RESEARCH ARTICLE

Tissue expression of SKA1 (Spindle kinetochore-associated complex 1) in oral cancers and oral potentially malignant disorders: An association with disease progression

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Abstract

Objective: To determine the tissue expression of spindle kinetochore-associated complex sub-unit 1 in both oral squamous cell carcinomas and oral potentially malignant disorders, and to evaluate its association with the two lesions.

Method: The analytical, cross-sectional study was conducted at Dow University of Health Sciences, Karachi, and comprised clinically and histopathological confirmed biopsy samples of oral squamous cell carcinoma and oral dysplasia that were collected from the Otolaryngology ward/outpatient department of Dr Ruth Pfau Civil Hospital Karachi, Dr Ishrat-ul-Ebad Khan Institute of Oral Health Sciences, Karachi, and the histopathology section of Dow Diagnostic Reference and Research Laboratory, Karachi, during July 2022 and April 2023. Detailed clinical history as well as radiological and histopathological findings were noted. Tissue expression of spindle kinetochore-associated complex sub-unit 1 was analysed on the samples through immunohistochemistry. Data was analysed using SPSS 21.

Results: Of the 90 cases, 45(50%) had oral squamous cell carcinoma; 34(75.6%) males, 11(24.4%) females, 24(53.3%) aged <50 years and 21(46.7%) aged >50 years. The remaining 45(50%) cases had oral potentially malignant disorders; 35(77.8%) males, 10(22.2%) females, 24(53.3%) aged <50 years and 21(46.7%) aged >50 years. Tissue expressions of spindle kinetochore-associated complex sub-unit 1 were strongly positive in 25(55.6%) cases of oral squamous cell carcinoma and 13(28.9%) cases of oral potentially malignant disorders. Moderately positive expressions were seen in 20(44.4%) cases of oral squamous cell carcinoma and 32(71.1%) cases of oral potentially malignant disorders ($p<0.05$). In oral squamous cell carcinoma cases, strong tissue positivity was observed in poorly differentiated tumours compared to moderately differentiated and well-differentiated tumours ($p<0.05$). In cases of oral potentially malignant disorders, strong positivity was seen in grade III dysplasia compared to grades I and II ($p<0.05$).

Conclusion: There was a significant difference between tissue expressions of spindle kinetochore-associated complex sub-unit 1 in oral squamous cell carcinoma and oral potentially malignant disorders, and this difference was more pronounced in different tumour grades of oral squamous cell carcinoma and in varying grades of dysplasia in oral potentially malignant disorders.

Keywords: Oral squamous cell carcinoma, Oral potentially malignant disorders, Immunohistochemistry.

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Introduction

Squamous cell carcinoma (SCC) of the lip and oral cavity is amongst the most common cancers, especially in Asian countries, including Pakistan, where the prevalence is quite high in both genders.[1] The Dow cancer registry in Karachi reported 4,400 new oral cancer cases between 2010 and 2019, making it the most common cancer among males, and the second to breast cancer among females.[2] There is an increased mortality rate associated with oral cancer as a result of its aggressiveness and early loco-regional spread. In our region, oral SCC (OSCC) patients usually present at stage III/IV compared to stage I/II, and, like many other malignancies, early-stage cancers have a better prognosis than advanced stages.[3,4] Hence, a timely diagnosis of oral cancer at the initial stages of oral carcinogenesis may have positive implications over its prognosis. Widespread use of smokeless tobacco (SLT) in Pakistan has been the most important factor in the surge of OSCC.[5] Studies have shown that consumption of SLT carcinogens leads to changing of the normal epithelium into dysplastic epithelium, clinically known as oral potentially malignant disorders (OPMDs). The most frequently reported OPMDs include leukoplakia, erythroplakia and oral sub-mucous fibrosis (OSMF).[6,7] Researches point to a greater tendency among these lesions for malignant transformation over the passage of time.[8,9]

Spindle kinetochore-associated complex sub-unit 1 (SKA1)

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is a cell cycle regulatory protein that regulate the progression of cell cycle by maintaining the structure of microtubule. During cell cycle, it facilitates the timely transition of metaphase to anaphase. Recent studies have highlighted its role as an oncogene involved in the early carcinogenesis, progression and invasion of tumour.[10] Studies have documented SKA1's role in the pathogenesis of various tumours, including OSCC,[11] hepatocellular carcinoma (HCC),[12] gliomas,[13] prostate carcinoma,[14] gastric carcinoma,[15] bladder carcinoma,[16] adenoid cystic carcinoma,[17] oesophageal carcinoma[18] and non-small lung carcinoma.[19] A study on papillary thyroid carcinoma reported increased tissue expression of SKA1 in advanced clinical stage, extra thyroidal invasion, and there is also an increased rate of recurrence of tumour in patients who have over-expressed levels of SKA1.[20] Another study on gastric carcinoma cell lines reported that SKA1 represents a molecular marker for early gastric carcinogenesis. Functional experiments involving SKA1 knockdown based on small interfering ribonucleic acid (siRNA) showed a significant inhibition of cancer cell proliferation and progression that validates the role of this gene in tumour formation.[15]

To our knowledge, there is a gap in literature regarding the role of SKA1 as a predictor of malignant transformation of OPMDs into OSCC, and there is no study available that estimated the immunohistochemical (IHC) tissue expression of SKA1 in OSCC and OPMD cases simultaneously. The current study was planned to fill the gap in literature by determining the tissue expression of SKA1 in OSCC and OPMD, and to evaluate its association with the two lesions.

Patients and Methods

The analytical, cross-sectional study was conducted at Dow University of Health Sciences (DUHS), Karachi, and comprised OSCC and oral dysplasia samples that were collected from the Otolaryngology ward/outpatient department (OPD) of Dr Ruth Pfau Civil Hospital Karachi, Dr Ishrat-ul-Ebad Khan Institute of Oral Health Sciences, Karachi, and the histopathology section of Dow Diagnostic Reference and Research Laboratory (DDRRL), Karachi, during July 2022 and April 2023. The sample size was determined using PASS version 11[21] based on 95% confidence interval (CI) and 80% power of the test, while the effect size[11] between tumour-node-metastasis (TNM) stage and SKA1 was kept at 0.345 degree of freedom.[1] However, considering the study duration, feasibility of recruitment, and available resources, the OSCC sample size target could not be met. A group of OPMD cases was created for the purpose of discerning potential differences between SKA1 expression in malignant and potentially malignant lesions. Approval was taken from Dow University of Health Sciences Ethics Review Committee. The data and tissue samples were collected using non-probability purposive sampling and simple random sampling techniques. The inclusion criteria comprised of clinically and histopathological confirmed cases of OSCC and oral dysplasia. Patients who received chemotherapy and radiotherapy were excluded.

The tissue samples of OSCC and OPMD were taken at the time of biopsy and surgery. These samples were placed in 10% buffered formalin. The formalin-fixed tissue samples were sectioned, and tissue blocks were made that were subjected to different processes, including tissue processing, embedding, cutting and haematoxylin and Eosin (H&E) staining. The H&E-stained tissue slides were reviewed by two histopathologists. After confirmation from the histopathologists, the formalin-fixed paraffin-embedded (FFPE) tissue samples were immune-stained. The IHC staining process included cutting of 3-4µm FFPE tissue blocks, cutting/mounting onto glass slides and then heating at 50°C for 20 minutes. The sections then went through de-paraffinisation and hydration process, followed by antigen retrieval through pressure cooker method for which citric acid buffer was used. The slides were then washed with phosphate buffer saline (PBS) for 3 minutes and incubated with 3% hydrogen peroxide for 10 minutes. The sections were then washed three times with PBS for 3 minutes each, incubated with primary polyclonal antibody SKA1 (diluted as 1:100; Thermofisher Scientific, United States, Catalogue # PA5-85456). The sections were then incubated with secondary horseradish peroxidase (HRP)-conjugated anti-rabbit antibody for 30 minutes and washed with PBS. Finally, the slides were treated with diaminobenzidine (DAB) for 1 minute, rinsed with distilled water and counterstained with haematoxylin. For negative control, PBS was used instead of the SKA1 antibody.

Results of IHC staining were estimated by two different histopathologists, who were blinded to the demographic and clinical data of the patients. The staining pattern of SKA1 was evaluated by intensity and the proportion of cells that had nucleus and cytoplasmic staining. The staining evaluation protocol was based on a study by Zhao et al11. The proportion of cells (cell immunopositivity) was calculated as: 0-10% positive cells, score 0; 11-30% positive cells, score 1; 31-70% positive cells, score 2; and 71-100% positive cells, score 3. The staining intensity was calculated as: bright yellow, score 0; yellow, score 1; brown, score 2; and dark brown, score 3. The final scores were calculated by multiplying stain intensity score with immunopositivity score and were documented as: negative score 0; weakly positive score 1; moderately positive- score 2-4; and

strongly positive score 6-9.[11]

In view of moderate and strongly positive staining of SKA1, two groups were generated; moderately positive score 2-4), and strongly positive score 6-9.

Data was analysed using SPSS 21. To compare the expression levels of SKA1 between the groups, and to examine the association of SKA1 tissue expression with various clinic-pathological parameters, chi-square test was used. The Fisher Exact test was used when the expected cell counts were <5. P<0.05 was considered statistically significant.

Results

Of the 90 cases, 45(50%) had oral squamous cell carcinoma; 34(75.6%) males, 11(24.4%) females, 24(53.3%) aged <50 years and 21(46.7%) aged >50 years. The remaining 45(50%) cases had oral potentially malignant disorders; 35(77.8%) males, 10(22.2%) females, 24(53.3%) aged <50 years and 21(46.7%) aged >50 years.

Table-1: SSKA1 tissue expression in OSCC and oral potentially malignant disorders cases.

Groups	n	Moderately positive Score (2-4)	Strongly positive Score (6-9)	*p*-value
OSCC	45	20 (44.4%)	25 (55.6%)	0.01
OPMDs	45	32 (71.1%)	13 (28.9%)	

SKA1: Spindle kinetochore-associated complex 1, OSCC: Oral squamous cell carcinomas, OPMD: Oral potentially malignant disorders.

Table-2: Comparison of SKA1 tissue expression with clinico-pathological parameters of OSCC cases.

Groups	Moderately Positive **SKA1** [n(%)]	Strongly Positive **SKA1** [n(%)]	Total	*p*-value
Gender				
Male	15(44.1)	19 (55.9%)	34	0.93
Female	5(45.5)	6 (54.5)	11	
Age (years)				0.96
< 50	8 (33.3)	16 (66.7)	24	
>50	12 (57.1)	9(42.9)	21	
Risk Factors				0.06
Smoking	2 (40)	3 (60.0)	5	
SLT	12 (36.4)	21 (63.6)	33	
Both	6 (85.7)	1 (14.3)	7	
Histological Grading of Oral Cancer				<0.01
Grade I	3 (100.0)	0 (0.0)	3	
Grade II	17 (44.7)	21 (55.3)	38	
Grade III	0 (0.0%)	4 (100.0)	4	
TNM Staging				0.579
I	7 (58.3)	5 (41.7)	12	
II	1 (33.3)	2 (66.7)	3	
III	2 (22.2)	7 (77.8)	9	
IV	10 (47.6)	11 (52.4)	21	

SKA1: Spindle kinetochore-associated complex 1, OSCC: Oral squamous cell carcinomas, SLT: Smokeless tobacco, TNM: Tumour-Node-Metastasis.

Tissue expressions of SKA1 were strongly positive in 25(55.6%) cases of OSCC and 13(28.9%) cases of OPMDs. Moderately positive expressions were seen in 20(44.4%) OSCC and 32(71.1%) OPMD cases (p<0.05) (Table 1).

In OSCC cases, strong tissue positivity was observed in poorly differentiated tumours compared to moderately

Table-3: Comparison of SKA1 tissue expression with clinico-pathological parameters of OPMDs cases.

Groups	Moderately Positive SKA1 [n(%)]	Strongly Positive SKA1 [n(%)]	Total	*p*-value
Gender				
Male	26 (74.3)	9 (25.7)	35	0.44
Female	6 (60.0)	4 (40)	10	
Age (years)				0.96
< 50	17 (70.8)	7 (29.2)	24	
>50	15 (71.4)	6(28.6)	21	
Risk Factors				0.10
Smoking	1 (100.0)	0 (0.0)	1	
SLT	24 (64.9)	13 (35.1)	37	
Both	7 (100.0)	0 (0.0)	7	
Histological Grading of Dysplasia				< 0.001
Grade I	28 (96.6%)	1 (3.4%)	29	
Grade II	4 (66.7%)	2 (33.3%)	6	
Grade III	0 (0.0%)	10 (100.0%)	10	
Clinical Presentation				0.620
Leukoplakia	23 (67.6%)	11 (32.4%)	34	
Erythroplakia	6 (85.7%)	1 (14.3%)	7	
Oral Submucous Fibrosis	3 (75.0%)	1 (25.0%)	4	

SKA1: Spindle kinetochore-associated complex 1, OPMD: Oral potentially malignant disorders, SLT: Smokeless tobacco.

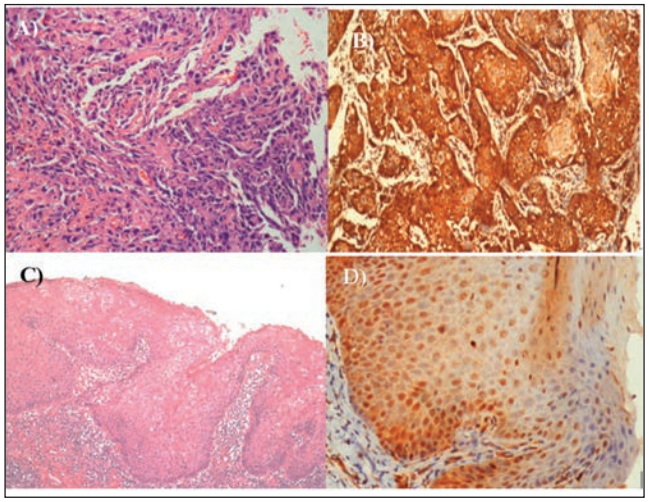

Figure: (A) Photomicrograph of poorly-differentiated oral squamous cell carcinoma (OSCC) (Hematoxylin and Eosin [H&E] x 200 magnification), (B) Photomicrograph of strong immunohistochemistry (IHC) staining of spindle kinetochore-associated complex 1 (SKA1) in poorly-differentiated OSCC (IHC x 200 magnification), (C) Photomicrograph of stratified squamous epithelium with mild dysplasia (H&E x 100 magnification), and (D) Photomicrograph of moderate staining of SKA1 in mild dysplasia (IHC x 200 magnification).

differentiated and well-differentiated tumours (p<0.05) (Table 2). In OPMD cases, strong positivity was seen in grade III dysplasia compared to grades I and II (p<0.05) (Table 3, Figure).

Discussion

The role of SKA1 in the malignant transformation of various solid tumours has been studied worldwide, and the gene is found primarily involved in tumour progression by controlling different signalling pathways, thereby impacting tumour cell growth and spread.[11-13] The upregulation of SKA1 is linked to unfavourable clinical prognosis, tumour invasion and metastasis in different types of tumours, such as non-small cell lung cancer (NSCLC), bladder cancer and HCC.[12,16,19]

Studies exploring SKA1 tissue expression in oral cancers are limited, and here is also a dearth of data about its expression in OPMDs that have been consistently labelled as fore-runners for malignant transformation in oral mucosa.[11] To our knowledge, the current study is the first to investigate SKA1 expression simultaneously in OSCC and OPMDs.

The study found SKA1 expression in OSCC tissue samples moderately positive in half of the cases, while it remained strongly positive in another quarter of the samples. Similarly, in OPMDs, about two-third of the cases stained moderately, and pme-third strongly positive. Furthermore, the study observed an overall increased expression of SKA1 in OSCC compared to OPMDs (p<0.05). While testing this association with risk factors and conventional clinic-pathological parameters of oral cancers, the study do not find any significant association except for tumour grade. The results are in concurrence with the findings of Zhao, Lijuan et al. However, they reported a significant increased expression of SKA1 in tumour stage IV.[11] The current study did not find any significant association between SKA1 tissue expression and clinical stage.

The worsening prognosis and recurrence of oral cancer has been more commonly reported in poorly-differentiated tumours.[22] In the current study, poorly-differentiated tumour cases scored strongly positive with SKA1 compared to the other grades. Similar findings were reported by Pu, Yan et al. in clear renal cell carcinoma, and by Sun, Wei et al. in gastric cancer.[15,23] Hence, based on these observations, SKA1 tissue expression may serve as a marker of tumour progression in early-stage oral cancers. However, further large-scale studies are warranted in this domain.

In OPMD cases, the current study found significant association of tissue SKA1 expression and histological grading of oral dysplasia, namely grade I to III dysplasia. There was a strong positive expression of SKA1 noted in grade III (severe dysplasia) tissue samples compared to the other grades of oral dysplasia. These results point towards the role of SKA1 as a predictive marker for malignant transformation in dysplastic oral lesions.

The possible mechanism behind SKA1's role in malignant transformation of OPMD lesions into OSCC remains unclear. However, studies have confirmed the involvement of Cyclin D1 in the process of malignant transformation of head and neck premalignant lesions into head and neck cancer.[24-26] Cyclin D1 is a regulator of cell cycle progression as it modulates the transition from G1 to S phase through its action as allosteric regulator of the cyclin-dependent kinase 4 (CDK4) and CDK6.[27] Tian, Feng et al. provided evidence that downregulation of SKA1 on bladder cancer cell lines resulted in decrease expression of Cyclin D1.[16] Similarly, Zhao, Li-Juan et al. documented that knockdown of SKA1 in human adenoid cystic carcinoma cell lines results in the downregulation of Cyclin D1.[17] The findings suggest the role of SKA1 in regulating the Cyclin D1 through a potential pathway, but further investigation is needed to determine the precise role played by SKA1 in tumourigenesis.

The current study has limitations, as biopsies of normal healthy individuals were not included as controls due to ethical issues. The relatively small sample size has limited the generalisability of the findings. There is an absence of inter-observer reliability metrics for IHC scoring and a lack of molecular validation. Large-scale, multicentre studies using advanced molecular techniques are required to validate the current findings.

Conclusion

There was a difference between tissue expressions of SKA1 in different histological grades of OSCC and in varying grades of dysplasia of OPMDs, suggesting the role of this gene in oral carcinogenesis and tumour progression.

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Author Contribution:
SK: Concept, writing, data collection and statistical analysis.
MMA: Supervision, revision and final approval.
UB: Histopathological reporting of cases and help in writing.
MSF: Supervision, clinical assessment of patients and writing.
QA: Recruitment of patients in studies, clinical examination of patients and writing.