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Adipophilin Immunoexpression And Its Pathophysiology In Human Tooth Germ And Ameloblastoma

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ABSTRACT

Background: The process of tooth development is the result of a series of interactions between the ectoderm of the oral cavity and the neural crest ectomesenchyme. Ameloblastoma is a slow-growing, locally invasive odontogenic epithelial tumor that primarily develops from enamel tissue that has not undergone differentiation. The role of lipids in the histogenesis of tooth germ and pathogenesis of ameloblastoma is an area that has not been explored. Recently, interest has been drawn to the field of study of abnormal lipid metabolism in tumors. Adipophilin is a perilipin interacting protein that coats the exteriors of cytoplasmic lipid droplets. Elevated lipogenesis has been linked to poor prognosis in various tumors, suggesting potential therapeutic targets.

Aim: immunohistochemical expression of adipophilin in human tooth germ and ameloblastoma.

Materials and methods: Fifteen samples each of formalin-fixed, paraffin-embedded ameloblastoma and human tissue tooth germ were taken. Immunohistochemical expression of adipophilin was done and scored. Comparative analyses were performed using the Kruskal-Wallis test along with Spearman's correlation.

Results: Adipophilin was positive in all the tooth germ samples and the staining intensity was predominantly moderate (73.3%), with consistent staining shown in the epithelial components in all stages. Adipophilin was positive in 12 out of 15 ameloblastomas with strong immunostaining (80%). Consistent staining was present in peripheral cells and few central cells.

Conclusion: The diffuse cytoplasmic positivity of adipophilin in ameloblastoma indicates the production and accumulation of lipid droplets, offering new evidence of metabolic alterations that may be involved in tumor progression. For a better understanding of the idea, molecular analysis of the signaling pathways linked to the mechanism of adipophilin in ameloblastoma is required.

Keywords: *Ameloblastoma, tooth germ, adipophilin, odontogenic tumor, immunoexpression*

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INTRODUCTION

The process of tooth development is a very intricate course that is found to be the result of a series of interactions between the ectoderm of the oral cavity and the neural crest ectomesenchyme[1]. The ectoderm of the oral cavity gives rise to ameloblast, which in turn forms enamel. The tooth germ begins to grow and the cells forming the mineralized portion begin to differentiate at first, or during the first six weeks of intrauterine life. These cells then lay the matrices for dentin and enamel, which subsequently begin mineralizing[2]. Various molecular studies done assessing the growth of the tooth germ showed numerous paracrine signaling molecules mediating the communication between the ectoderm and ectomesenchyme during tooth development[3]. Various factors are involved in the histogenesis of tooth germ, yet all these factors are yet to be studied in depth. One such unexplored factor is the presence of lipids in enamel organ. The role of lipid molecules in the histogenesis of tooth germ is still obscure. Few studies have been done to identify the role of lipids in tooth formation but the results are ambiguous[4]. The effect lipids have on the histogenesis of teeth is yet to be understood.

Ameloblastoma is a slow-growing, locally invasive odontogenic epithelial tumor that primarily develops from enamel tissue that has not undergone differentiation[5,6]. Ivey and Churchill named it 'ameloblastoma' in 1930[7][8][9]. Ameloblastoma was listed as one of the benign epithelial odontogenic tumors by the World Health Organization (WHO) in 2017[10][11]. The incidence of ameloblastoma differs with geographic distribution, with 0.92 cases per million person-years worldwide[12]. Ameloblastoma is the second most prevalent benign odontogenic tumor, according to the majority of epidemiological studies[13]. The most typical presenting feature of ameloblastoma is a slow growing, painless swelling of the maxilla or mandible[14][6][15]. The ameloblastoma expands significantly as it grows in the buccolingual direction and can cause malocclusion, facial deformity, invasion of soft tissue, or loosening of the teeth[16][14][17].

Various metabolisms have been studied to understand the pathogenesis of ameloblastoma. Yet, the gradual step by step progression of the tumor is still to be elucidated. Significant importance has been given to the various signaling proteins involved in the progression of the disease. The role of lipids in the pathogenesis of ameloblastoma is an area that has not been evaluated. Recently, interest has been drawn to the field of study of abnormal metabolism of lipids in odontogenic tumors. A handful of studies have been performed to find the presence of lipids in odontogenic tumors[18]. Yet, the role of abnormal lipid metabolism in the pathogenesis of odontogenic tumors has not been studied.

The relatively new field of research into abnormal lipid metabolism in tumors has attracted attention lately. Lipid droplets are intracytoplasmic vesicles made of a phospholipid monolayer with several proteins attached surrounding a highly hydrophobic ester lipid core[19]. One of the major proteins involved with lipid biogenesis is adipophilin. Adipophilin, also referred to as perilipin 2, is a perilipin protein of PAT family lipid-regulating protein that is present in the exteriors of cytoplasmic lipid droplets[20]. Lipid droplets play a variety of physiological roles in cells, including protecting them from lipotoxicity and maintaining energy homeostasis[21]. However, increased lipogenesis and accumulation of lipid droplets have been linked to poor prognosis in tumors like colon, prostate and breast cancers, suggesting potential therapeutic targets[22]. The study aims to describe the immunohistochemical expression of adipophilin in human tooth germ and ameloblastoma.

MATERIALS AND METHODS

From the repository, fifteen samples of formalin-fixed, paraffin-embedded ameloblastoma (9 - conventional ameloblastoma, 6 - unicystic ameloblastoma) and fifteen samples of human tissue tooth germ were taken. To expose the antigenic epitopes for immunohistochemistry, 3-m sections were exposed to a heat retrieval solution. Blocking of endogenous peroxidases was done for 30 minutes using 0.9% hydrogen peroxide along with a peroxidase blocker. The

tissue samples were incubated with primary antibodies against adipophilin (rabbit polyclonal perilipin antibody, 1:50 dilution) for 60 min. The tissues were then incubated with a streptavidin-horseradish peroxidase complex for 30 min each. An immunoreactive score (IRS) was used to assess the cytoplasmic immunohistochemical expressions of adipophilin in epithelial tooth germ samples and ameloblastoma parenchyma samples. The scoring of positive cells is from 0 to 5 (0 - 0%, 1 - 1 to 10%, 2 - 11 to 30%, 3 - 31 to 50%, 4 - 51 to 80% and 5 - 81 to 100%) (Table 1).

TABLE 1: Table shows the scoring criteria for immunohistochemical staining of adipophilin in tooth germ and ameloblastoma.

Score	Percentage Of Positive Cells
0	0%
1	1% to 10%
2	11% to 30%
3	31% to 50%
4	51% to 80%
5	81% to 100%

The staining intensity of the positive cells were scored 0 to 3; 0 - negative, 1 -weak, 2 - moderate and 3 - strong (Table 2). A blinded evaluation was done using two trained oral pathologists. The results were primarily analyzed descriptively. Additionally, comparative analyses were done using the Kruskal-Wallis test along with Spearman's correlation using SPSS software (ver 23.0).

RESULTS

Adipophilin was found positive in all the tooth germ samples and the intensity of immunostaining was predominantly moderate in 11 out of 15 cases (73.3%), with consistent staining present in the epithelial components in all stages (Figure1). It was also positive in 12 out of 15 ameloblastomas and the intensity of immunostaining was predominantly strong in all the positive cases (80%), with consistent staining present in peripheral cells and few central cells too (Figure2).

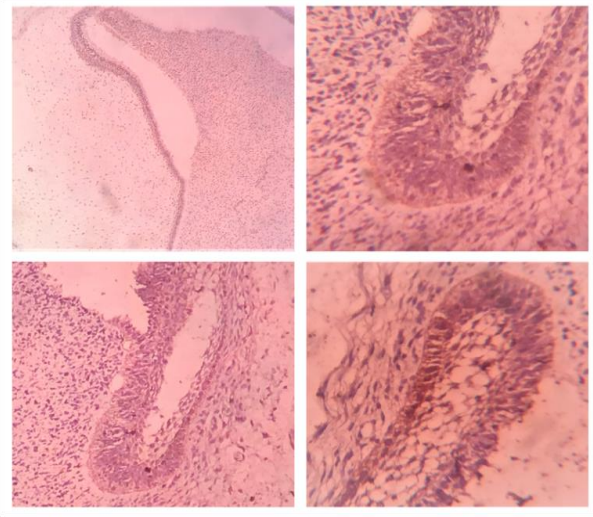

FIGURE 1: Figure shows immunohistochemical expression of adipophilin in tooth germ. There is moderate staining intensity in the epithelial components of the tooth germ.

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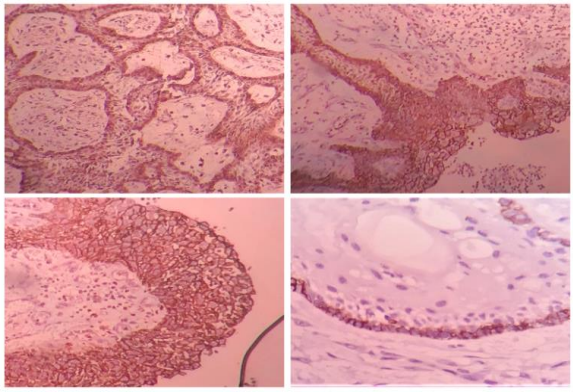

FIGURE 2: Figure shows immunohistochemical expression of adipophilin in ameloblastoma. There is intense staining intensity in the epithelial components of the tooth germ.

TABLE 2: Table shows the staining intensity of adipophilin in tooth germ and ameloblastoma. Tooth germ predominantly showed moderate intensity (73.3.%) while ameloblastoma predominantly showed strong intensity (80%).

	Negative	Weak	Moderate	Strong
TOOTH GERM	0	2	13	0
AMELOBLASTOMA	2	0	2	11

TABLE 3: Table shows Spearman's correlation between the staining intensity of adipophilin in tooth germ and ameloblastoma. The correlation was insignificant.

Correlations				
			Tooth Germ	Ameloblastoma
Spearman's rho	Tooth Germ	Correlation Coefficient	1.000	-.190
		Sig. (2-tailed)		.364
		N	25	25
	Ameloblastoma	Correlation Coefficient	-.190	1.000
		Sig. (2-tailed)	.364	
		N	25	25

The immunohistochemical expression of adipophilin in the tooth germ and ameloblastoma samples were found not to be statistically significant ($p>0.05$). Spearman's correlation also showed insignificant correlation ($p>0.05$) (Table3).

DISCUSSION

Metabolic changes are important in tumor progression and increased synthesis of fatty acids is one of the primary abnormalities of cancer cell metabolism which is activated to support increased proliferation. The presence of adipophilin in a variety of cell types in close proximity to lipid droplets suggests that this protein may play a general role in lipid deposition and turnover. The diverse origin of the various clones of lipids producing molecules identified using expressed sequence tags contributes to adipophilin's widespread distribution[23]. Furthermore, studies reported a broader expression in various cultured cells, claiming that the protein is a ubiquitously expressed lipid-storage droplet-associated protein[24]. These studies emphasize the role of adipophilin in physiological conditions. In pathological conditions, adipophilin is found to enhance lipid

accumulation which in turn helps in the progression of the disease. Studies focusing on the role of adipophilin in ameloblastoma are yet to be done. In this study we aimed to do the same.

Our study focused on the determination of immunohistochemical expression of adipophilin in human tooth germ and ameloblastoma. The difference in the intensity of expression or the pattern of expression could give us a direction for research towards the role of adipophilin in the pathogenesis of ameloblastoma . Adipophilin was found positive in all the tooth germ samples and the immunostaining intensity was predominantly moderate in 11 out of 15 cases (73.3%), with consistent staining present in the epithelial components in all stages, although the results of correlation were found to be insignificant ($p>0.05$). Recent studies on lipid metabolism in tooth germ of in-utero mice showed that lipids play an essential role in tooth development. When haploid insufficiency was introduced in the alleles responsible for lipid formation, there was a significant decrease in the rate of tooth germ development[25]. The FAS (Fas cell surface death receptor) gene, is found to be responsible for lipid production during embryogenesis[26][27][28]. In heterozygous subjects, at least one functional allele is needed for the proper development of the tooth. The absence of functional alleles can cause abnormal tooth development or even the absence of tooth development[29].

Adipophilin was found positive in 12 out of 15 ameloblastomas and the immunostaining intensity was predominantly strong in all the positive cases (80%), with consistent staining present in peripheral cells and few central cells. Studies analyzing adipophilin expression in odontogenic tumors found that adipophilin was found to be more abundant in ameloblastic carcinoma samples than in ameloblastoma samples[30][17]. These expression patterns indicate the presence and function of lipid droplets during development of the tooth and in ameloblastoma tumor progression. These findings have to be correlated with the role of adipophilin in tooth germ. Few studies have been conducted to investigate the role of lipid metabolism in tooth development. Perilipin 1 (a peptidylprolyl cis/trans isomerase) was found to be an important regulator of adipogenic and odontogenic differentiation of human dental pulp stem cells[31]. Furthermore, studies show that immunohistochemical localization of perilippin1 in mouse tooth germ stages revealed positivity in dental lamina epithelial cells, odontoblasts, and sub-odontoblast layer[32]. The distribution of adipophilin staining in the tooth germ was similar to our study, indicating that the positively stained areas could be areas with increased lipid activity.

To date, there has not been a single study done to evaluate the role of adipophilin in the pathogenesis of ameloblastoma. But, similar studies have been done in other tumors. Lipid droplets, as determined by adipophilin immunohistochemical expression, have been found in non-cutaneous head and neck tumors, primarily in salivary gland tumors such as mammary analog secretory carcinoma, high-grade transformation adenoid cystic carcinoma and carcinoma ex pleomorphic adenoma[33][34][35][36]. It has been stated that adipophilin helps in sustained cell proliferation[20][9]. The pathogenesis of various neoplasias is related to metabolic changes in cell proliferation, based on the dysregulated metabolism which provides energy for cell division and growth[37]. In this regard, a study published in 2016 by Das Santos et al. found increased expression of the glucose transporter 1 (GLUT1) in the high-grade transformation of adenoid cystic carcinoma. GLUT 1 is seen as a potential marker for malignant transformation as it is regulated by lipid components[38][39][38]. This implies that the process of high-grade transformation may alter the metabolic state of tumor cells, particularly the lipid metabolism[40][41][42]. Aside from increased tumor glycolytic capacity, other cancer-associated metabolic changes have also been noted that can lead to the accumulation of intracytoplasmic lipid droplets in various human carcinomas is the activation of lipogenic pathways[43][44][45][46].

The increased expression of adipophilin in ameloblastoma compared to tooth germ indicates that lipid droplets have an important role to play in tumor progression. Accumulation of lipid droplets in cancer cells is mediated by intricate mechanisms such as de novo lipid synthesis,

increased lipid uptake, remodeling, and lipolysis regulation[47][48][49]. Tumor lipogenesis is triggered by signaling pathways that result in the presence of newly formed lipid droplets[50]. The key regulators in this phenomenon are sterol regulatory element-binding proteins (SREBPs) which is a key regulator in maintaining lipid homeostasis, and the mammalian target of rapamycin (mTOR) which is a sensor that links extracellular nutrients to the cellular growth. SREBP1 overexpression promotes tumor growth and lipid droplet accumulation in conjunction with lipogenesis enzyme overexpression[51].

The amplification of eicosanoid, an important lipid in tumor cells via compartmentalization of eicosanoid-synthetic machinery at lipid droplets may have implications for tumor growth by regulating cancer cells paracrinally as well as regulating the complex interactions which maintain the tumor microenvironment[52][53]. This evidence amounts to the statement that lipid droplets have an intricate role in tumor progression.

Although no definitive studies have established a causal link between an increase in the number of lipid droplets and the development of cancer, recent studies are beginning to shed light on this process. It was recently discovered that cell cycle progression regulates the cellular localization of lipid droplets in non-transformed cells, with an increase in lipid droplet numbers and dispersed subcellular localization upon entering the S phase[54]. Additionally, a comprehensive examination of the location of lipid droplets during mitosis revealed that they polarized before cell division.[55]. These results indicate that lipid homeostasis and cell cycle progression are coordinated by a common mechanism at the G1/S transition, indicating that lipid droplet upkeep, biogenesis, or consumption is involved in S phase cell cycle progression. These findings are consistent with our results as there is an increased intensity in the expression of adipophilin in ameloblastoma compared to tooth germ. Ameloblastoma has increased cell proliferation when compared to tooth germ. The increased intensity of adipophilin expressed in ameloblastoma indicates that adipophilin plays a role in tumor progression.

CONCLUSION

Adipophilin is found to have a significant role in human tooth development across all phases. The diffuse cytoplasmic positivity of adipophilin in ameloblastoma indicates the production and accumulation of lipid droplets within the tumor cells. This indicates that altered lipid metabolisms in ameloblastoma can cause progression of the lesion and the consequent local aggressiveness of the tumor. Only few studies have been done to evaluate the expression of surface proteins of intracellular lipid droplets. The association of lipid accumulation and aggressiveness of ameloblastoma is yet to be studied. The signaling pathways associated with adipophilin in ameloblastoma is still ambiguous. For a better understanding of the role of adipophilin and altered lipid metabolism in ameloblastoma, molecular analysis of the signaling pathways of adipophilin in ameloblastoma are needed.

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