, Garrido C. Dual role of heat shock proteins as regulators of apoptosis and innate immunity. J Innate Immun 2010;2(3):238-47.
7. Beckmann RP, Mizzen LE, Welch WJ. Interaction of HSP 70 with newly synthesized proteins: implications for protein folding and assembly. Science 1990;248(4957):850-4.
8. Voellmy R. On mechanisms that control heat shock transcription factor activity in metazoan cells. Cell Stress Chaperones 2004;9:122-33.
9. Mosser DD, Morimoto RI. Molecular chaperones and the stress of oncogenesis. Oncogene. 2004;23(16):2907-18.
10. Ciocca DR, Calderwood SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 2005;10(2):86-103.
11. Kaur J, Srivastava A, Ralhan R. p53-HSP70 complexes in oral dysplasia and cancer: potential prognostic implications. Eur J Cancer B Oral Oncol 1996;32B(1):45-9.
12. Sugerman PB, Savage NW, Xu LJ, Walsh LJ, Seymour GJ. Heat shock protein expression in oral epithelial dysplasia and squamous cell carcinoma. Eur J Cancer B Oral Oncol 1995;31B(1):63-7.
13. Kaur J, Das SN, Srivastava A, Ralhan R. Cell surface expression of 70 kDa heat shock protein in human oral dysplasia and squamous cell carcinoma: correlation with clinicopathological features. Oral Oncol 1998;34(2):93-8.
14. Ito T, Kawabe R, Kurasono Y, Hara M, Kitamura H, Fujita K, Kanisawa M. Expression of heat shock proteins in squamous cell carcinoma of the tongue: an immunohistochemical study. J Oral Pathol Med 1998;27(1):18-22.
15. Kaur J, Kaur J, Ralhan R. Induction of apoptosis by abrogation of HSP70 expression in human oral cancer cells. Int J Cancer 2000;85(1):1-5.
16. Leonardi R, Pannone G, Magro G, Kudo Y, Takata T, Lo Muzio L. Differential expression of heat shock protein 27 in normal oral mucosa, oral epithelial dysplasia and squamous cell carcinoma. Oncol Rep 2002;9(2):261-6.
17. Mese H, Sasaki A, Nakayama S, Yoshioka N, Yoshihama Y, Kishimoto K, Matsumura T. Prognostic significance of heat shock protein 27 (HSP27) in patients with oral squamous cell carcinoma. Oncol Rep 2002;9(2):341-4.
18. Lo Muzio L, Leonardi R, Mariggiò MA, Mignogna MD, Rubini C, Vinella A, Pannone G, Giannetti L, Serpico R, Testa NF, De Rosa G, Staibano S. HSP 27 as possible prognostic factor in patients with oral squamous cell carcinoma. Histol Histopathol 2004;19(1):119-28.
19. Lee SS, Tsai CH, Ho YC, Chang YC. The upregulation of heat shock protein 70 expression in areca quid chewing-associated oral squamous cell carcinomas. Oral Oncol 2008;44(9):884-90.
20. Markopoulos AK, Deligianni E, Antoniades DZ. Heat shock protein 70 membrane expression in oral cancer: a possible new target in antineoplastic therapy? Chemotherapy 2009;55(4):211-4.
21. Wang A, Liu X, Sheng S, Ye H, Peng T, Shi F, Crowe DL, Zhou X. Dysregulation of heat shock protein 27 expression in oral tongue squamous cell carcinoma. BMC Cancer 2009;9:167.

22. Tekkeşin MS , Mutlu S, Aksakalli N, Olgaç O. Expression of heat shock proteins 27, 60 and 70 in oral carcinogenesis: An immunohistochemical study. Türk Onkoloji Dergisi 2011;26(3):115-20.
23. Thubashini M, Malathi N, Kannan L. Expression of heat shock protein70 in oral submucous fibrosis and oral squamous cell carcinoma: An immunohistochemical study. Indian J Dent Res 2011;22:256-9.
24. Kaur J, Das SN, Srivastava A, Ralhan R. Cell surface expression of 70 kDa heat shock protein in human oral dysplasia and squamous cell carcinoma: correlation with clinicopathological features. Oral Oncol 1998;34(2):93-8.
25. Ito T, Kawabe R, Kurasono Y, Hara M, Kitamura H, Fujita K, Kanisawa M. Expression of heat shock proteins in squamous cell carcinoma of the tongue: an immunohistochemical study. J Oral Pathol Med 1998;27(1):18-22.
26. Mese H, Sasaki A, Nakayama S, Yoshioka N, Yoshihama Y, Kishimoto K, Matsumura T. Prognostic significance of heat shock protein 27 (HSP27) in patients with oral squamous cell carcinoma. Oncol Rep 2002;9(2):341-4.
27. Lo Muzio L, Leonardi R, Mariggiò MA, Mignogna MD, Rubini C, Vinella A, Pannone G, Giannetti L, Serpico R, Testa NF, De Rosa G, Staibano S. HSP 27 as possible prognostic factor in patients with oral squamous cell carcinoma. Histol Histopathol 2004;19(1):119-28.
28. Lo Muzio L, Campisi G, Farina A, Rubini C, Ferrari F, Falaschini S, Leonardi R, Carinci F, Stalbano S, De Rosa G. Prognostic value of HSP27 in head and neck squamous cell carcinoma: a retrospective analysis of 57 tumors. Anticancer Res 2006;26(2B):1343-9.
29. Lee SS, Tsai CH, Ho YC, Chang YC. The upregulation of heat shock protein 70 expression in areca quid chewing-associated oral squamous cell carcinomas. Oral Oncol 2008;44(9):884-90.
30. Wang A, Liu X, Sheng S, Ye H, Peng T, Shi F, Crowe DL, Zhou X. Dysregulation of heat shock protein 27 expression in oral tongue squamous cell carcinoma. BMC Cancer 2009;9:167.
31. Fourati A, El May MV, Ben Abdallah M, Gamoudi A, Mokni N, Goucha A, Boussen H, Ladgham A, El May A. Prognostic evaluation of p53, heat shock protein 70, Ki67, and CD34 expression in cancer of the tongue in Tunisia. J Otolaryngol Head Neck Surg 2009;38(2):191-6.
32. Huang TT, Chen JY, Tseng CE, Su YC, Ho HC, Lee MS, Chang CT, Wong YK, Chen HR. Decreased GRP78 protein expression is a potential prognostic marker of oral squamous cell carcinoma in Taiwan. J Formos Med Assoc 2010;109(5):326-37.
33. Tavassol F, Starke OF, Kokemüller H, Wegener G, Müller-Tavassol CC, Gellrich NC, Eckardt A. Prognostic significance of heat shock protein 70 (HSP70) in patients with oral cancer. Head Neck Oncol 2011;3:10.
34. Kaur J, Kaur J, Ralhan R. Induction of apoptosis by abrogation of HSP70 expression in human oral cancer cells. Int J Cancer 2000;85(1):1-5.
35. Yonekura N, Yokota S, Yonekura K, Dehari H, Arata S, Kohama G, Fujii N. Interferon-gamma downregulates HSP27 expression and suppresses the negative regulation of cell death in oral squamous cell carcinoma lines. Cell Death Differ 2003;10(3):313-22.
36. Atre N, Thomas L, Mistry R, Pathak K, Chiplunkar S. Role of nitric oxide in heat shock protein induced apoptosis of gammadeltaT cells. Int J Cancer 2006;119(6):1368-76.
37. Lee SS, Tsai CH, Ho YC, Chang YC. The upregulation of heat shock protein 70 expression in areca quid chewing-associated oral squamous cell carcinomas. Oral Oncol 2008;44(9):884-90.
38. Kim RH, Kim R, Chen W, Hu S, Shin KH, Park NH, Kang MK. Association of HSP90 to the hTERT promoter is necessary for hTERT expression in human oral cancer cells. Carcinogenesis 2008;29(12):2425-31.
39. Lee SS, Tsai CH, Ho YC, Yu CC, Chang YC. Heat shock protein 27 expression in areca quid chewing-associated oral squamous cell carcinomas. Oral Dis 2012;18(7):713-9.
40. Kim J, Jung H, Lim W, Kim S, Ko Y, Karna S, Kim O, Choi Y, Choi H, Kim O. Down-regulation of heat-shock protein 27-induced resistance to photodynamic therapy in oral cancer cells. J Oral Pathol Med 2013;42(1):9-16.