Original Article

Immunohistochemical expression of paxillin in potentially malignant disorders and squamous cell carcinoma patients

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Abstract:

Background: Cell adhesion molecules are essential to maintain the integrity of stratified squamous epithelium but their expression has to be dynamic to aid the mobility and turnover of cells. Paxillin is one such multi-domain protein which integrates numerous signals from cell surface receptors, integrins and growth factors. It thus functions as a regulator of various physiological and pathological processes including tissue remodeling, cell motility, gene expression, matrix organization, cell proliferation, metastasis and survival. Hence, the assessment of paxillin expression in normal control, potentially malignant disorders and oral squamous cell carcinoma patients was carried out.

Material and Methods: The present retrospective study comprised of 20 each clinically and histologically confirmed case of normal control, potentially malignant disorders, and oral squamous cell carcinomas. All the slides were stained immunohistochemically using Paxillin antibody.

Results: The localization, staining intensity and percentage of positivity for paxillin expression was statistically significant among normal control and potentially malignant disorders, whereas oral squamous cell carcinoma showed a non-significant difference. Upon comparison of histopathological grading of potentially malignant disorders, mild versus severe and moderate versus severe epithelial dysplasia showed a statistical significant difference among all the parameters of paxillin expression. However, WDSCC & MDSCC a statistically significant difference among localization and staining intensity of paxillin.

Conclusion: Paxillin may play an important role in pathogenesis of oral squamous cell carcinoma by altering the adhesive properties of the tumor cells interacting with the extracellular matrix which in turn affects their invasive behavior and histologic differentiation.

Keywords: Cell adhesion, focal adhesion, neoplasm invasiveness, oral squamous cell carcinoma, paxillin

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INTRODUCTION

Squamous cell carcinoma (SCC) is the most common oral malignancy, accounting for more than 90% of all cancers. Oral SCC (OSCC) is the sixth most common cancer worldwide.[1] Furthermore, oral potentially malignant disorders (OPMD) have a statistically increased risk of progressing to cancer, but the risk varies according to a range of patient-or lesion-related factors. The study was planned to analyse the immunohistochemical expression of paxillin in leukoplakia, oral submucous fibrosis and OSCC patients. the study also assess the expression of paxillin in different age groups, gender, different grades of epithelial dysplasia in OPMD'S & histopathological grades of OSCC. It is difficult to predict the risk of progression in any individual patient, and the clinician must make a judgment based on assessment of each case. The most commonly encountered OPMD is leukoplakia, but other lesions such as lichen planus, oral submucous fibrosis and erythroplakia may also be seen.[2]

Despite the availability of newer diagnostic and therapeutic strategies; the 5-year survival rate is still low (40%–50%) making it a global health problem.[1] This low survival rate has led to the research of molecular aspect of carcinogenesis. Carcinogenesis is a multistep process characterized by acquisition of numerous mutation and epigenetic abnormalities in the expression of multiple genes that have highly diverse functions. At first, there is loss of control of cell cycle through increased proliferation, reduced apoptosis and increased tumor cell motility leading to invasion and metastasis. Neoplastic epithelial cells are able to infiltrate the basement membrane and invade the underlying tissues, and eventually travel to regional lymph nodes.[3]

The cell adhesion molecules bind the cells to other cells and extracellular matrix (ECM). These include integrins, cadherins, selectins, and immunoglobulin superfamily. The adjacent or lateral surfaces of epithelial cells are linked by cell junctions so that the epithelium forms a continuous cohesive layer. Loss of cell cohesiveness is feature of SCC which helps in tumor invasion and metastasis.[4] This adhesion process depends on the integrin receptors rooted in the plasma membrane. These integrin receptors are known to establish and maintain two types of junctions, i.e., focal adhesions (FAs) which are linked to the actin cytoskeleton and the hemidesmosomes that are connected to the intermediate filaments.[5]

Integrin molecule functions as a cell-surface receptor that connects the cytoplasm and the ECM. It is composed of a transmembrane-type heterodimer that consists of α integrin chain and β integrin chain.[4] Directly associated with β-integrin tails is a multi-domain protein known as paxillin which localizes specifically to sites of FAs. It is derived from the Latin paxillus, a stake or peg, consistent with its proposed function in linking actin filaments to integrins-rich cell adhesion sites. Paxillin primarily functions as a molecular adapter or scaffold protein for various signaling and structural proteins. Paxillin binds to numerous proteins that are concerned in implementing changes in the organization of the actin cytoskeleton, which are essential for cell motility associated with tumor metastasis. It has also been postulated to play a role in cell proliferation, survival and angiogenesis.[6]

However, there are only few studies[7,8] carried out on Paxillin expression in the OSCC and in potentially malignant disorders. Hence, this study was planned to analyze the immunohistochemical expression of Paxillin in leukoplakia, oral submucous fibrosis and OSCC patients.

SUBJECTS AND METHODS

The present study consisted of 60 formalin fixed-paraffin embedded tissue blocks, 20 each of normal controls, OPMD and OSCC, were retrieved from the archives of department of oral pathology and microbiology. Clinical information related to the type of lesion, age, gender, site and anatomical side was obtained from the submitted biopsy requisition forms and tabulated on customized data sheets. Cases with incomplete data were revaluated for the missing information. Patients with systemic disorders such as diabetes, hypertension, bleeding disorder, etc., were excluded. The significance of difference was assessed using the Chi-square and Fisher's exact test.

The samples were processed as per the standard protocols.[9] Two 4 μ thick sections were obtained from formalin fixed paraffin-embedded tissues blocks. One section was stained with hematoxylin and eosin[9] and another was immunostained with primary antibody against paxillin (Biogenex, Monoclonal Rabbit Anti-paxillin, Clone Y113;).[6] Hematoxylin and eosin-stained slide was evaluated for the confirmation of the diagnosis. Histopathological grading of epithelial dysplasia in OPMD and the degree of differentiation in OSCC was established.[10,11]

Immunohistochemical evaluation criteria: According to Shekhar and Angadi,[12] localization, intensity and percentage of staining were analyzed and scored. The criteria used to define localization were fixed as score 1 for cytoplasmic only and 2 for cytoplasmic ± membrane staining. Furthermore, the criteria used to define intensity were set as score 0 for

absence of staining, 1 for mild staining and 2 for intense staining. Similarly, the criteria used to define the percentage of positive cells with paxillin expression were set as score 0 for negative reaction, 1 for 1%–25% positive reaction, 2 for 26%–50% and 3 for >51% positive reaction.

RESULTS

A total of 60 cases consisting 20 each of normal control, PMD and OSCC were included. According to the age distribution, normal control, PMD and OSCC showed 3 (15%), 3 (15%), and 0 (0%), in <20 years, 9 (45%), 7 (35%), and 8 (40%), in 21–40 years, 8 (40%), 9 (45%), and 10 (50%) in 41–60 years, and 0 (0%), 1 (5%), and 2 (10%) in >60 years, respectively.

According to the gender distribution, normal control, PMD and OSCC showed 13 (65%), 15 (75%), and 16 (80%), in males; while 7 (35%), 5 (25%) and 4 (20%), in females, respectively. Upon statistical comparison, it was nonsignificant with $P = 0.766$.

According to the site distribution, normal control, PMD and OSCC showed 4 (20%), 9 (45%), and 13 (65%), in left buccal mucosa, 0 (0%), 2 (10%), and 0 (0%), in left alveolar mucosa, 0 (0%), 0 (0%), and 3 (15%) in left lateral border of tongue, 1 (5%), 0 (0%), and 0 (0%) in left lower gingiva, 4 (20%), 0 (0%) and 0 (0%) in left upper gingiva, 6 (30%), 9 (45%) and 4 (20%) in right buccal mucosa, 1 (5%), 0 (0%) and 0 (0%) in right lower gingiva and 4 (20%), 0 (0%) and 0 (0%) in right upper gingiva, respectively.

According to the presence of smoking and smokeless tobacco habit, the normal control, showed 14 (70%), and 12 (60%), PMD showed 11 (55%), and 18 (90%) and OSCC showed 14 (70%) and 15 (75%) cases, respectively. Upon statistical comparison, it was nonsignificant [Table 1].

On the basis of histopathological grading of epithelial dysplasia in PMD, 10 (50%) cases showed mild dysplasia followed by moderate dysplasia in 8 (40%) and 2 (10%) cases in severe dysplasia [Graph 1].

On the basis of histopathological grading of OSCC, well differentiated SCC was present in 8 (40%) cases and moderately differentiated SCC in 12 (60%) cases [Graph 2].

Table 1: Presence and absence of tobacco smoking and smokeless tobacco habit among study groups

Study Groups	Tobacco Smoking Habit		*P*	Smokeless Tobacco Habit		*P*
	Presence Cases(%)	Absence Cases(%)		Presence Cases(%)	Absence Cases(%)	
Normal Control	14 (70%)	6 (30%)	0.571 (Non-Significant)	12 (60%)	8 (40%)	0.182 (Non-Significant)
PMD	11 (55%)	9 (45%)		18 (90%)	2 (10%)	
OSCC	14 (70%)	6 (30%)		15 (75%)	5 (25%)	

Table 2: Immunohistochemical expression of Paxillin according to the localization among study groups

Study Groups	Localization			*P*
	0 (Absent)	1 (Cytoplasmic)	2 (Cytoplasmic+Membranous)	
Normal Controls	0 (0%)	20 (100%)	0 (0%)	<0.001(Significant)
PMD	0 (0%)	15 (75%)	5 (25%)	<0.001(Significant)
OSCC	2 (10%)	8 (40%)	10 (50%)	0.082 (Non-Significant)
P			<0.001 (Significant)	

Table 3: Immunohistochemical expression of Paxillin according to the intensity among study groups

Study Groups	Staining Intensity			*P*
	0 (Absence)	1 (mild)	2 (Intense)	
Normal Controls	0 (0%)	10 (50%)	10 (50%)	<0.001(Significant)
PMD	0 (0%)	13 (65%)	7 (35%)	<0.001(Significant)
OSCC	2 (10%)	11 (55%)	7 (35%)	0.0534(Non-Significant)
P			0.799(Non-Significant)	

Table 4: Immunohistochemical expression of Paxillin according to the percentage of positivity among study groups

Study Groups	Percentage of Positivity				*P*
	0 (Absent)	1 (1-25%)	2 (26-50%)	3 (>50%)	
Normal Controls	0 (0%)	6 (30%)	14 (70%)	0 (0%)	<0.001(Significant)
PMD	0 (0%)	13 (65%)	7 (35%)	0 (0%)	<0.001(Significant)
OSCC	2 (10%)	5 (25%)	3 (15%)	10 (50%)	0.055(Non-Significant)
P			<0.001(Significant)		

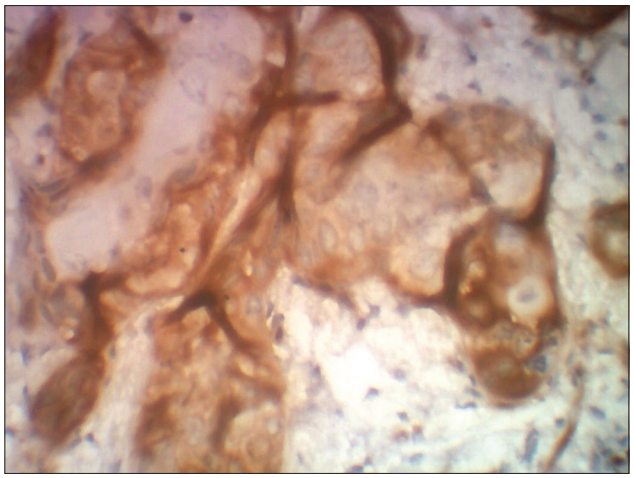


Figure 1: The photomicrograph depicting the localization of paxillin expression in cytoplasmic and membrane staining positivity (Immunohistochemistry, ×100)

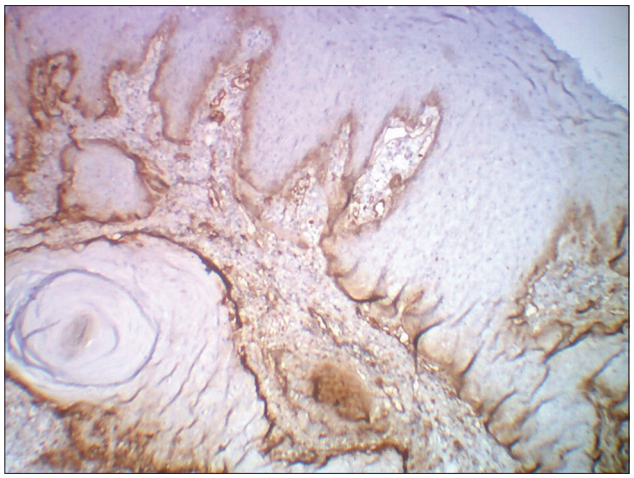


Figure 2: The photomicrograph depicting the intensity of paxillin expression as intense staining (Immunohistochemistry, ×100)

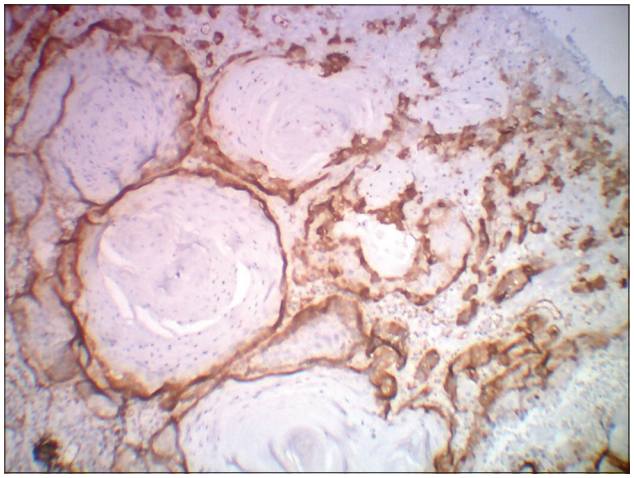


Figure 3: The photomicrograph depicting the percentage of positivity of paxillin expression as score 2 (26%–50%) (Immunohistochemistry, ×40)

According to the immunohistochemical staining with Paxillin antibody, positivity was demonstrated in 20 (100%) cases each of normal controls and PMD, whereas 18 (96.4%) cases of OSCC [Graph 3].

According to the localization of paxillin [Figure 1] staining, 0 (absent), 1 (cytoplasmic) and 2 (cytoplasmic ± membranous) in normal control showed 0 (0%), 20 (100%) and 0 (0%), in PMD showed 0 (0%), 15 (75%) and 5 (25%) and in OSCC showed 2 (10%), 8 (40%) and 10 (50%), respectively. Upon statistical comparison, it was significant with $P = 0.001$ [Table 2].

According to the intensity of paxillin [Figure 2] staining, 0 (absence), 1 (mild) and 2 (intense) in normal control showed 0 (0%), 10 (50%) and 10 (50%) in PMD showed 0 (0%), 13 (65%) and 7 (35%) and in OSCC showed 2 (10%), 11 (55%) and 7 (35%), respectively. Upon statistical comparison, it was nonsignificant with $P = 0.799$ [Table 3].

The percentage of positivity [Figure 3] assessed according to the grades of 0 (absent), 1 (1%–25%), 2 (26%–50%) and 3 (>50%) in normal control showed 0 (0%), 6 (30%), 14 (70%), 0 (0%), in PMD showed 0 (0%), 13 (65%), 7 (35%), 0 (0%) and in OSCC showed 2 (10%), 5 (25%), 3 (15%) and 10 (50%), respectively. Upon intergroup analysis, a statistical significant difference was noted with the $P = 0.001$ [Table 4].

The mean ± SD immunohistochemical expression of paxillin in normal control, PMD and OSCC was 1.40 ± 0.25, 1.31 ± 0.32 and 1.56 ± 0.71, respectively. Upon statistical comparison, it was nonsignificant with the $P = 0.234$. Upon intercomparison of the study groups, normal control versus PMD, normal control versus OSCC and PMD versus OSCC showed a nonsignificant $P = 0.55$, 0.275 and 0.094, respectively [Table 5].

On intergroup comparison of histopathological grading of PMD according to localization showed a nonsignificant difference in mild versus moderate with the $P = 0.397$ and in mild versus severe and moderate versus severe showed statistically significant difference with the $P = 0.001$ each, respectively. According to intensity, all three groups i.e., mild versus moderate, mild versus severe and moderate versus severe grading, showed statistically significant differences with $P = 0.003$, 0.001 and 0.001, respectively. According to the percentage of positivity, statistically significant difference among mild versus severe with the $P = 0.003$ was seen whereas mild versus moderate, and moderate versus severe showed statistically nonsignificant difference with the $P = 0.294$ and 0.873, respectively [Table 6].

Table 5: Intercomparison of the mean of immunohistochemical expression of paxillin among the study groups

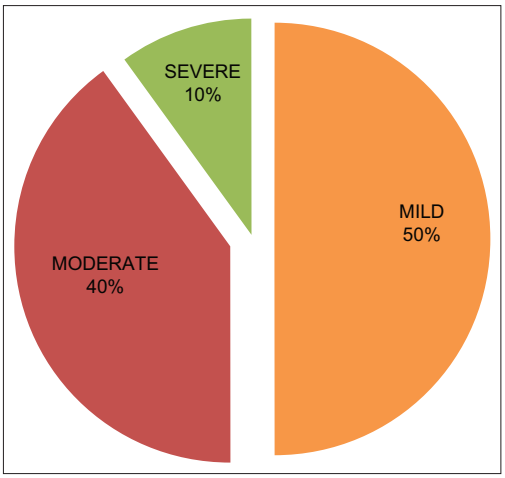
Mean±SD			*P*	*P*		
Normal Control	PMD	OSCC		Normal Control Vs PMD	Normal Control Vs OSCC	PMD Vs OSCC
1.40±0.25	1.31±0.32	1.56±0.71	0.234 (Non-Significant)	0.55 (Non-Significant)	0.275 (Non-Significant)	0.094 (Non-Significant)

Table 6: Intercomparison of Localization, Intensity and Percentage of Positivity in Histopathological Grading of PMD

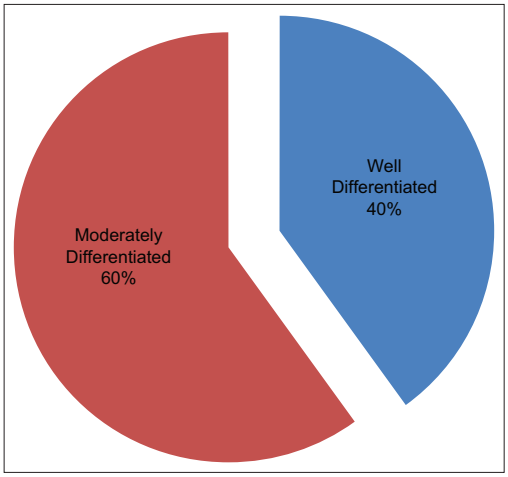
IHC Evaluation Criteria	Mild (*n*=10)	Moderate (*n*=8)	Severe (*n*=2)	*P*		
				Mild- Moderate	Mild- Severe	Moderate-Severe
Localization						
Absence	0 (0%)	0 (0%)	0 (0%)	0.397	0.001	0.001
Cytoplasmic	8 (80%)	6 (75%)	1 (50%)	(Non-Significant)	(Significant)	(Significant)
Cytoplasmic + Membrane	2 (20%)	2 (25%)	1 (50%)			
Staining Intensity						
Absence	0 (0%)	0 (0%)	0 (0%)	0.003	0.001	0.001
Mild	7 (70%)	4 (50%)	2 (100%)	(Significant)	(Significant)	(Significant)
Intense	3 (30%)	4 (50%)	0 (0%)			
Percentage of Positivity						
Negative	0 (0%)	0 (0%)	0 (0%)	0.294	0.003	0.873
1-25%	7 (70%)	5 (62.5%)	1 (50%)	(Non-Significant)	(Significant)	(Non-Significant)
26-50%	3 (30%)	3 (37.5%)	1 (50%)			
> 50%	0 (0%)	0 (0%)	0 (0%)			

Table 7: Intercomparison of Localization, Intensity and Percentage of Positivity in Histopathological Grading of OSCC

IHC Evaluation Criteria	Well Differentiated (*n*=8)	Moderately Differentiated (*n*=12)	*P*
Localization			
Absence	1 (12.5%)	1 (8.3%)	
Cytoplasmic	4 (50%)	4 (33.3%)	0.012
Cytoplasmic + Membrane	3 (37.5%)	7 (58.3%)	(Significant)
Staining Intensity			
Absence	1 (12.5%)	1 (8.3%)	0.014
Mild	3 (37.5%)	8 (66.7%)	(Significant)
Intense	4 (50%)	3 (25%)	
Percentage of Positivity			
Negative	1 (12.5%)	1 (8.3%)	0.632
1-25%	2 (25%)	3 (25%)	(Non-
26-50%	1 (12.5%)	2 (16.7%)	Significant)
> 50%	4 (50%)	6 (50%)	



Graph 1: Distribution of histopathological grading in PMD

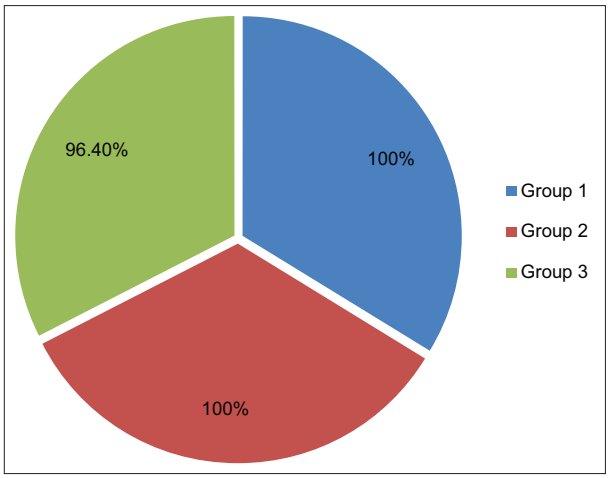


Graph 2: Distribution of histopathological grading of OSCC

On intergroup comparison of histopathological grading of OSCC according to localization and intensity showed a significant difference in well versus moderately differentiated SCC with the $P = 0.012$ and 0.014, respectively. However, percentage of positivity showed statistically nonsignificant difference with the $P = 0.632$ [Table 7].

DISCUSSION

Epithelial cells bond to their epithelial neighbors by a range of intercellular adhesion complexes; these not only physically maintain the epithelial barriers but also take part in a broad range of signaling pathways that control cell behavior. These complexes consist of tight junctions desmosomes and adherens junctions. In addition, epithelial sheets connect to the basement membrane underneath via hemidesmosomes and FAs, which also offer signaling indication for the guideline of cell behavior, as well as cell polarity, proliferation and migration.[13]



Graph 3: Immunohistochemical positive expression of Paxillin among study groups

Paxillin is one such 68Kda FAs molecule, which is a key component of cellular adhesion, contributing to the formation of structural link between ECM and actin in the cytoskeleton. It is a multidomain adaptor protein which integrates numerous signals from cell surface receptors, integrins and growth factors. Throughout these protein–protein interactions, paxillin functions as a regulator of various physiological processes including tissue remodeling, cell motility, gene expression, matrix organization, cell proliferation, metastasis and survival.[14]

Paxillin is involved in these functions as adaptor protein that employees signaling molecules into its adhesion complex. Some interactions are regulated by phosphotyrosine-dependent interactions, whereas of others the paxillin-binding allies relate through LD motif interactions. Chief function for paxillin is in the dissemination and integration of signals from growth factor receptors and integrins to effect competent cellular movement. Motility is a composite multistep procedure that necessitate the organization of membrane trafficking and the restructuring of the actin and tubulin cytoskeleton networks to understand net cellular movement. The actions of numerous p21 GTPase families are vital to this process, and paxillin is a vital mediator of signal cross-talk between these families during its phosphorylation and multipotent relations.[12,14]

The present study was carried out to observe the expression of Paxillin in normal control, OPMD and OSCC. Paxillin expression was noted in 100% of normal control, OPMD and depicted 98.7% positivity in OSCC. There are few studies of paxillin in OSCC which are PCR based gene expression[15] and immunohistochemical studies,[12] while no studies have been found in the literature reporting the immunohistochemistry protein expression of paxillin in normal control and OPMD.

In the present study, intercomparison of mean immunohistochemical expression of paxillin among all study groups showed a nonsignificant result. However, Mackinnon *et al*.[15] suggested in 2010 that the paxillin is over expressed in premalignant areas of lung squamous metaplasia, hyperplasia and goblet cell metaplasia, in addition to dysplasia and lung carcinoma.

In the present study, well-differentiated SCC (WDSCC) demonstrated decreased staining when compared to moderately differentiated SCC (MDSCC), which was contrasting to the result of Shekhar and Angadi,[12] who reported progressive increase of paxillin expression in WDSCC but less in MDSCC. This suggested that the paxillin overexpression may be associated with aggressive phenotype.

According to the localization of paxillin, a statistically significant result was noted in cytoplasmic and cytoplasmic ± membrane staining among WDSCC and MDSCC. A study done by Shekhar and Angadi[12] showed a statistically significant difference in the percentage of cytoplasmic staining with decrease in the grade of differentiation. A study conducted by Shi *et al*.[16] showed the upregulation of paxillin expression in salivary adenoid cystic carcinoma while cytoplasmic staining was statistically significant and the membrane staining was similar to the results observed in a study done by Madan *et al*.,[17] of invasive breast carcinoma which was also significant.

Most studies in breast,[18] gastric, colorectal,[19] laryngeal carcinoma and urothelial carcinomas[20] have demonstrated cytoplasmic localization of paxillin which progressively increased with histologic grade as seen in the present study. This coincides with the normal localization of paxillin as an adaptor protein entangled with the actin cytoskeleton.[15]

In the present study, staining intensity and percentage of positivity with paxillin showed statistically significant difference among WDSCC and MDSCC which was similar to the study done by Shekhar and Angadi.[12] The increased staining intensity observed in most cases was consistent with other studies of breast,[18] colorectal[19] and gastric carcinomas.[15,19] According to Chen, *et al*.,[19] MDSCC and WDSCC demonstrated expression throughout the tumor cells, the WDSCC showed paxillin expression only in the peripheral cell and no expression was evident in central keratinizing areas.

In the present study, paxillin has been suggested to play an adhesive role in the more aggressive neoplasms and demonstrated decreased expression as compared to the aggressive undifferentiated phenotype. This supports the fact that, paxillin promotes cell spreading and motility, a precise function which is not clearly elucidated.[21] The propensity of paxillin to be phosphorylated by integrin and growth factor receptor ligation[6,22] which has a significant role in tumorgenesis and invasion.[23,24] In addition to interactions with cytoskeleton, paxillin could also bind to several oncogene proteins for instance BCR-Abl, E6 and v-src. These proteins could utilize paxillin as the docking site to disrupt or delude the normal growth factor and adhesion signaling pathways that are crucial for controlled growth and migration.[24]

Jagadeeswaran, *et al*.[25] assessed the occurrence of paxillin mutations in lung SCC, which included large cell carcinomas, adenocarcinoma and SCCs. In lung cancer tissues, they established that paxillin was elevated and linked with amplified epidermal growth factor receptor. Thus, they concluded that paxillin played a vital molecule in metastasis and tumor growth.

Even though the cytoskeleton and endothelial cell junctions during inflammation go through reorganization, slight is identified about any more class of cellular structures, the FAs. They scrutinized numerous FAs proteins during an inflammatory response, in this study. They established that there was selective loss of FAs kinase (FAK) and paxillin from FAs in propinquity to transmigrating neutrophils, whereas the levels of the FAs proteins vinculin and b1-integrin were unaffected. During neutrophil transmigration, paxillin was lost from FAs equally under flow and static conditions. Neutrophil transmigration was blocked as down-regulating endothelial paxillin with siRNA, whereas having no effect on adhesion or rolling. FAK partly regulates paxillin dynamics; the function of FAK using two complementary methods in neutrophils transmigration was examined. To down-regulate total FAK protein siRNA was used although dominant-negative, kinase-deficient FAK was expressed to obstruct FAK signaling. Interference of the FAK signaling or FAK protein reduced neutrophil transmigration. Together these results disclose a new role for FAK and endothelial FAs proteins paxillin in adaptable neutrophil transmigration. Whereas in our present study also inflammatory infiltrate where positive for the expression of paxillin.

Many studies using different approaches to deal with the role of paxillin in the cell have fashioned the same conclusion that paxillin controls cell spreading and motility but is context dependent. Thus, paxillin could be considered as a useful biomarker for the treatment and prognosis. However, further studies using a large sample size, different geographic location, local lesion biopsies, along with other molecular analytical methods may be essential to draw a definite conclusion between the association of paxillin amid the exact pathogenesis of potentially malignant disorders and OSCC.

CONCLUSION

Paxillin is overexpressed in premalignant areas of hyperplasia, squamous metaplasia and goblet cell metaplasia, as well as dysplastic lesions and carcinoma in high-risk patients. Paxillin expression appeared strongest in the basal layer and areas of dysplasia. Paxillin expression was upregulated in non-neoplastic precursor lesions before malignant changes were microscopically evident and can remain elevated during the formation of pre-invasive epithelial lesions. The present study was carried out to observe the expression of Paxillin using various parameters in normal control, potentially malignant disorders and different grades of oral squamous cell carcinoma.

There are only few studies done on oral squamous cell carcinoma using paxillin antibody. Hence the present study was conducted at the protein level using immunohistochemistry to determine the role of paxillin in normal control, PMD and different grades of oral squamous cell carcinoma.

Paxillin plays an important role in pathogenesis of oral squamous cell carcinoma by altering the adhesive properties of the tumor cells interacting with the extracellular matrix which in turn affects their invasive behavior and histologic

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Conflicts of interest
There are no conflicts of interest.

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