Original Research

Immunohistochemical analysis of p53 and p63 in selected odontogenic cysts and tumours

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Abstract

Background: It is a well-recognized fact that abnormal cell proliferation plays a crucial role in the development of odontogenic lesions. p53 is a tumour-suppressor gene which assists in cell cycle regulation and p63 is a homolog of p53 responsible for ectodermal differentiation and maintenance of stratified epithelial progenitor-cell. Analysing the tissue expression of p53 and p63 in odontogenic lesions may provide us with an insight into their potential role in the development of these lesions.

Objective: The objective is to study the expression of p53 and p63 in selected odontogenic lesions using immunohistochemistry.

Materials and Methods: Formalin-fixed paraffin-embedded tissues of 15 ameloblastomas, 10 adenomatoid odontogenic tumours (AOT), 15 odontogenic keratocysts (OKCs), 10 dentigerous cysts (DCs) along with 10 cases of normal mucosa were retrieved from the departmental archives. These specimens were then subjected to immunohistochemical staining using p53 and p63 oncoproteins.

Results: p53 and p63 immune-expression showed mainly intranuclear localization. The mean positivity of p53 in ameloblastoma (59.45%) and OKC (26.38%) was significantly higher than AOT (6.77%) and DC (4%). In contrast, there was no significant difference in the positivity of p63 in between ameloblastoma (77.55%), AOT (69.50%), OKC (76.47%), and DC (50.69%).

Conclusion: p53 expression can be correlated with the clinical behaviour of the odontogenic lesions and it can be used as a prognostic marker in odontogenic cysts and tumours. In contrast, p63 expression does not corelate with the biological behaviour of odontogenic lesions.

Keywords: Odontogenic cysts, odontogenic tumours, p53, p63, proliferation, survival

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INTRODUCTION

Odontogenic cysts and tumours form a remarkable group of lesions which are known for their inherent histologic diversity. Their diverse histologic appearance can be attributed to the complex development of the dental and paradental tissues. Any aberrations in this normal process

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of tooth development can lead to the formation of these cysts or tumours.[1] The etiopathogenesis of odontogenic cysts and tumours is an enigma; their development and progression appear to be promoted by various molecular and genetic alterations.[1,2]

Although odontogenic cysts and tumours arise from the same odontogenic apparatus, they are distinct entities with different pathogenesis.[2] Numerous theories have been put forward to explain the etio-pathogenesis of odontogenic cysts and tumours; it has been postulated that abnormal cell proliferation is an important factor in the development of odontogenic lesions; this can, in turn, result from disturbances in cell cycle, mutations of proto-oncogenes, or tumour-suppressor genes.[1] The molecules that are possibly associated with tumourigenesis of odontogenic tumours include oncogenes, tumour-suppressor genes, oncovirus, growth factors, telomerase, cell cycle regulators, apoptosis- related factors, regulators of tooth development, and hard tissue-related proteins.[1]

p53 is a well-recognized and studied tumour-suppressor gene which plays a central part in the regulation of DNA replication. The fact that it functions as a tumour-suppressor gene has been irrefutably established.[3] It acts by either causing cell cycle arrest or apoptosis whenever there is any genomic damage.[3] The concentration of p53 protein in normal cells is low owing to its short half-life; the presence of a mutation in the gene stabilizes the protein which in turn accumulates in the cell, facilitating its easy detection by immunohistochemistry.[4] Hence immunohistochemical demonstration of p53 protein in lesional cells is synonymous with mutated p53 gene.[4] Its role in other malignant lesions has been well documented, but very few studies are present regarding its role in odontogenic lesions.

p63 and p73 are homologs of p53 which were discovered in 1997, and they share a remarkable structural similarity with p53. Both the genes have diverse functions, which include p53-related and -independent functions. The p53-related functions are either synergistic or interfering in nature.[5] In contrast to the suppressing functions of p53, the p63 homolog is known to function primarily in ectodermal differentiation and maintenance of stratified epithelial progenitor cell. It has also been observed that p63 can act as an oncogene.[6]

Immunoexpression of p53 has been found to be variable and diffuse in odontogenic cysts and tumours; it has also been observed that increased expression of p53 is seen in locally aggressive tumours.[7] Immunohistochemical expression of p63 has been detected in the cells of odontogenic tumours as well as cysts; higher p63 expression is seen in locally aggressive odontogenic tumours than in nonaggressive tumour.[8]

In the present study, we have attempted to investigate the expression of p53 and p63 in selected odontogenic lesions using immunohistochemistry and further compare their expression in the selected lesions.

MATERIAL AND METHODS

The study was conducted in the Department of Oral Pathology and Microbiology, SDM College of Dental Sciences and Hospital, Dharwad. Prior to the commencement of the study, ethical approval was obtained from the Institutional Ethics Committee. A total of 60 cases of histopathologically diagnosed odontogenic tumours and cysts were included in the present study. These included 15 ameloblastomas, 10 adenomatoid odontogenic tumours (AOT), 15 odontogenic keratocysts (OKCs), 10 dentigerous cysts (DCs) along with 10 cases of normal mucosa. Formalin-fixed paraffin embedded tissues were retrieved from the departmental archives. These specimens were then subjected to immunohistochemical staining using p53 and p63 oncoproteins.

Immunohistochemical staining procedure

The staining was carried out using Super-sensitive polymer HRP detection system, a biotin-free detection system supplied by Biogenex Life Sciences Limited (CA, USA). The primary antibodies used were p53 [Clone DO 7, IgG2b immunoglobulin] and p63 [Clone 4A4, IgG2a immunoglobulin]. The procedure followed was as per the instructions mentioned by Biogenex. Antigen retrieval was done using a pressure cooker and the reaction was visualized using DAB chromogen. Subsequently, the slides were counter stained with Harris haematoxylin, mounted with DPX and examined under a light microscope.

Evaluation methodology of IHC staining

The presence of coloured products was considered as positive for the expression of p53 and p63, which was appreciated in positive control sections. All the sections were scanned under low power to ascertain that even staining was obtained. The fields with even staining were chosen and number of positive cells out of 400 were calculated (for DC 100 cells were counted). The average in percentage was taken for each case for statistical analysis. An eyepiece (×10), having an oculometer grid with 100 blocks (10 × 10) was fitted to a binocular microscope and the cell counting was performed under 40 × magnification.

Four hundred cells were counted in each slide in a step ladder pattern fashion to avoid recounting of the same areas. The percentage positivity of the tumour cells was calculated by the following method:

$$\% \text{ of positive tumour cells} = \frac{\text{Total no. of positive tumour cells}}{\text{Total no. of tumour cells}} \times 100$$

Statistical analysis

The results were tabulated and statistically analysed. The overall differences between the quantitative expression of p53 and p63 in different groups were calculated using the Kruskal–Wallis ANOVA test and the pairwise comparison between different groups was calculated using the Mann–Whitney *U* test. The level of significance was set at 5%. All statistical calculations were performed with OpenEpi Ver 2.3.

RESULTS

A statistically significant difference was observed in the expression of p53 between ameloblastoma and AOT with increased expression in ameloblastoma ($P < 0.05$). Similarly, increased expression of p53 was seen in OKC as compared to DC ($P < 0.05$). No significant difference was seen in the expression of p63 between ameloblastoma and AOT ($P > 0.05$).

Immunohistochemistry

All the cases of normal mucosa were negative for p53 expression, while p63 was prominently expressed in the basal and supra-basal layers of the epithelium. [Figure 1a and b] In contrast, all the cases of ameloblastoma showed positivity for both p53 and p63. [Table 1] The positivity of p53 was seen ranging from 30% to 90% (mean = 59.45%), while p63 positive cells ranged from 40% to 93% (mean = 77.55%). Overall, the cells showed much more intense staining with p63 than p53. Interestingly, it was observed that more intense p53 staining was seen in the peripheral ameloblast-like cells as compared to the stellate reticulum-like cells, such a difference was not seen in the case of p63. [Figures 2a and 3a].

In case of AOT, four cases showed positivity for p53 and most of the positivity was seen in the cells lining the duct-like structures. In contrast, there was diffuse and intense staining with p63. [Figures 2b and 3b] The percentage positivity of p53 was seen ranging from 8 to 30% (mean = 6.77%), while p63 positive cells ranged from 25 to 95% (mean = 69.50%). [Table 1].

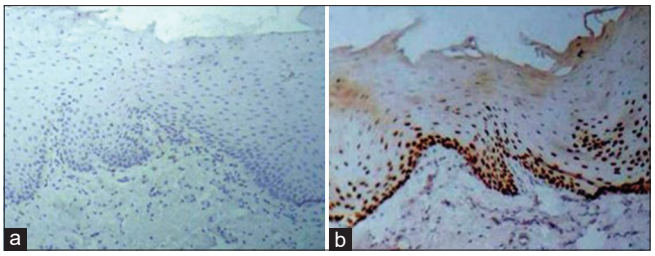

Figure 1: (a) Negative p53 expression seen in normal oral mucosa (10×). (b) Intense p63 expression seen in normal oral mucosa (10×)

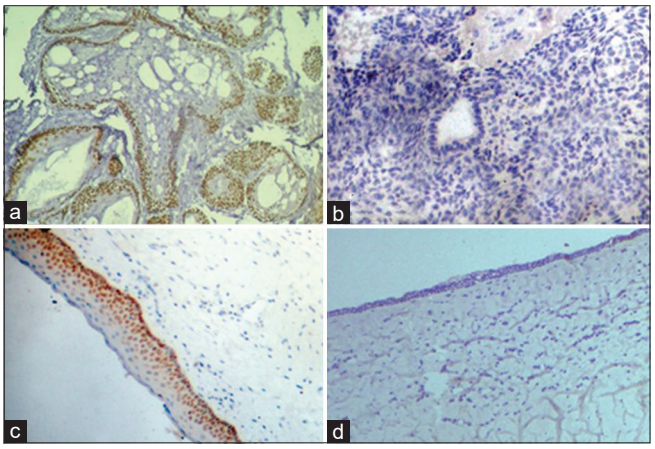

Figure 2: (a) p53 expression in follicular ameloblastoma showing staining predominantly in peripheral ameloblast-like cells (10×). (b) Negative p53 expression in AOT (10×). (c) p53 expression in OKC showing moderate intensity (10×). (d) Negative p53 expression in DC (10×)

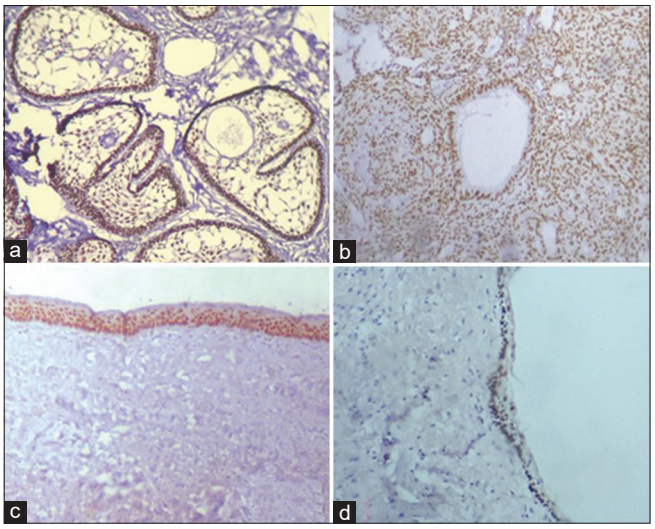

Figure 3: (a) p63 expression in follicular ameloblastoma showing intense staining predominantly in peripheral ameloblast-like cells (10×). (b) p63 expression in AOT showing intense positivity (10×). (c) p63 expression in OKC showing intense positivity in basal and parabasal layer (10×). (d) p63 expression in DC showing moderate intensity, predominantly in basal cell layer (10×)

In total, 94% of the cases of OKC showed positivity for p53, while all the cases were positive for p63. The percentage positivity of p53 ranged from 0 to

60% (mean = 26.38%), while the p63 positivity ranged from 40 to 93% (mean = 76.47%). [Table 1] Similar to ameloblastoma staining was much more intense with p63 as compared to p53. [Figures 2c and 3c] Interestingly, it was seen that one case of orthokeratinised odontogenic cyst did not show any positivity for p53 but expressed positive p63 immunoreactivity.

In DC, only two cases showed positivity for p53 while all the cases showed positivity for p63. The percentage positivity of p53 was seen to be 8.2 and 4%, respectively, in the two cases, while the percentage positivity for p63 positivity ranged from 32 to 75% (mean = 50.69%). [Table 1] The intensity of p63 was found to be less than other lesions. [Figures 2d and 3d].

A statistically significant difference was found in the quantitative expression of p53 between ameloblastoma and AOT ($P < 0.05$); a similar difference was seen in the expression of p53 between OKC and DC ($P < 0.05$). However, no statistically significant difference was observed between AOT and DC. [Table 2].

No statistically significant difference was found in the quantitative expression of p63 between ameloblastoma and AOT as well as between AOT and DC. However statistical significance was observed between OKC and DC ($P < 0.05$). [Table 3].

Table 1: Quantitative expression of p53 and p63 expression in ameloblastoma, AOT, OKC, and dentigerous cyst

Groups	P53		P63	
	Mean	SD	Mean	Mean
Ameloblastoma	59.45	18.77	77.55	16.61
OKC	26.38	13.20	76.47	14.40
AOT	6.77	10.11	69.50	25.31
DC	1.22	2.76	50.69	15.05

SD: Standard deviation; OKC: Odontogenic keratocyst; AOT: Adenomatoid odontogenic tumour; DC: Dentigerous cyst

Table 2: Comparison of p53 expression between different groups

Group	Rank Sum	*P*	Significance
Ameloblastoma	269.00	0.0000	Significant
AOT	56.00		
OKC	264.00	0.0001	Significant
DC	61.00		
OKC	253.00	0.0013	Significant
AOT	72.00		
AOT	118.50	0.3075	Not significant
DC	91.50		

OKC: Odontogenic keratocyst; AOT: Adenomatoid odontogenic tumour; DC: Dentigerous cyst

Table 3: Comparison of p63 expression between different groups

Group	Rank Sum	*P*	Significance
Ameloblastoma	203.50	0.6373	Not significant
AOT	121.50		
OKC	255.50	0.0008	Significant
DC	69.50		
OKC	198.00	0.8678	Not significant
AOT	127.00		
AOT	126.00	0.1124	Not significant
DC	84.00		

OKC: Odontogenic keratocyst; AOT: Adenomatoid odontogenic tumour; DC: Dentigerous cyst

DISCUSSION

Numerous theories have been put forward which attempt to explain the etiopathogenesis and further progression of odontogenic cysts. Almost all the cysts are thought to arise due to the accumulation of fluid or semifluid and subsequent expansion of the lesion without any intrinsic growth potential. For DC, it has been hypothesized that it develops due to the accumulation of fluid between the newly formed tooth and the reduced enamel epithelium surrounding the tooth. It is only for OKC, that evidence has been accumulated regarding the intrinsic growth potential of its cystic lining.[9,10]

Little is known about the pathogenesis of odontogenic tumours, and various studies conducted have shown perturbations in cell cycle, proto-oncogenes expression, and tumour-suppressor gene mutations.[11] Alterations in the expression of p53 gene, which is a tumour-suppressor gene, may be one of the causes for the proliferation of cells.[4]

In our study, the overexpression of p53 in ameloblastoma as compared to AOT suggests that it has a greater proliferative potential. This is also evident from its aggressive behaviour and tendency to recur. However, this was in contrast to a study where none of the cases of ameloblastoma showed positivity for p53.[12] They attributed their finding to three possible explanations: firstly, there may be no mutation of the wild-type p53 gene, thus the protein had a short half-life and was undetectable; second, the mutation did not result in stabilization of the protein; and lastly, the p53 gene may have been deleted.[12]

Regarding AOT, only 40% of the cases showed positivity for p53, and the percentage positivity of cells was very low (8–38%). The staining intensity was seen to be mild to moderate with focal distribution. Similar findings have been previously reported with low or absent p53 labelling index in AOT.[12,13] These findings indicated a low cellular proliferative potential in AOT. When the expression of p53 in ameloblastoma and AOT was compared and analysed, a statistically significant difference was evident,

with ameloblastoma showing an increased expression of p53. The results indicate that the proliferative potential is much higher in ameloblastoma than in AOT, which is also reflected by the fact that ameloblastoma is much more aggressive and invasive.[14]

Staining results of p53 expression in the epithelial lining of OKC revealed 94% of the cases with positivity which was similar to previous studies.[15] Furthermore, in our study, it was also seen that the p53 expression was more prominent in the basal as well as suprabasal layers. This can be explained by the fact that OKC differs from other odontogenic cysts by the increased epithelial mitotic activity in suprabasal layers.[16] In contrast to OKC only 20% of the DC cases showed p53 positivity, which was confined to the basal layer. These findings were concordant with previous studies.[17,18] In our study, the expression of p53 was higher in OKCs than in DCs. This difference suggests a disturbance in the cell cycle with a consequent increase in cell proliferation, which could explain the clinical behaviour of OKC.[19]

The expression of p53 among the epithelial layers was found to be more uniform and homogenous in OKC. This can be explained by the fact that the protein may be stabilized due to perturbance in p53 gene, which subsequently leads the lining to acquire intrinsic growth potential.[17,18] Though OKC is considered to be a cyst, its proliferative activity is significantly higher than DC and is similar to that of ameloblastoma. Hence, while treating OKC its aggressive nature should be taken into consideration.

Our findings are similar to previous studies wherein it has been observed that increased expression of p53 is seen in aggressive lesions like ameloblastoma and OKC.[20,21] This finding is clinically significant as it reinforces the utility of p53 as a prognostic marker in odontogenic lesions. Additionally, it can also help in identifying aggressive lesions and prevent recurrences by suitably modifying the treatment protocol in such lesions.

In oral mucosa, p63 expression is predominantly seen in undifferentiated cells which are chiefly localized in the basal and suprabasal layers of the squamous epithelium. On the other hand, there is a scant or complete absence of its expression in the spinous layer where the terminal differentiation of cells occurs.[22,23] Hence, p63 expression is associated only with proliferative areas in the epithelium. Similar reasoning can be applied in the case of odontogenic epithelium.

The p63 staining in our study was seen to be intense and diffuse in all the variants of ameloblastoma analysed. It was further observed that in some cases peripheral cells in follicular ameloblastoma showed more intense positivity than the stellate reticulum-like cells, which can be explained by the fact that in ameloblastoma the proliferative activity is much higher in the peripheral columnar cells.[24] Our study suggests that p63 may be associated with the proliferation and maintenance of odontogenic epithelium.

Similar to ameloblastoma the p63 staining in AOT was also intense and homogenous. Furthermore, in DCs also, the p63 positivity was confined to the basal layer of the epithelium. These findings confirm the progenitor characteristics of the odontogenic epithelial cells that make up this benign tumour, which has low-grade proliferative potential and possesses a wide phenotypic morphological variety.[25] This lends credence to the fact that p63 may play an important role in the differentiation and maintenance of odontogenic epithelial cells.

Contrary to the DC, the p63 expression in OKC demonstrated intense staining that was not only confined to the basal but in a few cases was also seen in the suprabasal layers. The more intense and diffuse expression of p63 in OKCs as compared to DCs indicates an altered cell cycle leading to the acquisition of intrinsic growth potential.[8] The difference seen in the expression of p63 in OKC and DC could possibly explain their divergent clinical and pathologic behaviour.

Limitations

Even though our study sheds important light on the molecular properties of these lesions, there are several limitations that need to be taken into consideration. First of all, the study had a small sample size, which would have limited the generalizability of results to more extensive diseases of odontogenic lesions. Additionally, our data and the outcomes may be subject to variation due to the inherent heterogeneity in immunohistochemical procedures, including antibody choice, staining protocols, and interpretation. Furthermore, our cross-sectional approach only provides a static picture of p53 and p63 expression, whereas longitudinal investigations can offer a more dynamic viewpoint. Other significant drawbacks include the clinical variability of odontogenic lesions, the dearth of functional data, the disregard for confounding variables, and geographic variation.

CONCLUSION

The quantitative expression of p53 was significantly higher in OKC and was similar to that of ameloblastoma; this

finding attests to the intrinsic growth potential present in the lining of OKC and further attests to its aggressive biological behaviour. p53 expression can be correlated with the aggressive behaviour of the odontogenic lesion and it can be used as a prognostic marker in odontogenic cysts and tumours; furthermore, it may also be useful in identifying aggressive odontogenic lesions. On the other hand, p63 plays an important role in the proliferation and maintenance of odontogenic epithelial cells but increased expression does not correlate with the biological behaviour of odontogenic lesions.

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Conflicts of interest
There are no conflicts of interest.

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