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Systematic Review

The Role of Heat Shock Protein 70 Expression in Oral Potentially Malignant Disorders

Farzaneh Pakdel [1], Sepideh Bohlouli [1], Hasti Farokhnia [1], Fatemeh Pournaghi Azar [2], Fatemeh Salehnia [3], Paria Motahari [1] *

[1]Department of Oral and Maxillofacial Medicine, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Operative Dentistry, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Tabriz University of Medical Sciences, Tabriz, Iran.

*** Corresponding Author:** Paria Motahari, Assistant Professor, Department of Oral Medicine, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran. Email: Paria.motahari@yahoo.com

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Abstract

Introduction: Oral Potentially Malignant Disorders (OPMD) are chronic conditions that can progress to malignancy. Heat Shock Proteins (HSP) are a group of proteins that act as molecular chaperones. Actually, HSPs can promote the growth of tumor cells. On the other hand, they stimulate immune response against tumor cells. In this review it has been aimed to identify the role of HSP70 expression in the diagnosis and prognosis of OPMD.

Methods: In this systematic review study, all English and Persian articles with the keywords of "oral lichen planus", " Leukoplakia ", " Oral Submucous Fibrosis ","heat shock protein 70", " oral premalignant disorders " along with their Persian equivalents were searched from Google scholar, PubMed, science direct, Cochrane, Scopus and Sid databases until March 2020. The quality of the selected studies were evaluated by the Newcastle-Ottawa scale method.

Results: Totally, 20 articles were selected and reviewed. The results of this study showed that there was an overexpression of HSP70 in OPMD. A significant correlation of HSP70 expression was observed with the severity of epithelial dysplasia. Actually, the expression of HSP70 can be a marker for the presence of dysplasia in OPMD.

Conclusion: Enhanced HSP70 levels in pre-malignant and malignant cells suggests that not only the oncogenes and tumorsuppressor genes are involved in the process of oral carcinogenesis, but HSP70s may also be implicated in tumorigenesis. Taking all these into account, it can be supposed that in the future, HSP70 can be a target for an anticancer immunotherapy.

Keywords: Heat Shock Protein 70, Leukoplakia, Oral Lichen Planus, Oral Premalignant Lesion, Oral Submucous Fibrosis

Introduction

Oral Squamous Cell Carcinoma (OSCC) is the common malignancy of the mouth, which is more common in men.[1] The survival rates of OSCC are low, and they vary among societies and age groups. Therefore, early identification seems to be important to improve the treatment and survival of this disorder.[2]

Oral Potentially Malignant Disorders (OPMD) are chronic conditions that precede OSCC.[3] Many etiological factors are related to the development of OPMD; however, the main associated factors are tobacco and alcohol. These disorders are associated with genetic changes that may lead to OSCC transformation.[4]

Oral Leukoplakia (OL), Oral Erythroplakia (OE), Oral Submucous Fibrosis (OSMF) and Oral Lichen Planus (OLP) are the main disorders that are known as OPMDs. The OL and OE are associated with smoking and alcohol drinking which are commonly reported in western countries.[5] The OSMF is most commonly reported in areca nut users; therefore, its prevalence is higher among Asian countries.[6] The OLP is a recurrent inflammatory disorder of the skin and mucous membranes, and there is little evidence of the risk of malignant transformation.[7, 8]

Diagnosis of OPMD depends on the individual's history, clinical evaluation, and histopathological confirmation of epithelial changes.[9] According to the World Health Organization (WHO) classification, epithelial dysplasia is graded as mild, moderate, or severe, based on the degree of cytological atypia in the epithelial layer.[1] Histopathological examination is the gold standard for the diagnosis of OPMD. Based on the clinical and histological findings, clinicians can find the prognosis of the patient and plan the correct treatment.[10] Red lesions have a higher risk of malignant transformation.[9] The malignant transformation rates of OPMD vary by the subtypes of OPMD and degrees of epithelial dysplasia.[11] A meta-analysis reported a malignant transformation rate of approximately 12% for oral dysplasia.[12]

Heat Shock Proteins (HSPs) are a group of highly conserved proteins which expression is induced by heat and other stresses[13]. More recently the attention of investigation has shifted to understanding the roles of HSPs as molecular chaperones[14-16]. They are now known to play diverse roles, even in successful folding, intracellular localization,

secretion, regulation, and the degradation of other proteins.[17] Failure of these actions is believed to trigger several diseases.[18] It appears that HSPs play dual and contradictory roles in cancer pathogenesis. On the one hand, they tolerate tumor cells with resistance to stress and also help the growth and survival of tumor cells by attractive misfolded or accumulated 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.[19] Altered expression of HSP has been reported in OPMD. Since clinical and histopathological features alone cannot predict that malignant premalignant lesions remain stable, regress or progress to malignancy, identification of molecular markers may be helpful in predicting disease. In this article we have systematically reviewed the data available on the role of HSPs expression in OPMD with special emphasis to their role in the diagnosis and prognosis of the disease.

Materials and Methods

Search Strategy

This systematic review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews. [20]

In this review study, all published English and Persian articles with the keywords of "oral lichen planus" and "Leukoplakia" and "Oral Submucous Fibrosis" and "heat shock protein 70"and "oral premalignant disorders" and their Persian equivalents from Google scholar, PubMed, science direct, Cochrane, Scopus and Sid databases were searched until March 2020. In the initial phase, duplicate articles were excluded from the study. Then, the titles and abstracts of the articles were reviewed by two independent individuals based on the inclusion and exclusion criteria. Disagreements were resolved with the third author's discussion. Next, the full text of the selected articles was reviewed and articles which were completely relevant to the subject of the study were selected. Endnote X5 resource management software was used to organize, study titles and abstracts as well as to identify duplicates. The quality of the studies were evaluated by the Newcastle-Ottawa scale method.[21] The data of the selected articles were extracted using the data extraction form. This form includes the author's name / year of publication and the results of the studies.

Inclusion Criteria: Studies that have investigated the expression of the HSP70 in patients with OPMD.

Exclusion criteria: Review and case report articles, cell culture models and animal studies and studies that have investigated the HSP70 levels in the serum of patients with OPMD.

Results

The Selection of Included Studies

In an initial search, 503 articles were extracted. From among these articles, 81 were excluded from the study in the first step due to duplication. From the 26 articles obtained after reviewing the abstracts, finally 20 appropriate articles were included in this study based on the entry and exit criteria (Figure 1). The characteristics of the included studies and their results are shown in Table 1.[22-41]

The Characteristics of Included Studies

Among the 20 studies which had examined the level of HSP70 in OPMD, four studies were related to the expression of this protein in OLP which in three studies, an increase in HSP70 expression was observed compared to normal mucosa.[23,32,38] Twelve studies examined the expression of HSP70 in oral leukoplakia which in only one study,[24] there was a significant decrease in the expression of HSP70 compared to the control group, and in the other studies, there was a significant increase in the expression of this protein.[22,25-29,33,34,37,39,41] These studies showed that the expression of HSP70 can be a marker for the presence of dysplasia in oral leukoplakia and with increasing severity of dysplasia, the expression of HSP70 also increases significantly. In the other four studies, the expression of HSP70 was evaluated in other OPMD that were less common (OSMF, verrucous hyperplasia, tobacco pouch keratosis), and in all of them, the expression of HSP70 had increased.[31,35,36,40]

Diagnostic Implications of HSP70 in OPMD

The HSP70 expression levels can help indicate the presence of abnormal changes during the process of carcinogenesis. Actually, HSP70 intensely expressed in OSCC, shows an increased expression in the premalignant lesions and is not expressed in normal oral mucosa.[22-26]

Prognostic Implications of HSP70 in OPMD

Follow up studies have found out that HSP70 overexpression increases the risk of transition of premalignant lesions to malignancy.[28] Also, HSP70 expression correlates with the degree of dysplasia in OPMD. Most studies show an increased HSP70 expression in OPMD with severe dysplasia.[28,34,39,41]

Therapeutic Implications of HSP70 in OPMD

The P53-HSP70 complexes exist in both premalignant lesions and oral tumors suggesting that the association between p53 and HSP70 is an early occurrence in the process of oral tumorigenesis.[26] With this in mind, HSP70 can be a target for an anticancer immunotherapy.

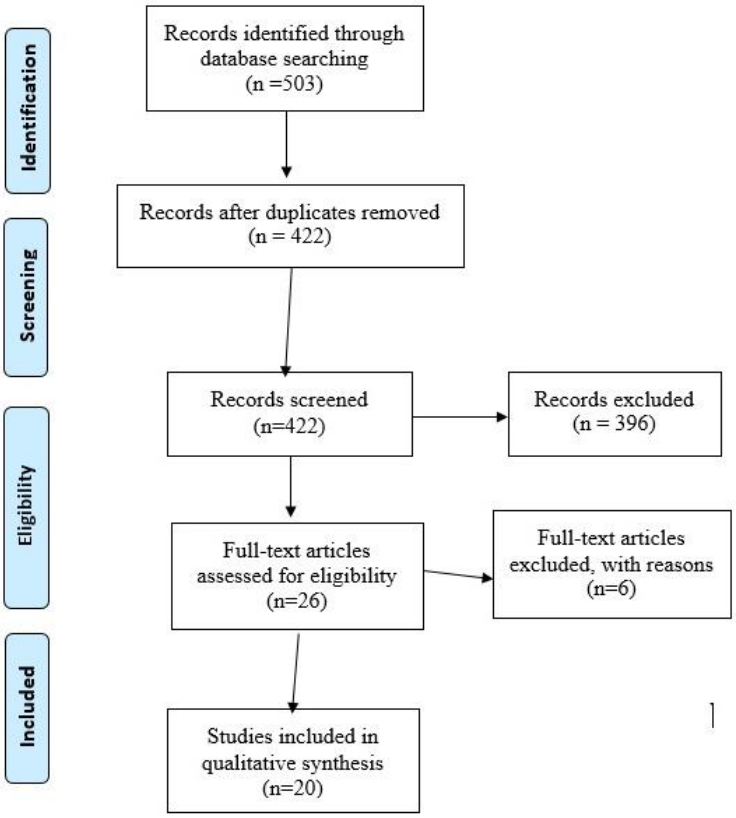

Figure1. The flowchart of searching strategy based on PRISMA guidelines

Table 1. Results of included studies in this review study.

Authors	Year	Results
Sugerman et al.[22]	1995	The intensity of HSP 70 expression in section of normal oral mucosa is less than that in oral epithelial dysplasia
Sugerman et al.[23]	1995	Epithelial HSP 70 staining intensity is greater in OLP lesions than in normal oral mucosa and that there are differences in the distribution of HSP 70 expression between the two groups.
Bramanti et al.[24]	1995	Hsp70 staining was observed at a less intense level in Leukoplakia than in controls.
Kaur et al. [25]	1995	Mild to moderate HSP70 expression was observed in oral dysplastic lesions (19/30) and basal low level of HSP70 was observed in normal oral tissues.
Kaur et al.[26]	1996	P53-HSP70 complex formation was observed in 19/52 cases of oral carcinoma and l0/53 cases of potentially malignant lesions (leukoplakia). Normal oral mucosa did not show the presence of p53-HSP70 complexes (O/20 cases).
Kaur et al.[27]	1998	The normal oral tissue specimens from cancer free patients showed a low percentage of HSP70 positive cells in comparison with dysplasia.
Kaur et al.[28]	1998	Overexpression of HSP70 protein was observed in 38 of 64 dysplastic lesions. A significant correlation of HSP70 expression was observed with severity of dysplasia and consumption of betel and tobacco.
Ito et al.[29]	1998	In the dysplastic lesions examined in this study, HSP70 were positively stained. In normal and hyperplastic mucosa around the tumors, HSP70 stained positively in the suprabasal cell layer
Chaiyarit et al.[30]	1999	No difference in HSP70 expression was evident between OLP and fibromas.
Merne et al.[31]	2002	A greater proportion of positive nuclei were detected in snuff users' samples than in control samples, which may be due to cellular stress caused by snuff.
Seoane et al.[32]	2004	It is concluded that there are no statistically significant differences in HSP70 expression between OLP and normal buccal mucosal specimens. The expression of HSP70 was significantly higher in oral leukoplakia than in OLP.
Seoane et al.[33]	2006	It is concluded that the nuclear HSP70 immunoexpression could be an objective marker for the presence of the epithelial dysplasia in Leukoplakia.
Markopoulos et al.[34]	2009	Dysplastic lesions were positive to a lesser extent for HSP70. Samples from normal oral tissue were negative for HSP70. Moreover, the expression of HSP70 in leukoplakias with dysplasia points to HSP70 immunoreactivity as a marker of oral malignant potential.
Thubashini et al.[35]	2011	Out of 30 samples of oral submucous fibrosis, weak heat shock protein70 expression was observed in 20 cases; and intense heat shock protein70 expression, in 10 cases. This intense heat shock protein70 expression was observed in advanced cases of oral submucous fibrosis (Pindborg histological criteria).

Lin et al.[36]	2011	HSP 70 was expressed mainly in the cytoplasm of parabasal and spinous cells of oral verrucous hyperplasia samples.
Tekkesin et al.[37]	2011	9 cases of oral mucosa (45%) and 20 cases of leukoplakia(100%) showed HSP70 overexpression
Tyagi et al. [38]	2012	An increased expression of HSP70 was noted in the basal and suprabasal cells of the epithelium of OLP. A higher count and intensity of HSP70 expression was seen in the basal layer of the epithelium.
Patil et al.[39]	2015	Cytoplasmic HSP70 expression was seen in 93% (28/30) of oral dysplastic lesions and in 20% (6/30) of normal oral mucosa. Significant difference was seen in the HSP70 expression between controls and mild, moderate and severe dysplasia.
Das et al.[40]	2018	By Immunohistochemical and proteomic analysis Hsp-70 1B exhibited higher expression in OSMF tissues compared to the control tissues.
Priyanka et al.[41]	2019	Among 15 cases of leukoplakia as the grade of dysplasia (mild, moderate, and severe dysplasia) increased the intensity and/or distribution of the staining increased; suggesting a positive association between HSP70 expression and severity of dysplastic lesions.

HSP70: heat shock protein70; OLP: oral lichen planus; OSMF: oral submucous fibrosis

Discussion

Early detection of OPMD lesions is very important in preventing the progression of these lesions and cancerous changes.[4] It can be mentioned that HSPs are overexpressed in a wide range of human cancers and are involved in tumor cell proliferation, differentiation and metastasis. They are useful biomarkers for tissues carcinogenesis.[42,43] Experimental evidence suggests that HSPs can stimulate tumorigenesis by suppressing apoptosis.[44] Also, it seems to be associated with mutations of the p53 gene and support the proliferation effect.[45]

Studies have aimed to determine the expression of the HSP70 in OPMD. An altered expression of HSP70 in epithelial cells have been reported in OLP.[23,24,30] When the OLP lesion has advanced, the types of cytokines produced by T lymphocytes could have up-regulated the HSPs gene expression in the nearby basal keratinocytes, and lead to lesion chronicity.[23, 30] This hypothesis suggests that OLP may be an autoimmune disease that HSPs act as an autoantigen.[23]

Several studies have shown that the expression of HSP70 in the oral dysplastic lesion increased when compared to normal epithelial mucosa. [22, 26-29, 32-34] In dysplastic oral lesions that positively stained with HSP70, suprabasal epithelial cells were immunostained for HSP70 and staining intensity increased with the severity of dysplastic changes.[25, 27, 33, 34] A significant increase in the cell surface expression of HSP70, in contrast to their normal intracellular site was detected as the tissue progressed from normal to dysplasia towards carcinoma.[25,27]

There was no significant relationship between HSP70 expression and clinical parameters like age, sex, site of the lesion. However, Kaur *et al.*[28] reported a significant association between HSP70 overexpression and habit of consumption of tobacco and betel with areca nut. Tobacco consumption causes an increased production of reactive free radicals as well as immunosuppression.

A significant increase in the expression of HSP70 was observed where the tissue progressed from OSMF to OSCC. This shows that stress plays an important role as a predisposing factor for OSMF and its following progression to OSCC. [35]

It can be stated that HSP70 is a molecular chaperone known to interact with mutantp53. Actually, it is the antigen presenter for p53 and is also involved in the translocation of mutant p53 from nucleus to the surface membrane. overexpression of mutant p53 and HSP70 proteins, detection of p53-HSP70 complexes and cell surface expression of HSP70 in oral premalignant and malignant lesions indicates that HSP70 has a role not only in the translocation of mutant p53 but also in stimulating the immune response against p53 during oral malignancy.[26] lin *et al.*[36] have reported that HSP70 might sequestrate the wild-type p53 protein in the cytoplasm, causing a decrease in the transport of functional wild-type p53 protein into the nuclei of epithelial cells of oral verrucous hyperplasia lesions. Enhanced HSP70 levels in pre-malignant and malignant cells may reflect immunological activation and/or chronic cellular stress.

These reports show poor agreement in the expression patterns of HSP70 in cytoplasm, nucleus, and cell surface. The discrepancy in these investigations may be related to immunohistochemical methods, which highlight the importance of controls within and standardization between studies and analysis procedures. Bearing in mind that HSP70 expression may occur in the early stages of oral tumorogenesis and that any degree of epithelial dysplasia (even a mild form) indicates an increased risk of malignant transformation for the patients, further research is needed on the capability of nuclear expression of HSP70 for classifying borderline situations between no dysplasia and oral epithelial dysplasia and also on the relationships between HSPs' expression and clinical outcomes (progression to carcinoma).

Most studies have shown that the expression levels of HSP70 in OPMD was higher than normal mucosa, which varied according to the type of precancerous lesion and the degree of dysplasia.[34-41] This means HSP70 expression levels can be used in the diagnosis of OPMD, but the limitation is that HSPs are expressed in a wide range of malignant cells and inflammatory tissues.[25] Moreover, in most studies, high expression of HSP70 was associated with a poor prognosis of

oral lesions,[34-41] although in a few studies this finding was not found.[24,30] These variable results may be accountable for the fact up to now, HSP70 are not in the list of useful prognostic markers in oral dysplasia

Conclusion

It can be concluded that the HSP70s are over expressed in a wide range of normal tissues and neoplasms and they are useful biomarkers for carcinogenesis. Enhanced HSP70 levels in pre-malignant and malignant cells suggests that not only the oncogenes and tumor suppressor genes are involved in the process of oral carcinogenesis, but that HSP70s may also be implicated in tumorigenesis. Taking all these into account, we can suppose that in the future, HSP70 can be a target for an anticancer immunotherapy.

Authors' Contributions

All authors contributed equally to this study.

Conflicts of Interests

The authors declare no potential conflict of interest with respect to the authorship and/or publication of this study.

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