Review Article

Immunohistochemical expression of paxillin in ameloblastoma and odontogenic keratocyst: An observational study

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Abstract

Background: Cell adhesion molecules (CAMs) are found on the surface of all cells, where they allow dynamic processes to take place. These include cadherins, integrins, selectins and Immunoglobulin superfamily. Directly associated with β-integrin tails is a multidomain protein known as paxillin. However, CAMs participate in cell-cell and extracellular matrix-cell interactions during histomorphogenesis in the various phases of odontogenesis. Some tumours or cysts like ameloblastoma (AB) or odontogenic keratocyst (OKC) having odontogenic origin show disturbance in the interaction of these CAMs. Hence, the assessment of paxillin expression in AB and OKC was carried out.

Materials and Methods: The present observational study comprised 30 clinically and histologically confirmed cases of AB and OKC. All the slides were stained immunohistochemically using a paxillin antibody.

Results: Upon comparison of staining intensity of paxillin among AB and OKC showed statistically significant result, whereas quantitative staining and final summation showed non-significant result. Gender-wise comparison of paxillin staining intensity, quantitative staining and final summation among OKC showed significant result; however, in AB, staining intensity showed non-significant result, whereas quantitative staining and final summation showed significant result.

Conclusion: Paxillin has the greatest influence on tissue morphogenesis and development. The regulation of cell mobility is aided by the multiple roles that paxillin plays in a range of cells and tissues. However, further studies using a large sample size, along with other molecular analytical methods, may be essential to draw a definite conclusion about the association of paxillin and its exact function in OKC and AB.

Keywords: Ameloblastoma, cell adhesion molecules, focal adhesions, integrins, odontogenic tumours, paxillin

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Submitted: 12-Jul-2023, **Revised:** 08-Sep-2023, **Accepted:** 09-Oct-2023, **Published:** 20-Dec-2023

INTRODUCTION

Cell adhesion molecules (CAMs) are found on the surface of all cells, where they allow dynamic processes to take place during tissue morphogenesis and during the formation and maintenance of adult tissues.[1] CAMs bind the cells to cells and cells to the extracellular matrix (ECM). These include cadherins, integrins, selectins and immunoglobulin (Ig) superfamily. Cell junctions connect the neighbouring or

Access this article online

Quick Response Code:

Website: https://journals.lww.com/JPAT/

DOI: 10.4103/jomfp.jomfp_312_23

How to cite this article: Singh A, Astekar MS, Sapra G, Agarwal A, Murari A. Immunohistochemical expression of paxillin in ameloblastoma and odontogenic keratocyst: An observational study. J Oral Maxillofac Pathol 2023;27:727-34.

lateral surfaces of epithelial cells, forming a continuous, cohesive layer for the epithelium. This adhesion process depends on the integrin receptors rooted in the plasma membrane. These integrin receptors have two chief functions. In the first place, they offer the molecular connection between the actin cytoskeleton and the adhesion molecules positioned in the ECM or on the surface of the cell. Secondly, they contribute to a process of integrin signalling, which is thoroughly linked to their skeletal/adhesive purpose. The adhesion complexes produced by the integrin receptors, which are linked to the basement membrane by epithelial cells, interact with the ECM beneath. These integrin receptors are known to establish and maintain two types of junctions, that is, Focal Adhesion (FA) which are linked to the actin cytoskeleton and the hemidesmosomes that are connected to the intermediate filaments.[2]

The integrin molecule functions as a cell surface receptor that connects the cytoplasm and the ECM. It consists of a transmembrane-type heterodimer that consists of α integrin chain and β integrin chain.[3] Directly associated with β-integrin tails is a multidomain protein known as paxillin, which localises specifically to sites of cell adhesion to the ECM called as FAs. Paxillin's origins in the Latin word *Paxillus*, which means a stake or peg, are compatible with the hypothesis that it links actin filaments to integrin-rich cell attachment sites. Paxillin was first identified in a screen for substrates for the oncogene tyrosine kinase v-src in Rous sarcoma virus (RSV)–transformed fibroblasts.[4] It mostly performs the role of a molecular adaptor protein for different signalling and structural proteins. It binds to numerous proteins that are involved in implementing changes in the cytoskeletal structure of actin. It has also been postulated that paxillin plays a role in cell proliferation, survival and angiogenesis. Paxillin is a scaffolding protein that performs various functions to coordinate the signalling activities of integrin ECM ligation.[5] Stimulation of paxillin recruits focal adhesion kinase (FAK) for FAs; thus, it is called the FAs protein. FAK-paxillin interactions play a crucial part in cell motility.[6,7] Epithelial-mesenchymal transition (EMT) is an evolutionary procedure that is crucial for normal tooth development, and it also involves the dissolution of cell-to-cell adhesions, loss of basolateral polarity and reorganisation of the cytoskeleton.[5] In addition to being drawn to developing FAs at the cell's front for adhesion complex assembly, paxillin is required for FAs to be deconstructed at the cell's back.[8,9] Paxillin is mostly found at FAs, but it is also found in the cytoplasm and the nucleus, where it may influence gene transcription, serving as a direct conduit from the cell membrane and cytoskeleton to the nucleus.[10] Although the function of CAMs in dental development is not currently well understood, it is known that CAMs participate in cell-cell and ECM-cell interactions during histomorphogenesis in the various phases of odontogenesis.[11,12] Some tumours or cysts like ameloblastoma (AB) or odontogenic keratocyst (OKC) of odontogenic origin, shows disturbance in the interaction of these CAMs.[13]

Both odontogenic tumours and cysts are pathologies arising from the enamel organ or ectomesenchymal portions of the odontogenic apparatus. AB is the second most common benign odontogenic tumour. It may arise from epithelial remnants of odontogenic apparatus, basal layer of the mucosa, and epithelial lining of odontogenic cysts. It is slow-growing but with unlimited growth potential and significant morbidity when untreated.[13-15] They are locally infiltrative benign tumours which rarely convert to malignancy, though they are locally invasive and carry an increased rate of recurrence.[16] Recurrence rates are up to 70% with conservative treatment, and the malignant transformation rate is around 2%.[15] OKC is an odontogenic origin lesion. It is one of the most aggressive and highly recurrent odontogenic cysts of the oral cavity and was previously named as keratocystic odontogenic tumour (KCOT). It may occur due to traumatic implantation or reduced enamel epithelium of the dental follicle or downgrowth of the basal cell layer of surface epithelium.[17] Paxillin expression in odontogenic cysts and tumours has been the subject of a very small number of investigations; hence, the present study was carried out to analyse the immunohistochemical expression of paxillin in OKC and AB in order to appraise their roles regarding cell-matrix interactions.

MATERIALS AND METHODS

Formalin-fixed paraffin-embedded tissue blocks and their slides were retrieved from the archives of the department. The standard histopathological criteria to diagnose AB and OKC were followed. The required demographic data of all the included cases were recorded. A total of 60 cases from the Oral Histopathology Laboratory's search for OKC and AB cases were randomly chosen. After reviewing the slides and confirming that the histological blocks from archives, cases were only included if cyst and tumour tissue were present in blocks and adequate clinical information in the biopsy records. The significance of the difference was assessed using the Chi-square test.

Two 4 μm thick sections were obtained from formalin-fixed paraffin-embedded tissue blocks. One section was stained with haematoxylin and eosin, and another

was immunostained with primary antibody against paxillin (Biogenex, Monoclonal Rabbit Anti-paxillin, Clone Y113;). Haematoxylin and eosin-stained slides were evaluated for the confirmation of the diagnosis.

Immunohistochemical Evaluation Criteria: According to Bello IO *et al*.,[6] 2021, the intensity of staining, quantitative staining evaluation and summation of both will be analysed and scored. The staining intensity was graded as 0 (no cytoplasmic staining), 1 (weak cytoplasmic staining), 2 (moderate cytoplasmic staining), 3 (strong cytoplasmic staining), and 4 (very strong cytoplasmic staining). Quantitative staining evaluation was graded as 0 (no positive staining), 1 (<25% of tumour cells showing cytoplasmic positivity), 2 (25–50% of cells), 3 (50–75% of cells), and 4 (>75% of cells). The summation of both the intensity and quantitative staining was performed to reach at a final score for protein expression; thus, 0 = no staining, 1–4 = weak staining, and 5–8 = strong staining.

RESULTS

According to the age distribution, the maximum number of OKC and AB showed 16 (53%) and 11 (36%) in the age group 21–30 years. According to the gender distribution, OKC and AB showed male predominance 19 (63%) and 21 (70%), respectively. According to the distribution of histopathological variants, parakeratinised OKC [28 (93%)] and plexiform AB [18 (60%)] showed predominance over other variants.

Upon comparison of cytoplasmic staining intensity scores of paxillin among OKC and AB, score 0 (no staining) was seen in 1 (3%) and 0 (0%), score 1 (weak staining) was seen in 13 (43%) [Figure 1] and 6 (20%), score 2 (moderate staining) was seen in 10 (33%) [Figure 2] and 6 (20%), score 3 (strong staining) was seen in 5 (17%) and 8 (27%) [Figure 3] and score 4 (very strong staining) was seen in 1 (3%) and 10 (33%), [Figure 4] respectively. Upon statistical comparison, it was significant, with a *P* value of 0.013 [Table 1].

Based on the comparison of cytoplasmic quantitative staining of paxillin among OKC and AB, score 0 (no staining) was seen in 1 (3%) and 0 (0%), score 1 (<25% of stained cells) was seen in 9 (30%) and 5 (17%), score 2 (25–50% of stained cells) was seen in 5 (17%) [Figure 5] each, score 3 (50–75% of stained cells) was seen in 5 (17%), and 10 (33%) and score 4 (>75% of stained cells) was seen in 10 (33%) [Figure 6] each, respectively. Upon statistical comparison, it was non-significant, with a *P* value of 0.432 [Table 2].

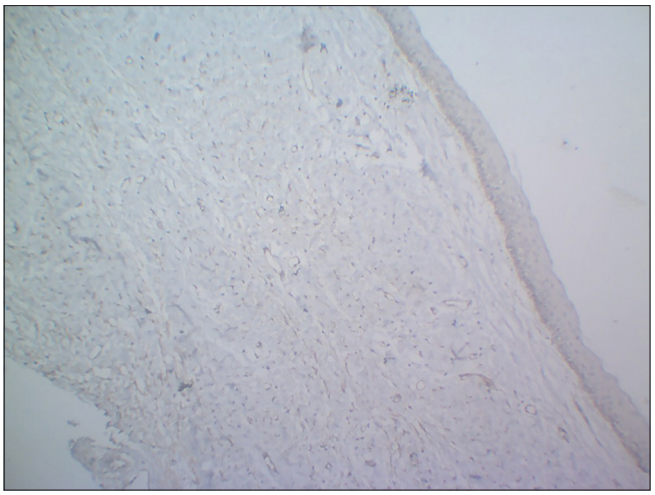

Figure 1: The given photomicrograph illustrating the staining intensity of paxillin in OKC as score one with weak staining. OKC = odontogenic keratocyst (IHC, X100)

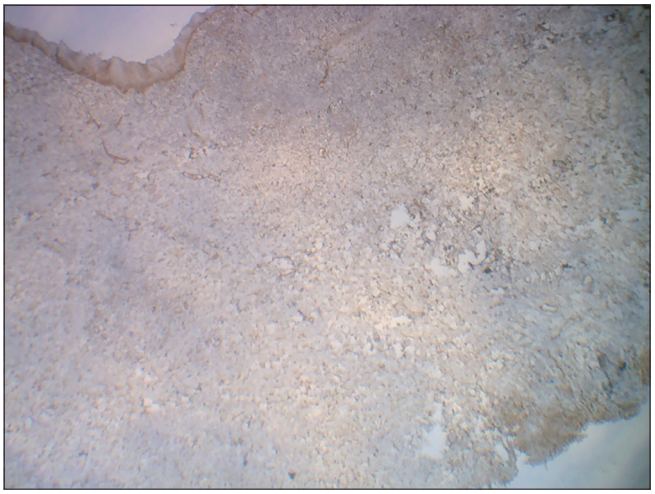

Figure 2: The given photomicrograph illustrating the staining intensity of paxillin in OKC as score two with moderate staining. OKC = odontogenic keratocyst (IHC, X40)

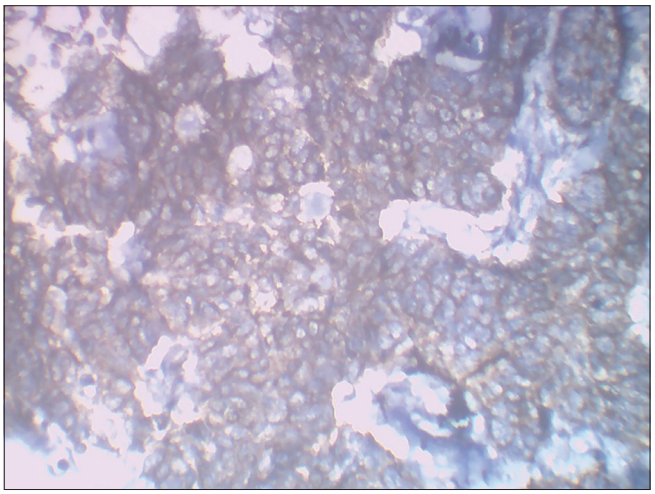

Figure 3: The given photomicrograph illustrating the staining intensity of paxillin in AB as score three with strong staining. AB = ameloblastoma (IHC, X100)

Table 1: Comparison of staining intensity of paxillin among the study samples

Staining intensity of paxillin	OKC		AB		*P*
	Samples	Percentage	Samples	Percentage	
0 (No stain)	1	3	0	0	0.013
1 (Weak stain)	13	43	6	20	(Significant)
2 (Moderate stain)	10	33	6	20	
3 (Strong stain)	5	17	8	27	
4 (Very strong stain)	1	3	10	33	
Total	30	100	30	100	

AB=Ameloblastoma, OKC=Odontogenic keratocyst

Table 2: Comparison of quantitative staining of paxillin among the study samples

Quantitative staining of paxillin	OKC		AB		*P*
	Samples	Percentage	Samples	Percentage	
0 (No staining)	1	3	0	0	0.432
1 (<25% of stained cells)	9	30	5	17	(Non-significant)
2 (25–50% of stained cells)	5	17	5	17	
3 (50–75% of stained cells)	5	17	10	33	
4 (>75% of stained cells)	10	33	10	33	
Total	30	100	30	100	

AB=Ameloblastoma, OKC=Odontogenic keratocyst

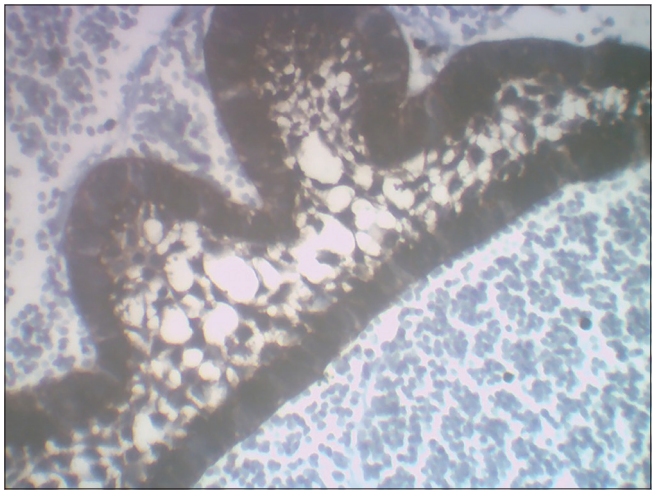

Figure 4: The given photomicrograph illustrating the staining intensity of paxillin in AB as score four with very strong staining. AB = ameloblastoma (IHC, X400)

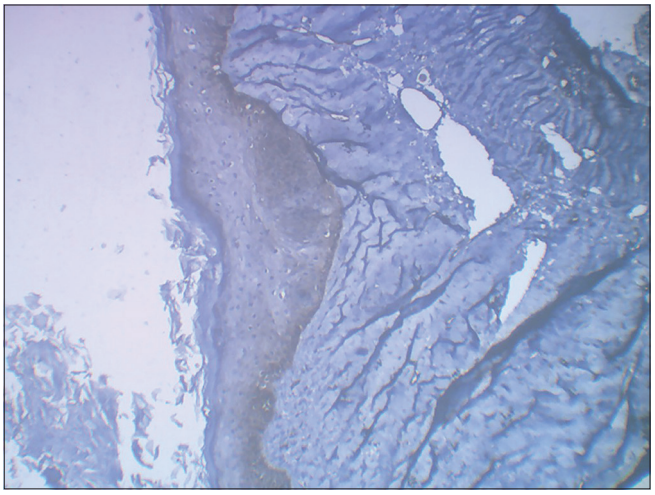

Figure 5: The given photomicrograph illustrating the quantitative staining of paxillin in OKC as score two with 25–50% stained cells. OKC = odontogenic keratocyst (IHC, X100)

The comparison of the final summation score in paxillin among OKC and AB showed score 0 (no staining) in 1 (3%) and 0 (0%), score 1–4 (weak staining) in 16 (53%) and 11 (37%) and score 5–8 (strong staining) in 13 (43%) and 19 (63%), respectively. Upon statistical comparison, it was non-significant, with a *P* value of 0.503 [Table 3].

The comparison of paxillin cytoplasmic staining intensity, quantitative staining and final summation score of paxillin in OKC among males and females showed significant results with *P* value < 0.05 [Table 4]. The comparison of paxillin cytoplasmic staining intensity in AB among males and females showed non-significant with a *P* value of 0.091, whereas quantitative staining and final summation score in paxillin among AB showed statistically significant values <0.001 and 0.027, respectively [Table 5]. An age-wise comparison of the final summation score in paxillin among OKC showed a weak stain, and AB showed a strong stain belonging to the age group of 21–30 years [Tables 6 and 7].

DISCUSSION

Over a diversity of intercellular adhesion complexes, epithelial cells are connected to their epithelial neighbours. These complexes take part in numerous signalling pathways that control cell behaviour in addition to assisting in maintaining the physical integrity of the epithelial barriers. These complexes are composed of adherens junctions (AJs), desmosomes, and tight junctions (TJs). Additionally, FAs and hemidesmosomes, which connect epithelial sheets to the basement membrane below, provide

Table 3: Comparison of final summation score in paxillin among the study samples

Final summation score	OKC		AB		*P*
	Samples	Percentage	Samples	Percentage	
0 (No stain)	1	3	0	0	0.503
1–4 (Weak stain)	16	53	11	37	(Non-significant)
5–8 (Strong stain)	13	43	19	63	
Total	30	100	30	100	

Table 4: Gender-wise comparison of final summation score in paxillin among OKC

Final summation score in OKC	Male		Female		*P*
	Samples	Percentage	Samples	Percentage	
0 (No stain)	0	0	1	9	0.015
1–4 (Weak stain)	10	53	6	55	(Significant)
5–8 (Strong stain)	9	47	4	36	
Total	19	100	11	100	

OKC=Odontogenic keratocyst

Table 5: Gender-wise comparison of final summation score in paxillin among AB

Final summation score in AB	Male		Female		*P*
	Samples	Percentage	Samples	Percentage	
0 (No stain)	0	0	0	0	0.027
1–4 (Weak stain)	6	29	4	44	(Significant)
5–8 (Strong stain)	15	71	5	56	
Total	21	100	9	100	

AB=Ameloblastoma

Table 6: Age-wise comparison of final summation score in paxillin among OKC

Final summation score in OKC (years)	0 (No stain)	Percentage	1–4 (Weak stain)	Percentage	5–8 (Strong stain)	Percentage
10–20	0	0	1	3	1	3
21–30	1	3	10	33	5	17
31–40	0	0	1	4	5	17
41–50	0	0	1	3	2	7
>50	0	0	3	10	0	0
Total	1	3	16	53	13	44

OKC=Odontogenic keratocyst

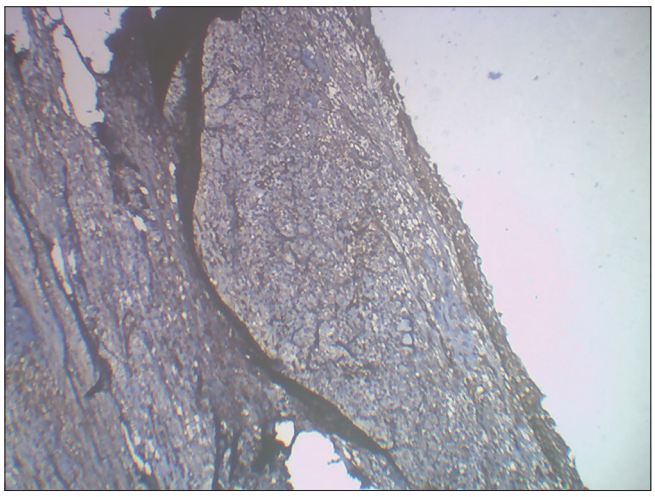

Figure 6: The given photomicrograph illustrating the quantitative staining of paxillin in OKC as score four with >75% stained cells. OKC = odontogenic keratocyst (IHC, X40)

signalling information for the control of cell behaviour, comprising cell polarity, migration and proliferation. The formation of FAs is a highly complex process that needs the assembly of multiple cellular proteins, including vinculin, talin, paxillin, tensin, zyxin, FAK, and α-actinin. The transmembrane component is an adhesion molecule from the integrin family. Integrins are heterodimers of different α and β subunits that occur in different combinations with specificity for various ECM molecules.[18]

All these specific adhesion structures present a characteristic association with the transmembrane adhesive glycoprotein that bodily connects epithelial cells to ECM or to adjoining cells. Adhesion receptors, the whole of their cytoplasmic domain, interrelate with scaffolding proteins, which secure these complexes to diverse cytoskeletal structures, together with microtubules, actin filaments and keratin intermediate filaments, consequently maintaining structural integrity throughout epithelial sheets.[19]

Cells recognise their extracellular localisation through interactions employing a range of CAMs. They relate with ECM components through syndecan and integrins molecules and with neighbouring cells through members

Table 7: Age-wise comparison of final summation score in paxillin among AB

Final summation score in ameloblastoma (Years)	0 (No stain)	Percentage	1–4 (Weak stain)	Percentage	5–8 (Strong stain)	Percentage
10–20	0	0	4	13	2	7
21–30	0	0	4	13	7	23
31–40	0	0	4	13	1	4
41–50	0	0	5	17	0	0
>50	0	0	3	10	0	0
Total	0	0	20	66	10	34

AB=Ameloblastoma

of the selectin, Ig-CAM families and cadherin, which coordinate signalling and structural functions. Such regulation may happen either as a result of actin-based and/or FAs-like structures or via one of a number of docking and scaffolding molecules.[20]

A cytoskeletal protein called paxillin localises to regions of cell/matrix interaction known as FAs.[21,22] It is a 68kDa FAs molecule, which is a key component of cellular adhesion, contributing to the formation of a 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. Paxillin acts as a framework for the tyrosine kinases sarcoma (Src), FAK, and Abelson tyrosine kinase (Abl) to be recruited to the cell membrane. In integrin-regulated signalling, FAK and paxillin play key roles. The hiring of FAK to strong FAs was revealed to be the main function for which paxillin was necessary.[23]

Paxillin regulates a number of physiological processes, including tissue remodelling, cell motility, gene expression, matrix architecture, cell proliferation, metastasis and survival, throughout these protein-protein interactions. Paxillin performs the role of adaptor protein that employs signalling molecules into its adhesion complex. Adhesion to ECM proteins, fibronectin, vitronectin, or laminin, through integrin receptors, stimulates the paxillin phosphorylation in fibroblasts.[24] Paxillin is an essential signal cross-talk mediator for these families during its phosphorylation and multipotent relations.[25]

AB is a benign odontogenic tumour. Since surgery is now the only treatment option for AB, additional therapeutic approaches are required to slow tumour growth and reduce the frequency of complicated, disfiguring operations. Numerous studies have discovered markers that are expressed by AB, and they provide insight into how tumours grow. To enhance the treatment choices for this benign tumour, it is crucial to identify which markers show the greatest promise as a possible target for therapy. The rapid growth and high recurrence rate of AB after the first surgical resection indicate that it may have aggressive biological behaviour. In previous studies, it has been reported that these adhesion molecules relate not only to the normal organisation but also to the creation of an epithelial neoplasm.[26,27] The loss of cadherin is associated with the occurrence of malignant tumours, especially invasion by the tumour and metastasis. In ameloblasts of tooth germ, these adhesion molecules are expressed during the process of tooth development, and play crucial roles in morphology.[28-30]

In the present study, paxillin seems to be well-expressed in the epithelium of both OKC and AB. Paxillin expression appears to be less important in the tumorigenic process and clinical behaviour unless it interacts with, and is phosphorylated by FAK.[31] FAK and paxillin are strongly expressed in the epithelial lining of odontogenic cysts and tumours, suggesting their role in tumorigenesis.[32]

In the present study, the staining intensity of paxillin among OKC and AB showed a significant difference. Since FAK and paxillin are closely related to each other, a study composed by Sarode *et al*.,[32] in 2017 showed statistically significant increased FAK expression in KCOT in comparison to orthokeratinised odontogenic cysts, radicular cysts, dentigerous cysts and dental follicle.

The inter-comparison of quantitative staining of paxillin among OKC and AB showed higher expression in AB as compared to OKC. However, Patil *et al*.,[33] in 2017, detected the presence of FAK in the odontogenic epithelium of AB and demonstrated higher expression in AB as compared to dental follicle. The fact that AB is neoplastic and may contribute to the tumour's invasiveness could be attributed to FAK. Through its ability to sense mechanical forces, FAK reacts to ECM interactions and controls cell invasion.[34]

In the present study, the summation score of paxillin showed more expression in AB as compared to OKC, which was, however, non-significant. In essence, it is acceptable to argue that while paxillin expression may be linked to the formation of epithelial odontogenic cysts and tumours, its interaction with FAK may play a more essential part in the relative aggressiveness of the cysts and

tumours. This could account for the similar expression of paxillin in both ABs and odontogenic cysts.

Paxillin is found in FAs in tissues and creates a structural connection between the actin cytoskeleton of cells and the ECM. Since it lacks intrinsic enzymatic activity, it mostly serves as an adapter protein, producing a large number of docking sites for other molecules that are required for the construction of FAs.[35] The formation and breakdown of FAs depend on paxillin's interaction with FAK. FAK falls when this interaction fails (as well as concomitant decreased phosphorylation of paxillin), thereby resulting in decreased cell adhesion, invasion, and migration.[35] Despite the fact that paxillin affects other family members, such as H(2)O(2)-inducible cDNA clone whose product was normally found at focal adhesions (Hic-5), in some tissues, its integrin-mediated, FAK-dependent phosphorylation appears to be the most prevalent in most cells, tissues, and neoplasms-derived from those tissues.[36]

Evidence suggests that inflammation plays an important role in tumour initiation and progression through various mechanisms.[37] According to reports, FAK signalling is activated by tumour necrosis factor-alpha, an inflammatory cytokine that functions as an endogenous tumour promoter and promotes tumour invasion.[38]

Paxillin may improve the adhesion between surrounding cells and the tumour cells and molecules, consequently helping the invasion and migration capacities of tumour cells.[25] The consequence of paxillin on invasion and cell motility is mostly mediated by tyrosine/serine phosphorylation.[39] In contrast, Sun *et al*.,[40] in 2016 suggested that paxillin overexpression in glioblastoma correlates with tumour progression and indicates poor prognosis.

A study done by Yang WJ,[41] in 2017 suggests the composition, uses, and development of paxillin, as well as its potential contribution to neovascularisation. This further promotes tumour progression. Comparison of the aforementioned results with earlier literature is not possible because no research has yet revealed the expression of paxillin in OKC. Knowing how and when these proteins associate, and what happens to other binding partners will be crucial to understanding how the cell uses the paxillin adaptor function to effectively adapt to alterations in the external environment and subsequently derive the desired functional outcome.

This study has limitations, the most important being that it is not a proof-of-concept study. It focused solely on the staining pattern of the lesions and significantly referenced research on paxillin's function in both OKCs and ABs. Another significant drawback is the sample size. This study suggests that paxillin expression is important in the biological behaviour of AB. Therefore, targeting this protein's binding sites, its interactive complexes, and the pathways related to this protein may be a good management option. Furthermore, as it has been noted that FAK plays a significant role in the functions of paxillin, tissue immunostaining for FAK and treatments that target it alone may be sufficient in such circumstances. In this study, it has been advised that the role of this integrin-activated downstream protein be further studied in OKC as well as benign and malignant AB cases.

CONCLUSION

Paxillin has the greatest influence on tissue morphogenesis and development. Paxillin has been gradually demonstrated to be necessary for cell migration by attracting cytoskeletal components and signalling molecules that play a role in cell attachment, spread and migration. These functions are linked to immunological response, epithelial morphogenesis, and embryonic development, as well as in pathological circumstances such as inflammation, oxidative stress, and interference with the endothelial cell barrier. However, further studies using a large sample size along with other molecular analytical methods may be essential to draw a definite conclusion.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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