ORIGINAL RESEARCH

Evaluation of Caveolin-1 Expression in Different Grades of Oral Epithelial Dysplasia

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Abstract

INTRODUCTION: Caveolae are 50-100 nm flask shaped invaginations seen in the plasma membrane of most cells, made up of three proteins. The role of caveolin-1 (Cav-1), one of these proteins, has been investigated in various tumors, including some malignancies of the head and neck region. However, its role in potentially malignant lesions is unknown. Therefore, we designed a study to evaluate the expression of Caveolin-1 in various grades of oral epithelial dysplasia.

MATERIALS AND METHODS: The present study was conducted using 45 archival tissue samples of histopathologically confirmed different grades of oral epithelial dysplasia (mild, moderate, and severe). Sections of 4-micron thickness were made from each block and slides were stained using Cav-1. The intensity of expression and percentage of immunopositive cells were evaluated for each case. Results obtained were compared using a one-way ANOVA test.

RESULTS: All 45 cases showed positivity for caveolin-1 expression, although the degree, extent, and intensity of staining were different among different groups. The number of cells taking up Cav-1 decreased as the severity of dysplasia increased. All three groups showed mild to moderate intensity of Cav-1 expression.

CONCLUSION: Cav-1 expression is altered in oral epithelial dysplasia. Expression is inversely related to the grade of dysplasia. Decreased expression was noticed when the severity of dysplasia increased, which probably indicates an increased tendency towards malignant change.

KEYWORDS: Caveolin-1, Immunohistochemistry, Oral epithelial dysplasia, Oxidative stress, Tumor suppressor,.

Introduction

Dysplasia is the diagnostic term used to describe the histopathological changes seen in chronic, progressive, and premalignant disorders of oral mucosa. It is a disturbance in a maturational sequence of stratified squamous epithelium and a disturbance in cell kinetics of the proliferative compartment with cytological changes.[1,2] Dysplasia is theoretically reversible and therefore not malignant. When the underlying provoking stimulus is removed, the dysplastic alterations revert to normal.[3]

Currently, there is no strong affirmation for the use of tumor markers in identifying the progression of oral dysplasia. Long-term studies indicate that the presence of loss of heterozygosity at specific loci (3p and 9p), survivin, matrix metalloproteinase (MMP) - 9 positivity and non-diploid deoxyribonucleic acid (DNA) content are potential markers for increased opportunity of progression of oral dysplasia to cancer. Other markers identified include tumor protein p53, p73, MMP1, MMP2, cathepsin L mRNA, B cell lymphoma-2 (Bcl-2), downstream of tyrosine kinase (DOK), Ras-related protein Rab11a, p53, cell line POE9n, and cluster of differentiation (CD) 44.[4,5]

Caveolae were the exclusive electron microscopic description of a membrane invaginated "smooth" vesicles of 50 to 100 nm in size. The caveolae family has three proteins: Caveolin (Cav) -1, Cav-2, and Cav-3.6 There are two isoforms of Cav-1, which differ in their molecular structure and are known as Cav-1α and Cav-1β. Both isoforms share a complete C-terminal end, but they differ in their N-terminal end. In the protein sequence, only Cav-1α has a complete N-terminal end. Cav-1α is made up of 178 amino acids. In contrast, Cav-1β is 32 amino acids shorter at the N-terminal end. Nevertheless, the two Cav-1 isoforms have a common

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hydrophobic stretch of amino acids, a framework domain, and an acetylated C-terminus. So far, differences in the expression of these two isoforms in the fibroblasts of the oral mucosa have not been published. Cav-1α and Cav-1β might differ not only in their molecular structure but also in their function. Tyrosine phosphorylation only occurs at residue 14 (tyrosine 14) in the

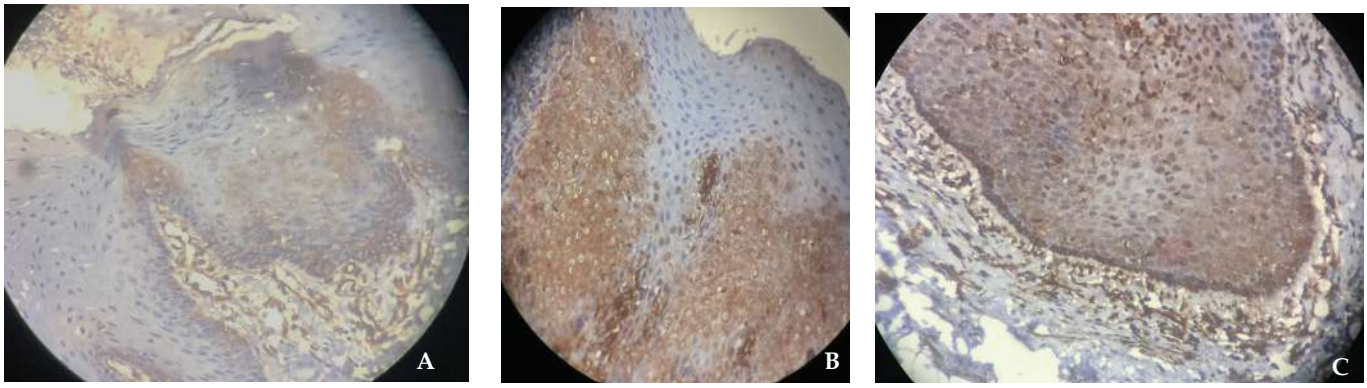

Fig.1. Photomicrograph of immunopositivity for Cav-1 **A)** 0 to 25% of positivity and mild expression. **B)** 26% to 50% of positivity and moderate expression. **C)** 51% to 75% of positivity and moderate expression. (20x)

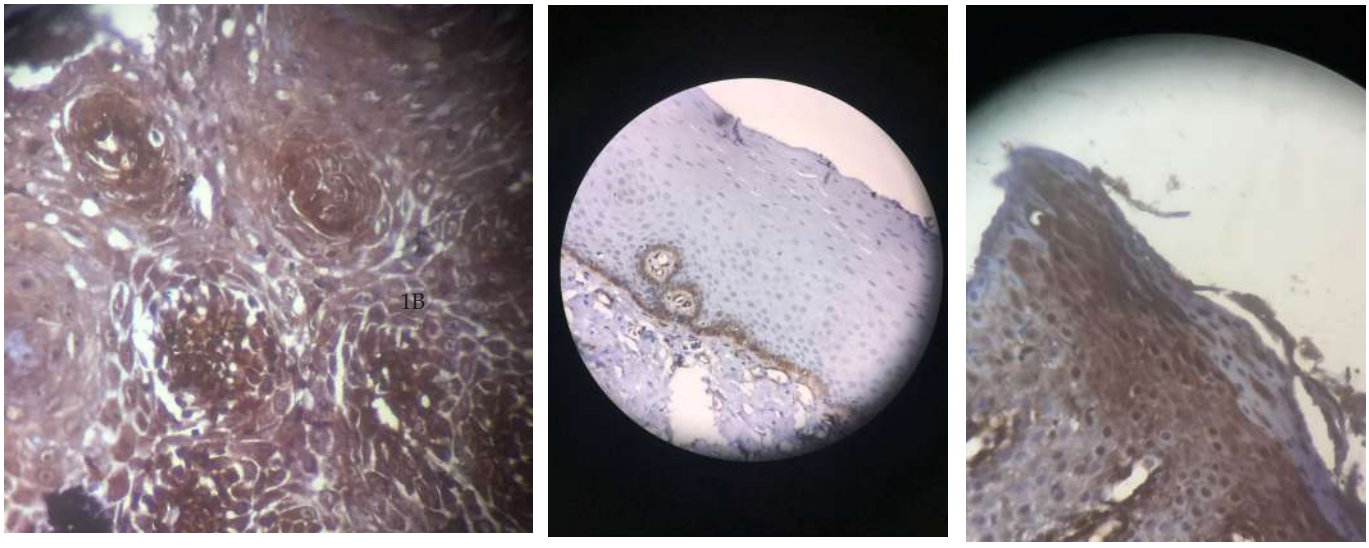

Fig. 2. Photomicrograph of immunopositivity for Cav-1. **A)** 75% to 100% of positivity and intense expression. **B)** exclusively in the basal cell layer **C)** in all the layers of the epithelium(20x)

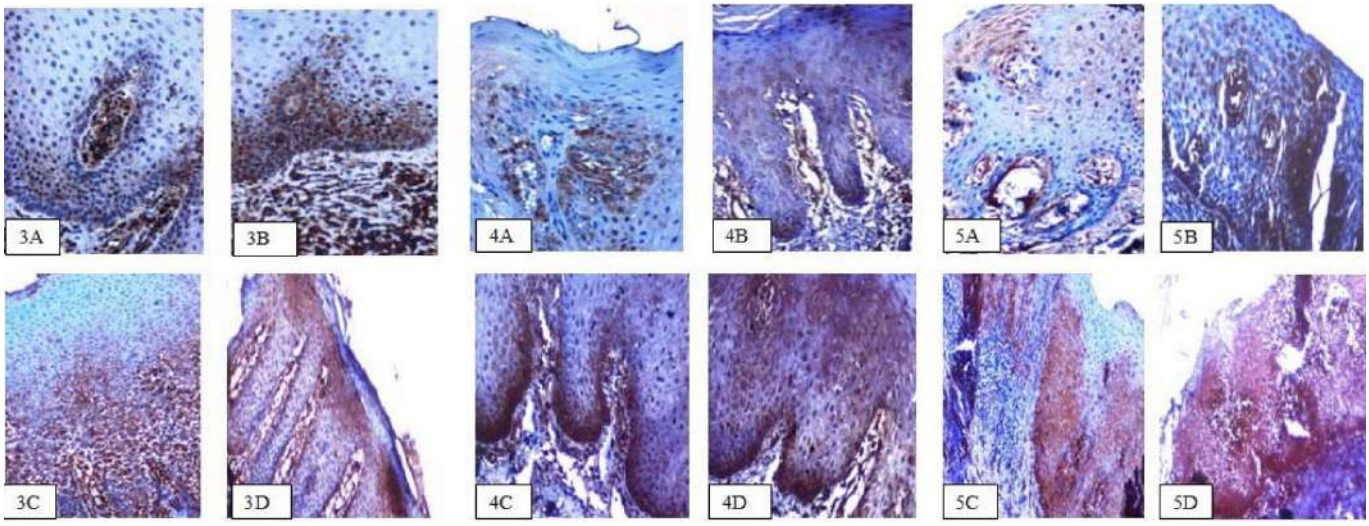

Fig.3,4,5. Photomicrograph of immunopositivity for Cav-1, **Fig.3**, in Mild Dysplasia. **Fig.4,** in Moderate Dysplasia. **Fig.5**, Severe Dysplasia. **A)** 25% of positivity. **B)** 26% to 50% of positivity. **C)** 51% to 75% of positivity, **D)** 76% to 100% of positivity (20X)

Cav-1α isoform which might result in different tasks of the isoforms within the cell. The differences in the molecular structure of the two isoforms of Cav-1 could explain the different roles that Cav-1 can play in tumor progression. The function of Cav-1 in tumor cells seems to be highly context-dependent exerting both tumor-suppressive and oncogenic effects.[6] The oncogenic role of Cav-1 in cancer has been widely investigated in multiple studies.[12]

Caveolin-1 expression has been reported during mouse odontogenesis, particularly in the lingual portion of the tooth germ in the initial stages of odontogenesis. With the progression of the developmental stages, a gradual increase in caveolin-1 in the inner enamel epithelium, cervical loop, and ameloblasts was observed.[12] Some studies show increased expression of Cav-1 in malignancies such as salivary gland tumors, melanoma, squamous cell carcinoma, pancreatic ductal adenocarcinoma, adenocarcinoma of the colon, and lung adenocarcinoma. Cav-1 is a tumor suppressor gene in ameloblastoma, ovarian carcinoma, and different sarcomas.[13] These distinct roles in different types of cancers could probably be due to both differential activation of different domains of Cav-1 and diverse molecules interacting with Cav-1.[8]

Caveolin 1 has been shown to interact with numerous oxidative enzymes and could therefore be involved in the regulation of oxidative stress-induced pathways. In a study in proliferating mouse myoblasts, hydrogen peroxide treatment decreased caveolin 1 expression suggesting that the protein is very quickly targeted by oxidative stress.[10]

Considering the role of altered expression of Cav-1 in the pathogenesis of some human malignant neoplasms, its expression in premalignant lesions becomes an important factor to study. The aim of the present work therefore, was to evaluate the expression of Caveolin-1 in various grades of oral epithelial dysplasia by immunohistochemistry.

Materials and Methods

A total of 45 samples of three different grades of histopathologically diagnosed oral epithelial dysplasia, namely mild (n=15), moderate (n=15), and severe (n=15)] dysplasia, were included in the study. These archival tissues were fixed in neutral buffered formalin, processed, and embedded in paraffin wax. Caveolin -1 normally expressed in endothelial cells. So the endothelial cells present in the tissue acts as an internal or positive control. While doing the procedure a section was not incubated with primary antibody and the rest of procedure was carried out and used as a negative control.

All 45 cases selected were subjected to immunohistochemical (IHC) staining to evaluate the expression of Caveolin-1. Four-micron-thickness sections were cut for immunohistochemical staining, deparaffinized and rehydrated, and then washed with distilled water. After antigen retrieval for 20 minutes in citrate buffer, sections were incubated with anti-caveolin-1 polyclonal rabbit antibody (1:1000, Abcam, US) at 21°C for 2 hours. Sections were then covered with super -enhancer for 20 minutes and washed with Tris buffer. Slides were then treated with a secondary antibody tagged with horse radish peroxidase enzyme (HRP) for 30 minutes. Immunostaining was developed by treatment with freshly prepared 3-diaminobenzidine tetrahydrochloride (DAB) solution for 5 minutes, followed by counterstaining in Harris hematoxylin, dehydration, and mounting. The presence of a brown-colored end product at the site of the target antigen (membrane and cytoplasmic positivity) was considered as positive immunoreactivity.

The immunostained slides were observed under a bright-field microscope at a magnification of 40x in five randomly selected fields to analyze the percentage of cells showing positivity and the color intensity as well. Semi-quantitative analysis of stained cells was done according to the immunoreactive score (IRS) by Remmele and Stegner, but this was modified regarding the grading of positive cells. Percentage of positive cells (PP) was graded on a point scale regarding - 0 point - No expression; 1 point - 1 to 25% of positive cells (Shown in Fig.1A,3A,4A,5A); 2 points - 26 to 50% of positive cells (Shown in Fig.1B,3B,4B,5B); 3 points – 51 to 75% of positive cells (Shown in Fig.1C,3C,4C,5C); 4 points - 76 to 100% of positive cells (Shown in Fig.2A,3D,4D,5D). Intensity of the staining (IOS) was also graded on a point scale (0 point - No color reaction; 1 point - mild color reaction; 2 points - moderate color reaction; 3 points - intense color reaction). Final immunoreactive scoring (IRS) was obtained by multiplying the points obtained for PP and IOS and interpreted as follows: negative – 0 to 1 point, mild positivity – 2 to 3 points, moderate positivity – 4 to 8 points, and strong positivity – 9 to 12 points. The data obtained were analyzed statistically using one-way ANOVA followed by the post hoc Tukey test. A p-value of less than 0.05 was considered to be statistically significant.

Results

The mean percentage of positive cells (PP) was found to be decreasing as the grades of dysplasia increased. Mean value of positive scores in the mild group was 1.60; in the moderate group, it was 1.40, and in the severe group, it was 1.20. These variations in the mean PP values were not statistically significant ($p = 0.321$). Intensity of staining (IOS) scores were compared among the three groups, we found that the mean value of IOS scores in the mild group was 1.73; in the moderate group, it was 1.47, and in the severe group, it was 1.53. Comparison of these values of IOS using ANOVA revealed no significant difference among the groups. ($p = 0.384$). Similarly, the mean immunoreactivity scores of the three groups were found to be 2.93 in the mild dysplasia group, 2.27 in the moderate dysplasia group, and 2.07 in the severe dysplasia group. These values were not significantly different statistically ($p = 0.435$).

We also qualitatively assessed all the slides to check which layer of the epithelium had taken up the stain. The site of staining (cytoplasmic, membranous or nuclear) was identified in each of the slides. We found that in the mild dysplasia group, all samples showed positive staining in basal and parabasal layers. However, 11 cases (73%) also showed positivity up to the granulosa layer, with only one sample showing positivity throughout the epithelium including the corneal layer (Shown in Fig.2C). In the moderate dysplasia group, most of the samples showed positivity in the basal layer. However, eight cases (53%) showed positivity up to the stratum granulosum also. In the severe dysplasia group, most of the samples showed positivity in the basal and parabasal layers. However, only two

cases (13%) showed positivity up to the stratum granulosum. (Table:1)

Overall comparison of percentage of positivity scores (PP), intensity of staining (IOS) and the immunoreactivity scores (IRS) among the three groups; The mean value of percentage of positivity (PP) scores, in the mild group it was 1.60; in the moderate group it was 1.40 and in the severe group it was 1.20. Values were not statistically significant (p = 0.321). (Table 2).

The mean value of intensity of staining scores (IOS), in the mild group it was 1.73; in the moderate group, it was 1.47, and in the severe group, it was 1.53. Comparison of these values using ANOVA revealed no significant difference among the groups. (p = 0.384) (Table 3).

The mean value immunoreactivity scores (IRS), in the mild group were found to be 2.93; in the moderate group, they were 2.27 and in the severe group, they were 2.07. Comparison of these mean values was done using ANOVA. It revealed no significant difference among the groups. (p = 0.435). (Table 4).

Discussion

Caveolae present on the plasma membranes play a significant role in important cellular functions like lipid transport, membrane transport, signal transduction, etc. There is an increased expression of Cav-1 in malignancies like salivary gland tumors, melanoma, esophageal squamous cell carcinoma, adenocarcinoma of the colon, lung adenocarcinoma, etc. However, its role in oral squamous cell carcinoma is unclear.[12] Some studies have shown an increased expression of Cav-1 in OSCC, while others observed a decreased expression or inactivation of Cav-1 in OSCC, leading researchers to assume that it has a biphasic role.[9]

In our study, all 45 cases showed positivity for caveolin-1 expression, although the degree, extent, and intensity of staining were different among different groups.(Fig.3,4,5) We found that the mean percentage of positivity (PP) score gradually decreased from the mild dysplasia group to the severe dysplasia group (mean PP score in mild dysplasia = 1.6; moderate dysplasia = 1.4; severe dysplasia = 1.2). Although this difference in PP scores was not significant statistically (p=0.32), it could be inferred that the number of cells taking up Cav-1 decreases as the severity of dysplasia increases. Ashkavandi et al., compared Caveolin 1 expression in oral lichen planus, dysplastic lesions, and squamous cell carcinoma, found that Cav-1 expression was increased with increasing grades of dysplasia, but the difference was not statistically significant.[7] This is in contrast to our findings where the number of positive cells decreased with increasing grades of dysplasia. Hung et al., evaluated Cav-1 expression in normal oral mucosa, dysplasia, and squamous cell carcinoma. They found that among the eight dysplastic tissues, four were Cav-1 ++, which indicates Cav-1 positivity over 50% of cells.[9] These findings are in accordance with our study where we found that all dysplastic tissues were showing positivity scores between 1 and 2 (score 1 - 1 to 25% positive cells; score 2 – 26 to 50% positivity). However, Hung et al. did not group dysplasia into different grades in their study.[9]

Intensity of staining (IOS) was assessed in the three groups of dysplasia. We found that there was no significant difference in IOS scores among the three groups. All three groups showed mild to moderate intensity of Cav-1 expression. Ashkavandi et al. evaluated the staining intensity for Cav-1 in different groups of dysplasia and found that 69.2% of the samples showed moderate staining.[7] This finding is in accordance with our study where most of the tissues showed mild to moderate staining for Cav-1.

When the overall immunoreactivity scores were compared, we found that the IRS decreased as the grade of dysplasia increased (mild – 2.93; moderate – 2.27; severe – 2.07). Our find-

Table 1: Extension of Percentage of positivity among the mild, moderate, and severe dysplasia.

Dysplasia group	Staining in basal and parabasal layers	Staining upto stratum granulosum	Staining upto stratum corneum
Mild Dysplasia (25 samples)	100%	11%	4%
Moderate Dysplasia (25 samples)	100%	53%	-
Severe Dysplasia (25 samples)	100%	13%	-

Table 2: Comparison of mean PP scores among the mild, moderate, and severe dysplasia using one way ANOVA

Group	N	Mean	SD	F value	Significance
Mild	15	1.6	0.63	1.167	0.321
Moderate	15	1.4	0.83		
Severe	15	1.2	0.68		

Table 3: Comparison of mean IOS scores among the mild, moderate and severe dysplasia using one way ANOVA

Group	N	Mean	SD	F value	Significance
Mild	15	1.73	0.46	0.978	0.384
Moderate	15	1.47	0.52		
Severe	15	1.53	0.64		

Table 4: Comparison of mean IRS among the mild, moderate, and severe dysplasia using one way ANOVA

Group	N	Mean	SD	F value	Significance
Mild	15	2.93	1.58	0.849	0.435
Moderate	15	2.27	1.98		
Severe	15	2.07	2.12		

ings are in contrast to the findings of Ashkavandi et al., since they noticed that 54.5% of their samples had a high score for immunoreactivity.[7] We found that only three cases out of 45 had such a high score for IRS (≥ 6). However, the technique used by Ashkavandi et al., to calculate the score was entirely different from the methodology we followed. 7 Cav-1 expression in premalignant lesions using Quantum Dot Immunofluorescent histochemistry QD's IHC by Xue et al., found that ten out of 15 cases of pre-malignant lesions showed less expression of Cav-1.11 Cav-1 expression, "mild" to "moderate" tongue epithelial dysplasia revealed basal or parabasal cells staining, whereas 5 "severe" tongue epithelial dysplasia samples revealed the whole epithelial layer staining.[11] Although their methodology for Cav-1 staining was radically different, their findings are almost similar to our findings with regard to Cav-1 expression in mild and moderate dysplastic group and contrast in the severe dysplastic group. We also found that almost all samples, irrespective of the grade of dysplasia, were positive in the basal layers. As the severity of dysplasia increases Cav-1 appears to become more localized in the basal and parabasal layers. Our findings are in accordance with the findings of Ashkavandi et al, showing that 99% of epithelial dysplasias were positive for Cav-1 in the basal layer (Fig.2.B) whereas only 30% showed positivity in the suprabasal layers. They also noted that the superficial layers of epithelium were negative for Cav-1 in all specimens.[7] According to Hung et al., Cav-1 immunoreactivity was confined to basal or parabasal cells in hyperplastic epithelia, mild dysplasia and relatively less expressed in other layers.[9] However, in Cav-1 positive dysplastic lesions, immunoreactivity was observed in the full thickness of the epithelium. In two samples of normal epithelial gingival tissue scarce immunohistochemical staining was observed, mainly restricted to the basal layer.

The role of Cav-1 in oral epithelial dysplasia and oral carcinoma is highly controversial. Several studies implicate Cav-1 as a tumor suppressor. However, studies of Ashkavandi et al., and Hung et al., have also established that Cav-1 may participate in tumor progression and metastasis. According to Ashkavandi et al., and Hung et al., overexpression of Cav-1 was observed in oral squamous cell carcinoma (OSCC).[7,9] Conversely, Cav-1 expression in oral epithelial dysplasia is variable, with some studies concluding that Cav-1 is over-expressed in epithelial dysplasia, while others showed no marked change or decreased expression of Cav-1.

It has been proposed that Cav-1 is differently expressed in different stages of tumorigenesis. Hung et al observed Immunoreactivity of Cav-1 was widely distributed in dysplastic lesions and more localized in hyperplastic cases. Cav-1 overexpression could be involved at a later stage of carcinogenesis in oral premalignant lesions.[9] Mishra et al, found increased Cav-1 as the grade of squamous cell carcinoma increases which contradicts our study.[14] However, in well-differentiated squamous cell carcinoma, the expression of Cav-1 was low. Cav-1 seems to have diverse effects in different tissues and cells probably due to differential activation of different domains of Cav-1 or the diverse molecules interact with it. Hung et al concluded that the inactivation of caveolin-1 by a mutation or by reduced expression may play a role in the pathogenesis of oral SCC.[9]

Among 12 Tooth Germs, only one sample was negative for caveolin- 1, and most samples presented strong positivity in the epithelial components. Immunostaining was also observed in the mesenchymal components of the bell stage, such as the secretory odontoblasts and the adjacent dental papilla, while in the early stages (bud and cap), the positivity was limited to the epithelial components (stellated reticulum, inner and outer enamel epithelium). Most of the blood vessels and adjacent osteoblasts were positive. The caveolin-1 immuno-expression patterns throughout the stages of TG show its importance during odontogenesis. The similar patterns of caveolin-1 overexpression in Ameloblastoma and Ameloblastic carcinoma suggest that it could play a role in protumoral events, probably through metabolic alterations, but not necessarily participate in the malignant transformation process.[13]

Expression of Cav-1 in the basal layers could be attributed to the proximity of the basal cells with the stroma. Stromal components like matrix metalloproteinase (MMP) have been established to interact with Cav-1, thereby resulting in their overexpression in basal and parabasal layers (Fig.2B). Cav-1 has also been identified as a potential target for oxidative stress-related changes in cells and tissues. Recent evidence has shown that oxidative stress processes in cancer cells are strongly associated with Cav-1.[10]. It has been noted that oxidative stress leads to a reduction of Cav-1 by modulating its expression and degradation. On the contrary, studies have also suggested that a decrease in Cav-1 promotes oxidative stress and mitochondrial dysfunction. Whether oxidative stress leads to Cav-1 loss or whether Cav-1 suppression results in increased oxidative stress is a subject of controversy. Oxidative stress is the main cause for downregulation of stromal caveolin-1 via autophagy in the tumor microenvironment. Oxidative stress facilitates activation of hypoxia-induced factor (HIF)-1α, which is the main transcription factor activated as a result of hypoxic response, and mediates the downregulation of caveolin-1.

Our finding of decreased Cav-1 expression in increasing grades of dysplasia supports the view that oxidative stress might play a role in Cav-1 suppression. This is very significant since prolonged oxidative stress might play a very important role in the malignant transformation of such lesions. Cav-1 could directly interact with NOS enzymes through its scaffolding region. Following Cav-1 loss, endothelial nitric oxide synthase (eNOS) will be released from the complex and activated through phosphorylation and mRNA overexpression, leading to the overproduction of nitric oxide (NO) and reactive nitrogen species (RNS). The high levels of NO and/or RNS would facilitate cell proliferation, apoptosis evasion, angiogenesis, and EMT process and finally induce carcinogenic transformation. Besides eNOS, inducible nitric oxide synthase (iNOS) will also be activated following Cav-1 loss. Since iNOS is capable of generating micromolar levels of NO, its activation will bring RNS burst and results in DNA damage and mitochondrial dysfunction, which finally promotes carcinogenesis.[12]

Conclusion

Based on the findings of our study we conclude that Cav-1 expression is altered in oral epithelial dysplasia. Expression is

probably directly related to the grade of dysplasia. Decreased expression is noticed when the severity of dysplasia increases, which suggests the potential role for Cav-1 in the tendency toward malignant transformation. Cav-1 could be a potential marker for oxidative stress and its role in carcinogenesis needs to be established.

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Statement of Ethics Published research

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