

# Can CAPRIN-1 Be Responsible for the Recurrence Potential of Odontogenic Keratocysts?

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## ABSTRACT

**Objectives:** The purpose of this retrospective study is to compare dentigerous cysts and odontogenic keratocysts for cytoplasmic activation/proliferation - associated protein-1 antibodies via immunohistochemical staining to obtain a new perspective about the specific behavioural characteristics of odontogenic keratocysts at the molecular level.

**Material and Methods:** Forty dentigerous cysts (DC) and forty odontogenic keratocysts (OKC) tissue samples were examined using immunohistochemical staining to detect cytoplasmic activation/proliferation - associated protein-1 (CAPRIN-1) antibodies. Nuclear and/or cytoplasmic staining was evaluated as “positive”. Cell staining rate (%) and cell staining intensity were determined, and a staining intensity distribution (SID) score was calculated for each sample. Cases were considered “negative” if they showed no staining for CAPRIN-1 antibodies, thus were given a SID score of zero. According to the SID scores, the expression levels were rated as negative, mild, moderate, or high.

**Results:** Of 80 samples, 16 that could adversely affect immunohistochemical evaluation were excluded. Ten negative, 21 positive and three negative, 30 positive CAPRIN-1 expressions were observed in DC and OKC groups, respectively. The difference between the negative and positive cases within groups was significant only in the OKC group ( $P = 0.000$ ). The SID score range and mean were 0 to 160 and 31.1 (SD 35.7) for DC and 0 to 160 and 57.3 (SD 42.3) for OKC groups. CAPRIN-1 expression was significantly higher in the OKC group ( $P = 0.043$ ).

**Conclusions:** The molecular basis for increased mitotic activity, high recurrence rates or presence of satellite cysts in odontogenic keratocysts may be attributed to the expression of cytoplasmic activation/proliferation - associated protein-1.

**Keywords:** cell proliferation; dentigerous cyst; jaw cysts; odontogenic cysts; recurrence.

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## INTRODUCTION

Dentigerous cyst (DC) is a developmental odontogenic cyst that originates from the follicle around the crown of an unerupted or partially erupted tooth [1]. DC is the second most common odontogenic cyst making up almost 20% of all odontogenic cysts [2]. Another developmental odontogenic cyst is the odontogenic keratocyst (OKC) which is the third most common odontogenic cyst responsible for almost 10 to 20% of all odontogenic cysts [3]. OKCs are unique pathologies due to their locally aggressive behaviour, high recurrence rate and characteristic histologic appearance. OKCs treated with enucleation only have a recurrence rate of approximately one in four cases. Recurrences are observed even when Carnoy's solution is applied or OKCs are treated with resection, but at lower rates [4].

p16 is an essential gene that controls the cell cycle. It slows down the cell cycle by inactivating certain cyclin-dependent kinases (CDKs) [5]. p16 prevents any uncontrollable proliferations at the G1 - S interphase of the cell cycle. Therefore, p16 is considered essential in tumour progression [6]. On the other hand, cytoplasmic activation/proliferation - associated protein-1 (CAPRIN-1) is an RNA-binding protein (RBP) that ensures cellular homeostasis via its involvement in RNA regulatory processes [7]. CAPRIN-1 accelerates the cell cycle from G1 to S phase and promotes cell growth. Cells with no CAPRIN-1 expression exhibit delays to progress from G1 to early S phase [8]. Thus, CAPRIN-1 has a role in tumour growth and tumour invasion, and is also blamed to accelerate processes related to tumorigenesis [9]. When suppressed, CAPRIN-1 decreases the cell's proliferation rate and prolongs the G1 phase of the cell cycle [10].

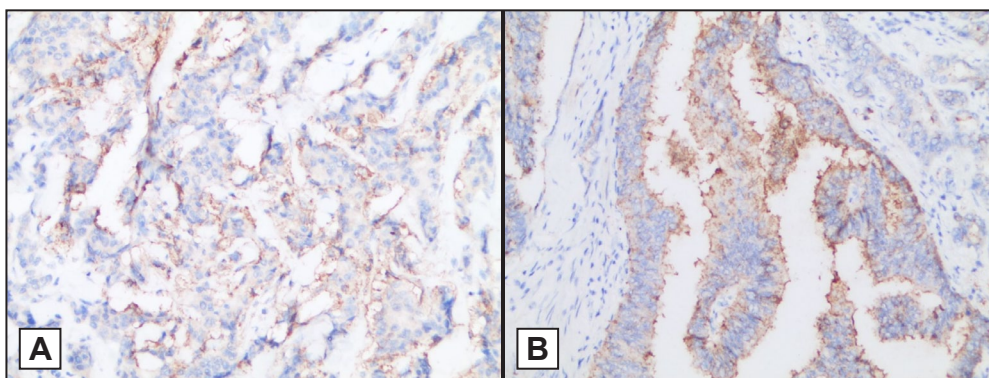
To the authors' knowledge, this study is the first to investigate and compare CAPRIN-1 expression

in both OKCs and DCs. It aims to provide an explanation for specific features of odontogenic keratocysts, such as their high recurrence potential and aggressive character, at a molecular level. Main null hypothesis of this retrospective study is that there will be no differences in cytoplasmic activation/proliferation - associated protein-1 expressions between odontogenic keratocysts and dentigerous cysts.

## MATERIAL AND METHODS

Forty patients each, with a diagnosis of either DC or OKC, were randomly selected from the hospital database. All patients were operated on at Akdeniz University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery between January 6, 2014 and December 27, 2019 and the diagnoses were made by the Department of Pathology at Akdeniz University, Faculty of Medicine (Antalya, Turkey). Syndromic cases of OKC were not included in this study. Paraffin-embedded tissue blocks of archived samples were used for immunohistochemical (IHC) analysis. Pathological diagnoses were made according to the updated fourth edition of World Health Organization's Classification of Head and Neck Tumors [1]. Patient details (age, gender, and location of pathology) were obtained from hospital records. This study followed The Declaration of Helsinki on medical protocol. This project has been reviewed and approved by the regional Ethical Review Board, Akdeniz University (Protocol No. 2018-746).

Two tissue sections were obtained from each paraffin-embedded tissue sample. One of them was stained using hematoxylin and eosin stain and was used as control. The other tissue section underwent IHC staining using CAPRIN-1 antibody. Breast and prostate cancer tissues were used for positive control testing (Figure 1).



**Figure 1.** Breast (A) and prostate cancer (B) tissue samples, CAPRIN-1 positive control testing (hematoxylin and eosin stain, original magnification x40).

IHC staining of paraffin-embedded tissue samples of DC and OKC were completed according to the protocol and guidelines of the manufacturer (Applied Biological Materials Inc.; British Columbia, Canada: <https://www.abmgood.com>) using the Dako Omnis (Agilent Technologies Company; Santa Clara, CA, USA) device.

All evaluations were made under a light microscope Leica DM2500 (Leica Microsystems CMS GmbH; Wetzlar, Germany). Both cytoplasmic and nuclei stainability for CAPRIN-1 in the epithelium was considered “positive”. Positive cases were further described by the rate of cell staining, expressed as percentage, according to the number of cells stained. A staining intensity value of +1, +2, or +3 was assigned for weakly, moderately, or strongly stained tissue samples, respectively. Then a staining intensity distribution (SID) score was calculated by multiplying the rate of cell staining by the staining intensity value. Cases with no staining were considered “negative” and were assigned a SID score of zero. CAPRIN-1 antibody expression level was graded according to the SID scores (Table 1).

**Statistical analysis**

Normal distribution of data was evaluated using the Shapiro-Wilk test. Either parametric or non-parametric tests were applied according to the distribution normality of the evaluated parameters. Continuous variables were expressed as mean,

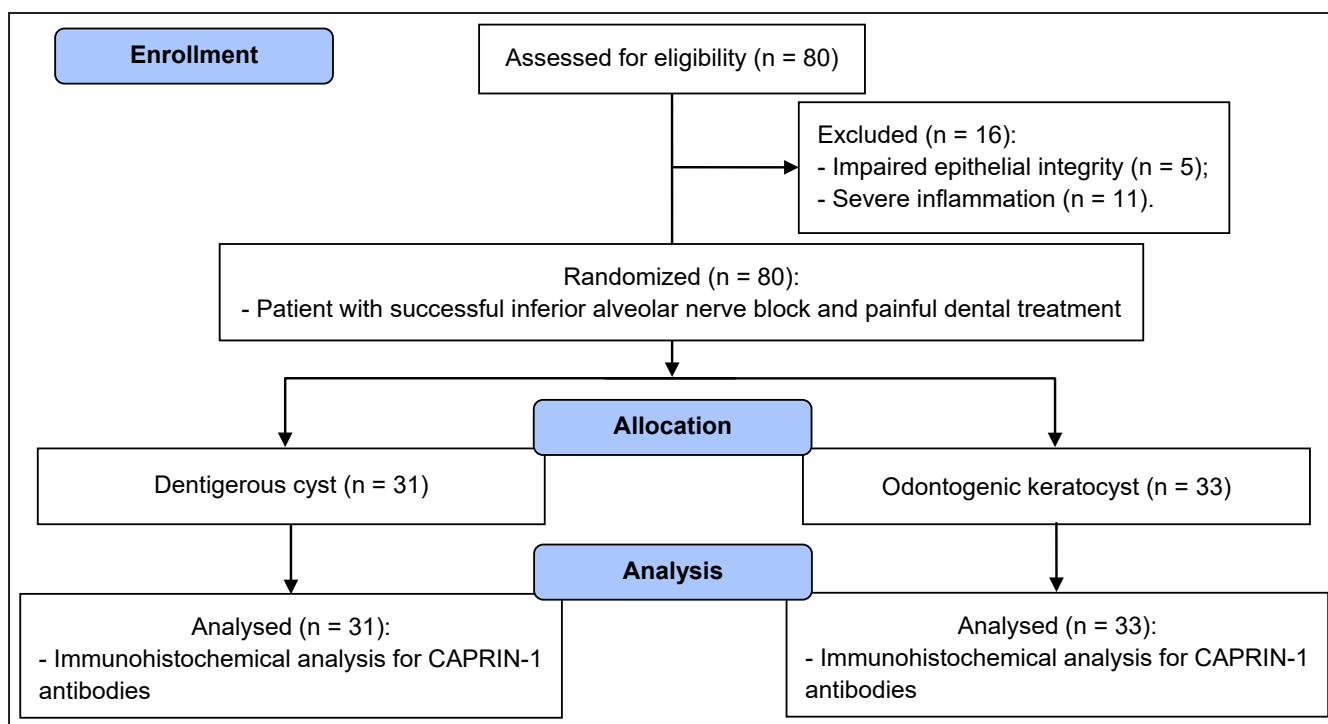
**Table 1.** CAPRIN-1 antibody expression level grading

Staining intensity distribution score	Overall CAPRIN-1 expression level
No expression = 0	Negative
1 - 100	Mild
101 - 200	Moderate
201 - 300	High

standard deviation (SD) or minimum and maximum values. Categorical variables were presented as numbers or percentages. One sample binomial, one sample chi-square ( $\chi^2$ ), one sample Kolmogorov-Smirnov, independent samples t-test or Mann-Whitney U test was used according to the normality or continuity of data. IBM SPSS® version 22 (IBM Corp.; Armonk, NY, USA) statistical package program was used for all calculations. A statistical significance level was set at  $P < 0.05$ .

**RESULTS**

Sixteen tissue sections, nine from the DC and seven from the OKC group, were excluded from the study due to impaired epithelial integrity (n = 5) and severe inflammation that could negatively affect the IHC evaluation (n = 11). Therefore, 31 and 33 tissue sections from the DC and OKC groups were examined, respectively. Consort flow diagram was used to describe the study design and groups (Figure 2).



**Figure 2.** The CONSORT flow diagram.

**Table 2.** Detailed study data

Parameter		Dentigerous cyst (n)	Odontogenic keratocyst (n)	P-value
Age (mean [SD])		44.97 (SD 14.4)	37.15 (SD 16.64)	0.049 <sup>a</sup>
Gender	Female	6	9	> 0.05
	Male	25	24	
Location	Maxilla	2	8	> 0.05
	Mandible	29	25	
Staining intensity distribution (mean [SD])		31.1 (SD 35.7)	57.3 (SD 42.3)	0.000 <sup>b</sup>
CAPRIN-1 expression level	Negative (0)	10	3	0.043 <sup>c</sup>
	Mild	20	26	
	Moderate	1	4	
	High	-	-	
CAPRIN-1 staining	Positive	21	30	0.04 <sup>d</sup>
	Negative	10	3	

<sup>a</sup>Statistically significant at P < 0.05 (one sample Kolmogorov-Smirnov test).

<sup>b</sup>Statistically significant at P < 0.05 (Mann-Whitney U test).

<sup>c</sup>Statistically significant at P < 0.05 (chi-square test).

<sup>d</sup>Statistically significant at P < 0.05 (chi-square test).

SD = standard deviation; n = number.

All analysed parameters are summarized in Table 2. The incidence of both DC and OKC (Figure 3 and 4) was found to be statistically significantly higher in males than females (DC, P = 0.001; OKC, P = 0.015). However, there was no statistically significant difference between the DC and OKC groups in terms of gender distribution (P = 0.455). The age ranges of DC and OKC groups were 10 to 76 and 15 to 70, respectively. A statistically significant difference was found in terms of age between the groups (P = 0.049). Both DC and OKC were observed more frequently in the mandible (DC, P = 0.005; OKC, P = 0.005), but the difference between groups was not significant (P = 0.052).

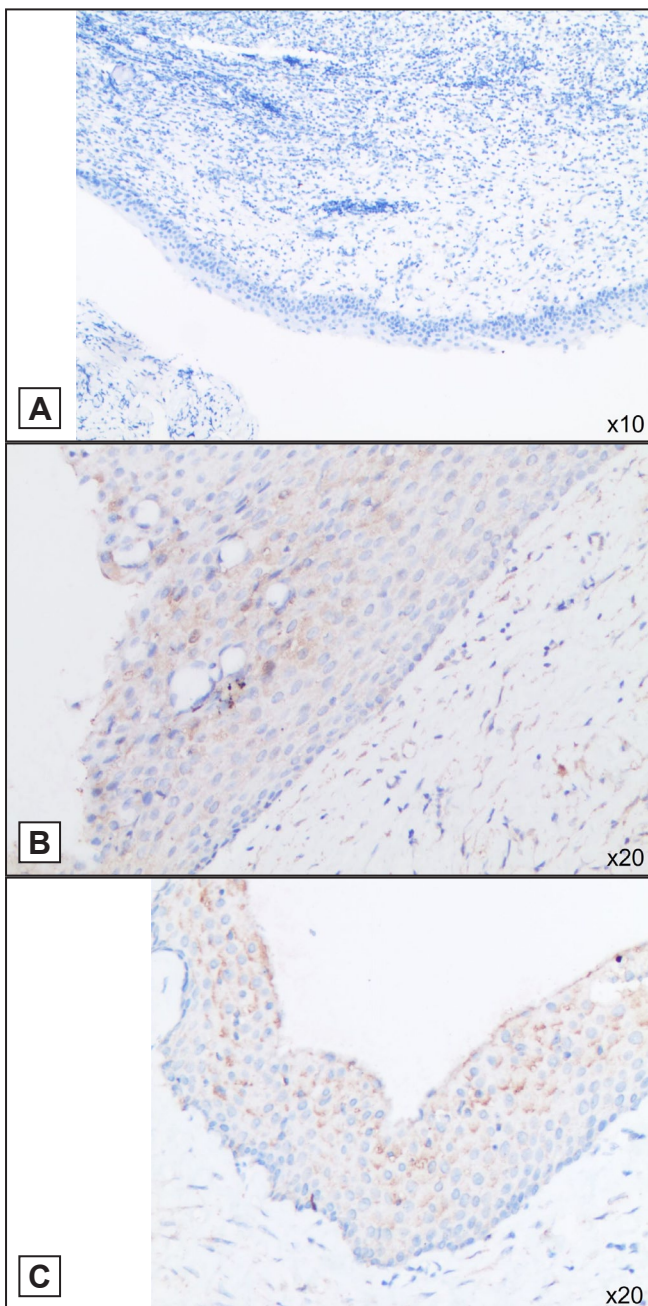
IHC analysis for CAPRIN-1 revealed that within the DC group, the difference between negative and positive staining was not statistically significant (P = 0.72). Unlike DC, the OKC group showed a statistically significant difference between negative and positive cases in terms of staining (P = 0.000). The analysis between DC and OKC groups revealed a statistically significant difference for CAPRIN-1 staining (P = 0.04), as well as in terms of expression levels (P = 0.043), thus the null hypothesis was rejected.

**DISCUSSION**

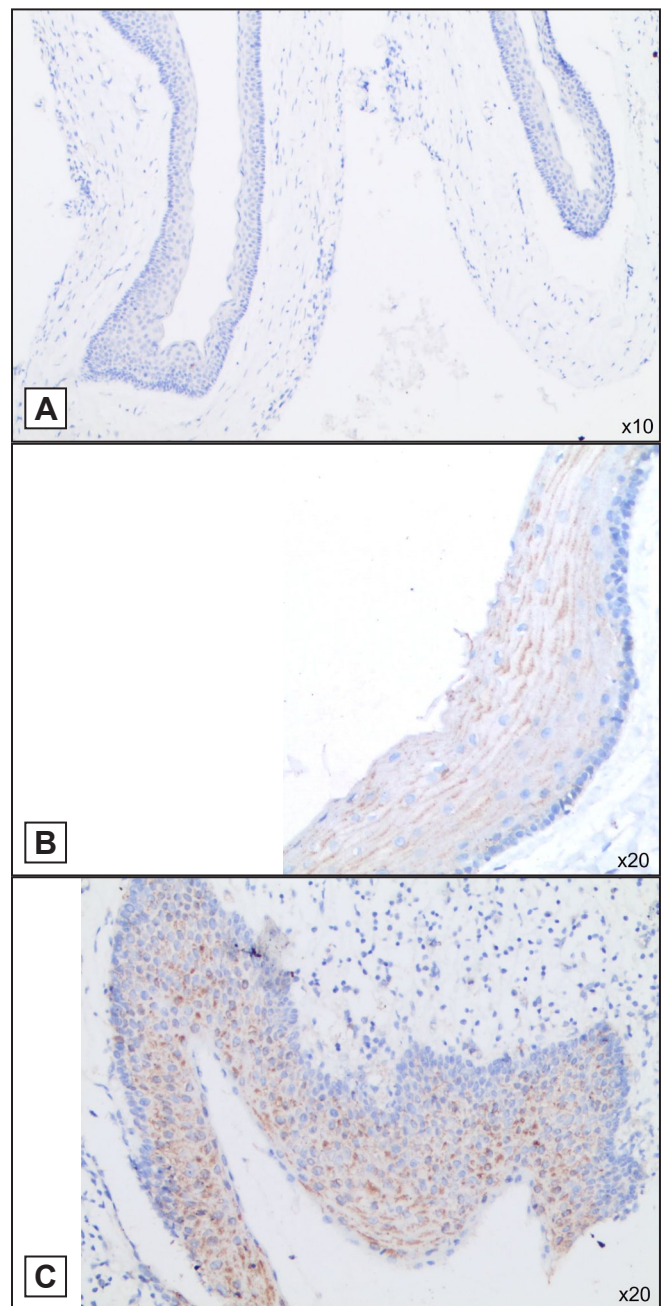
DCs and OKCs are two commonly encountered pathological entities of the maxillofacial region.

OKCs have been classified under cysts and tumours at different times. This study followed the present WHO classification (2017) guidelines for OKCs [2]. Literature supports that both DC and OKC are more common among men and that it is almost 1.5 times higher than in women [11,12]. Demographic data collected on gender from this study is in line with the literature. When it comes to age, DC and OKC are mostly diagnosed at an age distribution of 10 to 30 and 10 to 40 years of age, respectively [13]. Mean age for a diagnosis of DC is reported as 32.8 and of OKC is 40.5 years [12]. This study reports a higher mean age for DC than OKC, which contradicts the literature but has been attributed to the relatively smaller sample size. Both DC and OKC are encountered more in the mandible than maxilla, which is attributed to the third molars that often stay impacted [3,11,14,15]. The result from this study also supports this data.

OKCs were re-classified under odontogenic cysts in 2017 due to insufficient evidence for their neoplastic origin; however, features specific to OKCs, such as the presence of satellite cysts and the high recurrence rate, have not changed [1,15]. Nevertheless, a molecular or cellular mechanism for these properties has not been fully elucidated even though its pathological definition has changed from tumour to cyst [13,16]. Recent studies focus on tumour suppressor genes, tissue oncogenes or inflammatory mediators in order to shine light on the development and unique characteristics of pathological entities [17-19]. Several studies on OKCs revealed



**Figure 3.** Hematoxylin and eosin stain: A = DC negative CAPRIN-1 expression (original magnification x10); B = DC mild CAPRIN-1 expression (original magnification x20); C = DC moderate CAPRIN-1 expression (original magnification x20).



**Figure 4.** Hematoxylin and eosin stain: A = OKC negative CAPRIN-1 expression (original magnification x10); B = OKC mild CAPRIN-1 expression (original magnification x20); C = OKC moderate CAPRIN-1 expression (original magnification x20).

that the expression of certain proteins in the OKC epithelium differs from other odontogenic cysts, which may result in cell cycle abnormalities [20,21]. CAPRIN-1 is a phosphoprotein associated with activation and proliferation and it is observed in all vertebrates [10]. CAPRIN-1 has been detected in various organs of the human body, including thymus, spleen, kidney, and liver [7-9,22,23]. Research on CAPRIN-1 not only shows its critical role in cell proliferation but also its importance regarding the development and function of the immune system, due to increased levels of CAPRIN-1 in

B-lymphocytes, T-lymphoblasts, thymocytes and hematopoietic progenitor cells [8]. As an RNA-binding protein, CAPRIN-1 has fundamental role in the cell cycle, as well as cell metabolism, maturation and stress responses [7,18]. CAPRIN-1 is associated with oncogenesis and tumorigenesis due to its effective role in the cell cycle. The proliferation rate decreases and the G1 phase of the cell cycle is prolonged in cells where CAPRIN-1 is suppressed [10].

Clinical studies on CAPRIN-1 are very limited. There are no studies examining the expression of CAPRIN-1

in the pathologies included in this study, let alone any odontogenic tissues. For this reason, data obtained from other clinical studies with CAPRIN-1 were used to interpret the findings of this study.

Animal study by Wang et al. [8], revealed that external intervention of B lymphocyte series DT40 cells to create an absence of CAPRIN-1 leads to defects in cell proliferation. In detail, within the evaluated cells, a prolongation in the G1 phase of the cell cycle, a slowdown in proliferation and a decrease in cloning efficiency were observed [8]. The slow proliferation in CAPRIN-1-deficient cells has been associated with the fact that CAPRIN-1 is responsible for regulating RNA and protein synthesis of multiple signalling pathways that control this function, such as Ras, c-Myc, PI3K, and Rb [8]. Parallel to these results, the present study also concluded that CAPRIN-1 expressions were significantly higher in OKCs with a marked increase in mitotic activity and high proliferation in cyst epithelial cells compared to DCs. Another animal study by Sabile et al. [9], reported that ectopic expression of CAPRIN-1 increased primary tumour growth in mouse osteosarcoma cells, significantly increased the lung metastatic burden, and significantly reduced the survival rate of animals. In the light of these findings, it has been interpreted that CAPRIN-1 may have a function that accelerates the cell cycle of tumour cells in osteosarcoma metastasis [9]. On the study with human breast cancer cells, it was found that CAPRIN-1 promotes proliferation and invasion [10]. Similarly, externally created CAPRIN-1 deficiency resulted in the prolongation of the G1 phase of the cell cycle, slowing of proliferation and a decreased cloning efficiency [8]. CAPRIN-1 is responsible for regulating RNA and protein synthesis of multiple signalling pathways that control this function, such as Ras, c-Myc, PI3K, and Rb, which explains the slow rate of proliferation in CAPRIN-1-deficient cells has been associated [8]. This study, likewise, concluded that CAPRIN-1 expressions were significantly higher in OKCs, which are cysts characterized with a marked mitotic activity and higher proliferation rate in cyst epithelial cells compared to DCs.

Sabile et. al [9] reported that ectopic expression of CAPRIN-1 in mouse osteosarcoma cells increased the primary tumour growth and lung metastatic load and reduced the survival rate of animals. These findings suggested that CAPRIN-1 may accelerate the cell cycle of tumour cells in osteosarcoma metastasis [9]. Gong et al. [10] also reported that CAPRIN-1 may promote proliferation and invasion.

Tan et al. [24] studied hepatocellular carcinoma tissues obtained from patients who underwent liver

resection and reported that CAPRIN-1 showed a higher expression in cancer cells compared to the peri-tumoral tissues. They also associated this with a worse prognosis in patients [24].

These reference studies and the results from this study are compatible, although with minor differences. The high expression of CAPRIN-1 and its role on proliferation is emphasized in these reference studies, which are mainly on malignancies but the results from this study may also suggest an explanation to the local aggressive features of OKCs. Since the OKC group showed significantly higher CAPRIN-1 positive staining and had higher SID score averages than the DC group, CAPRIN-1 may be responsible for the high proliferative properties of not malignant cells but also of benign neoplasms.

To this date, many IHC analyses have been performed to investigate the changes observed at the molecular level in OKCs, to aid in the diagnosis of these lesions or to investigate them as potential therapeutic targets [25,26]. Sonic Hedgehog signalling proteins are of critical importance for tissue development and have been identified in OKCs [27]. Moreover, markers associated with proliferation and apoptosis, such as proliferating cell nuclear antigen (PCNA) and Ki-67, are also identified in OKCs [25,28]. It is noteworthy to mention that these markers are expressed in actively proliferating cells. More frequent and intense expressions of cell proliferation marker Ki-67 and tumour suppressor protein p53 are observed in OKCs [25]. Vascular endothelial growth factor (VEGF) and expressions of CD34, which is used to evaluate angiogenesis, and interleukin 1 alpha (IL-1a) and IL-6, which are cytokines that function in bone resorption, may also be suggested to have a role in the aggressive behaviour of OKCs [27,29].

In order to determine CAPRIN-1 as a useful diagnostic and prognostic factor in OKCs, studies with larger samples sizes as well as studies to compare cases with and without recurrence, syndrome-related cases or orthokeratotic odontogenic cysts should be planned. With a better understanding of the biology of OKCs, development of less aggressive treatments may be possible, especially for patients with large, recurrent, or multiple lesions. In the current literature, some molecular-based treatments have been tested and promising results have been reported. In 2011, Goldberg et al. [30] reported nearly complete resolution of three syndromic OKCs in a 55-year-old man treated with a sonic Hedgehog signalling pathway inhibitor. One cell culture study used cyclopamine, which also acts on the same pathway, was administered and a dose-dependent cell growth inhibition was reported [31].

As an RNA-binding protein, CAPRIN-1 may also be studied to develop targeted therapy drugs.

## CONCLUSIONS

This study is the first to analyse and compare cytoplasmic activation/proliferation - associated protein-1 expression in odontogenic keratocyst and dentigerous cyst. Cytoplasmic activation/proliferation - associated protein-1 expressions evaluated by staining intensity distribution scores statistically differed between the odontogenic keratocysts and dentigerous cysts groups and were higher in the odontogenic keratocysts group. Therefore, cytoplasmic activation/proliferation - associated protein-1, with its ribonucleic acid-binding mechanisms and roles in cellular metabolism, maturation, and proliferation processes, may explain the molecular basis of odontogenic keratocysts characteristic features such as increased mitotic activity, high recurrence risk or the presence of satellite cysts.

This study was undertaken to provide an explanation for specific features of odontogenic keratocysts, such as their high recurrence potential and aggressive character, at a molecular level. Cytoplasmic activation/proliferation - associated protein-1 expression was significantly higher in the odontogenic keratocyst group ( $P = 0.043$ ). A better understanding of the biology of odontogenic keratocysts; development of less aggressive treatments may be possible, especially for patients with large, recurrent, or multiple lesions.

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