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Expression of survivin in oral submucous fibrosis and oral squamous cell carcinoma

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Abstract
Introduction: Oral squamous cell carcinoma (OSCC) is the most common malignant tumor of the oral cavity and up to one third (3-33%) of oral precancerous lesions will eventually evolve into invasive OSCC. Survivin is a smallest member of the Inhibitor of Apoptosis (IAP) family of proteins which play an important role in apoptosis regulation. High expression of survivin is considered as an early event of carcinogenesis and may provide a useful tool for the identification of precancerous lesions at higher risk of progression into invasive carcinoma. The present study aims to evaluate the expression of survivin in oral submucous fibrosis and oral squamous cell carcinoma and also compares the expression of survivin in different histopathological grades of OSCC.
Methods and Material: 15 patients with oral squamous cell carcinoma, 15 patents with oral sub mucous fibrosis were selected as subjects for the present study and 15 patients with normal oral mucosa were selected as controls and all were evaluated for expression of survivin. All sections were H & E stained and were studied immunohistochemically for the expression of survivin. Statistical analysis carried out with Chi square test.
Results: Significant survivin expression was detected in oral submucous fibrosis and oral squamous cell carcinoma (P<0.001). Expression of Survivin was significant when compared with different histopathological grades of OSCC.
Conclusion: Expression of survivin in oral submucous fibrosis may indicate potential risk of malignant transformation.

Keywords: Oral submucous fibrosis, oral squamous cell carcinoma, survivin

Introduction
Oral squamous cell carcinoma (OSCC) is the most common malignant tumor of the oral cavity and the seventh most frequent cancer in humans. Most of the OSCC lesions arise from premalignant lesions and conditions. Oral submucous fibrosis (OSMF) is a chronic precancerous condition with a malignant potential ranging from 7-13%. A prophylactic surgical management of premalignant condition like oral submucous fibrosis is often impractical. Therefore, novel molecular predictors of malignant progression are needed to identify oral precancerous lesions and conditions at greater risk of invasive transformation.
Survivin is a recently characterized smallest member of the Inhibitor of Apoptosis (IAP) family of proteins. The gene encoding Survivin is located on chromosome 17q25 in humans. Among the IAP family members, Survivin has certain unique characteristics. The first is its structure which contains 142 amino acids, approximately 16.5 kDa, with a single baculovirus IAP repeat domain and lack of zinc binding C terminal Really Interesting New Gene (RING) finger domain and a caspase recruitment domain. The second is its dual role as a bifunctional protein [1]. Biological functions of Survivin include inhibition of apoptosis through several pathways and proper execution of mitosis and cell division. Survivin can directly interact with caspases leading to the inhibition of caspase activity. In addition to its anti-apoptotic function, Survivin can form a complex with Aurora B kinase and the inner centromere protein, called INCENP, during the Gap2/Mitotic phase (G2/M) of the cell cycle to help in the proper segregation of chromosomes. Several signalling pathways have been involved in the regulation of Survivin expression such as transforming growth factor β (TGF) and p53 signalling pathways [2]. Survivin also plays a role in promoting cell proliferation and angiogenesis [3]. Unlike other IAP proteins, Survivin is expressed during embryonic and fetal development and may be important in tissue homeostasis and differentiation. However,

Survivin is completely downregulated and undetectable in normal, terminally differentiated adult tissues, and becomes prominently expressed in most of the common human cancers, including cancer of the lung, colon, stomach, esophagus, uterus, ovary, pancreas, prostate, breast, melanoma skin cancer, hepato cellular carcinoma, odontogenic keratocysts, high grade non hodgkins lymphoma,. High Survivin expression in tumors correlates with more aggressive and invasive clinical phenotype [4, 5]. survivin plays an important role during the malignant transformation of OSMF and may provide an indication to early prevention and diagnosis in the progression of OSMF [6]. The present study was conducted to observe the expression of Survivin in oral submucous fibrosis and oral squamous cell carcinoma. This study also compares the expression of survivin intensity with respect to different histological grades of oral squamous cell carcinoma.

Materials and method

15 patients of oral squamous cell carcinoma, 15 patients of oral submucous fibrosis were selected as subjects for the present study. 15 apparently normal persons were taken as controls for the study. All sections were H & E stained and were studied immunohistochemically for the expression of survivin at the Department of Pathology, Osmania General Hospital, Hyderabad, Telangana.

The oral cavity was examined under artificial light. The presence of mucosal abnormality was identified and recorded for oral squamous cell carcinoma (Fig.1) and oral submucous fibrosis. (Fig.2) The details of the history and the clinical findings were recorded in the proforma.

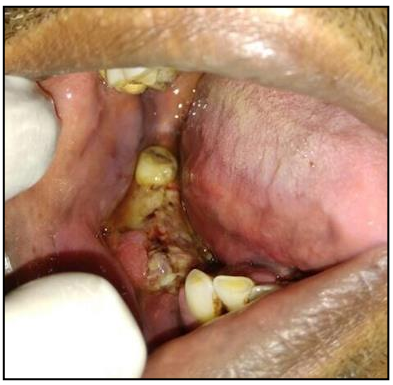

Fig 1: Carcinoma alveolus of the mandible

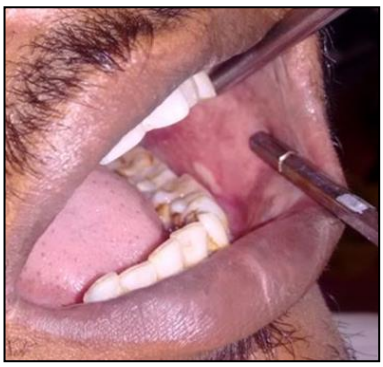

Fig 2: blanching with ulceration of buccal mucosa in OSMF

Biopsy

Incisional biopsy was performed under local anesthesia to confirm the clinical diagnosis of oral squamous cell carcinoma and oral submucous fibrosis.

Immunohistochemistry

All sections were H & E stained and were studied immunohistochemically for the expression of survivin at the Department of general pathology, Osmania general hospital, Hyderabad.

Results

The expression of survivin was evaluated immunohistochemically and compared with controls. Expression of survivin was evaluated based on percent of cells expressing survivin and grading was given according to that.

0 = negative, less than 5% of cells staining.

+1 = weak staining, between 5% and 25% of cells staining.

+2 = moderate staining, between 25% and 50% of the cells staining.

+3 = strong staining, more than 50% of cells staining.

15 Oral squamous cell carcinoma patients selected as subjects. The age of OSCC patients ranged from 34 to 76 years. The youngest patient was 34 years old and the oldest patient was 76 years. The average age was 47.6 years. Particulars are showed in the Table 1. Among 15 OSCC patients 3 females (20%) and 12 were males (80%). The particulars are shown in Table 2.

Table 1: Mean age distribution among the study population (age in years)

Group	Number	Minimum	Maximum	Mean	SD
SCC	15	34	76	47.67	12.18
OSMF	15	18	50	28.67	8.81
Normal	15	20	40	26.27	5.65
Total	45	18	76	36.16	12.74

Table 2: Sex distribution among the study population

Group		Frequency	Percent
SCC	F	3	20.00
	M	12	80.00
OSMF	F	2	13.33
	M	13	86.67
Normal	F	6	40.00
	M	9	60.00
TOTAL	F	24	34.8
	M	45	65.2

Out of 15 patients of Oral Squamous Cell Carcinoma 14 patients showed weak to strong expression i.e. 93.34% patients showed expression and 1 patient showed negative expression i.e. 6.67%. Out of 14 patients, 7 patients showed weak staining i.e. 46.7%, 4 patients showed moderate expression i.e. 26.7% and 3 patients showed strong expression i.e. 20%. (Fig.3) The particulars are shown in the Table 3.

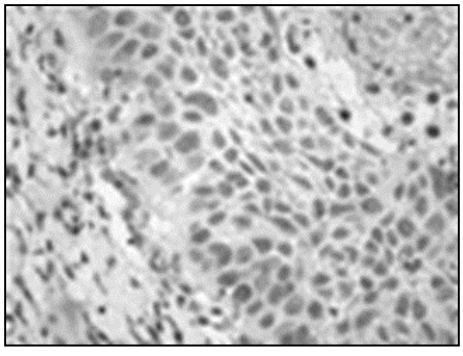

Fig 3: Expression of survivin

Table 3: Survivin expression among different categories (Chi Square test)

Group	Expression				p-value
	0	1	2	3	
SCC	1	7	4	3	<0.001
	6.7%	46.7%	26.7%	20.0%	
OSMF	8	7	0	0	
	53.3%	46.7%	.0%	.0%	
Normal	15	0	0	0	
	100.0%	.0%	.0%	.0%	

Out of 15 OSCC subjects 8 were well differentiated, 4 were moderately differentiated, 3 were poorly differentiated. Out of 8well diiferentited OSCC cases, 7 showed week surviving (+1) expression, 1 showed negative (0) expression. All the moderately differentiated OSCC subjects showed moderate survivin (+2) expression, all the poorly differentiated OSCC subjects showed strong surviving (+3) expression. These results indicate that surviving expression increases as the OSCC differentiation decreases. Particulars are shown in Table 4.

Table 4: Expression of survivn in different histopathological grades of SCC (Chi Square test)

SCC group	Expression				p-value
	0	1	2	3	
MDSCC	0	0	4	0	<0.001
	0	0	100	0	
PDSCC	0	0	0	3	
	0	0	0	100	
WDSCC	1	7	0	0	
	12.5	87.5	0	0	

Out of 15 controls, all controls i.e. 100% showed negative expression or no expression results were statistically analyzed by Chi square test. There was a significant difference in the distribution of expression among the groups of Oral Squamous Cell Carcinoma and controls. Majority of Oral Squamous Cell Carcinoma patients had some form of expression and 100% of the normal subjects did not show the expression which was highly significant (P<0.001).Particulars are shown in Table 3.

Oral Submucous Fibrosis

15 Oral Submucous Fibrosis patients selected as subjects. The age of oral submucous fibrosis patients range from 18 to 50 years with an average age of 28.7 years. The youngest patient was 18 years old and oldest was 50 years. 2 patients were in the age group of 11 to 20 years i.e. 13.34%, 8 were in the age group of 21 to 30 years i.e. 53.34%, 3 patients were in the age group of 31 to 40 i.e. 2% and 2 patients were in the age group of 41 years and above i.e. 13.34%. Particulars are shown in Table 1.

Among 15 Oral Submucous Fibrosis patients 13 were males i.e. 86.67% and 2 were females i.e. 13.34%. The particulars were shown in Table 2.

15 apparently normal patients were selected as controls and expression of survivin was compared with Oral Submucous Fibrosis patients. Out of 15 patients of Oral Submucous Fibrosis 8 patients showed negative or no expression (grade = 0) i.e. 53.3%, 7 patients showed weak expression (grade = 1) i.e. 46.7% and none of the patients were in the category of moderate or strong expression.

Out of 15 controls, all controls i.e. i.e. 100% showed negative expression or no expression. Particulars are shown in Table 3.

Expression of survivin among Oral Submucous Fibrosis and controls was compared and statistically analyzed by Chi square test, the expression was highly significant (P<0.001). Particulars are shown in Table 3.

Discussion:

Survivin, also called baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5, is a protein that, in humans, is encoded by the BIRC5 gene. As a member of the IAP family, Survivin functions to inhibit caspase activation, thereby leading to the negative regulation of apoptosis or programmed cell death. This has been shown by the disruption of Survivin induction pathways leading to an increase in apoptosis and decrease in tumor growth. Many studies on clinical specimens have shown that survivin expression is invariably up-regulated in human cancers and is associated with resistance to chemotherapy or radiation therapy, and linked to poor prognosis, suggesting that cancer cells survive with survivin [7].

There is a significant differential expression of survivin observed in cancer versus normal tissues, and is unlike any other IAPs. Survivin is strongly and broadly expressed in embryonic and fetal organs, however, becomes undetectable in most terminally differentiated normal tissues [8]. Survivin expression has been shown in various preneoplastic and benign lesions including polyps of the colon, breast adenomas, nearly all cases of Bowen's disease, cervical dysplasia, and hypertrophic actinic keratosis suggesting that expression of Survivin may occur early during malignant transformation [9]. Dramatic overexpression of Survivin has been demonstrated in prostate cancer, rectal cancer, esophageal squamous cell carcinoma, colorectal carcinoma, breast cancer, laryngeal squamous cell carcinoma, hepatocellular carcinoma, ovarian carcinoma, non-small cell lung carcinoma, glioblastoma, and pancreatic cancer which signal more aggressive and disseminated disease and unfavorable clinical outcome [10, 11]. Among the head and neck cancers, Survivin was expressed in brain tumours, OSCC [12, 13], B-cell lymphomas [14, 15], salivary gland cancer [16], and soft tissue sarcomas [17, 18].

Survivin was also found to be expressed in oral premalignant lesions and conditions as well as in odontogenic cysts [19-21]. Its overexpression in premalignancy suggests an early event during step-wise malignant transformation, and in head and neck cancers reflects the biologic aggressiveness of these tumours. Survivin has a definite role in tumor progression in OSCC and may provide prognostic information [22].

In a study, OSCC together with lymph node metastasis were analyzed for expression of Survivin by immunohistochemistry and Western blotting, it was found that Survivin expression was increased in poorly-differentiated tumors, and patients with low Survivin expression had better survival rates than the groups with medium and high Survivin expression [10]. In the present study the expression of survivn evaluated immunohistochemically with respect to differentiation grades of OSCC and the results showed that all the poorly differentiated OSCC cases i.e 3 cases (100%) showed strong suvivin expression (+3), all the moderately differentiated OSCC cases i.e.4 cases (100%) showed moderate survivin expression (+2) in, and 7 out of 8 (87.5%) well differentiated OSCC cases showed weak survivin expresiion(+1). These results indicate as the differentiation of cells in squamous cell carcinoma decreases there is increased expression of survivin.

In a study by Lo Muzio *et al*. [22] in 2003, the presence of survivin was noted in 33% of precancerous lesions and in 94% of pre-cancerous lesions which became malignant.

Survivin positivity was 100% in all malignancies which progressed from oral submucous fibrosis [23]. In the present study weak expression (+1) of suvivin noted in 46.7% of OSMF cases. The present study concludes that the expression of survivin in oral submucous fibrosis may indicate potential risk of malignant transformation. To further validate survivin as a prognostic marker, a large scale study with greater sample size along with clinical follow-up data is needed.

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