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Immunohistochemical Evaluation of USP22 Expression in Ameloblastoma

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Abstract

Aim & Objective: To evaluate the expression of USP22 in Ameloblastoma by immunohistochemical staining procedure and to correlate the expression of USP22 in Ameloblastoma with that of normal tissue

Need for Study: The expression of USP22 has been evaluated in various malignancies. But there is subtle literature on expression of USP22 in benign tumors and odontogenic tumors. So, this study was designed to fill these lacunae in literature.

Material and Methods: 15 archival tissue blocks of histopathologically diagnosed Ameloblastoma and normal oral tissue were retrieved from the archives of department of Oral Pathology. 3 micron thick sections were prepared and the tissue sections were subjected to routine immunohistochemical staining procedure to

determine USP22 expression in Ameloblastoma and in normal oral mucosa tissue.

Results: The Expression of USP22 was observed in the nuclei of Ameloblastic islands. Statistical analysis using Mann- whitney U test had shown a statistically significant (P= 0.041*) difference in the mean expression of USP22 in Ameloblastoma and in normal tissues.

Conclusion: The higher expression of USP22 is higher in Ameloblastoma compared to normal oral mucosal epithelium.

Keywords: Odontogenic Tumors, Ameloblastoma, USP22, Oral Mucosa

Introduction

Ubiquitin-Specific Peptidase 22 (USP22) is a molecular marker for predicting the disease progression and prognosis. Ubiquitylation or ubiquitination is one of the post-translational modifications in which the conjugation of ubiquitin at specific lysine (K) or amino-terminal methionine (M1) residues on the target proteins occurs. Various essential developmental processes, including cell division, fate specification, and migration, are governed by ubiquitylation. As Ameloblastoma is a slow growing tumor with high rate of recurrence, USP22 overexpression in Ameloblastoma may be related to disease progression with malignant transformation as seen in OSCC[4]. Ameloblastoma is defined as a tumor that is “usually unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent”. Of the tumors that form in the mandible and maxilla, Ameloblastoma is one of the most prevalent Benign Odontogenic Tumors of the jaw, accounting for around 10% of cases. The tumor is slow-growing yet locally invasive, causing painless enlargement of the maxilla or mandible. It has a very high recurrence rate with great potential for malignant transformation and metastasis. Ameloblastoma most commonly occurs in mandibular molar and ramus area with slight male predilection. Facial asymmetry, tooth displacement, malocclusion and pathological fractures may result due to larger lesions. The present study was designed to evaluate and correlate the expression of USP22 in Ameloblastoma with that of normal mucosal tissue.

Material and Methods

15 tissue blocks of histopathologically diagnosed Ameloblastoma and 5 normal tissues were retrieved from the archives of department of oral and maxillofacial pathology. Three micrometers tissue sections were prepared using semiautomatic microtome and the tissue sections were subsequently subjected to routine standard IHC protocol using USP22 antibody. The stained slides were mounted using DPX. Both positive and negative controls were used. The sections so stained were then viewed under the microscope (Trinocular Olympus Bx53 Progress CT research microscope) and assessed for staining characteristics. Photomicrographs of the epithelial lining focused under 40X magnification were taken with ProgRes R Capture Pro 2.8.8 JENOPTIK. For each case, 5 photomicrographs of different fields of epithelium were taken. Stained cells were counted using Image J analysis software. H score was calculated from the data obtained. Based on IHC staining intensity the cells of each selected field were categorized into

- Type1 cells: unstained cells
- Type 2 cells: bluish brown stain
- Type 3 cells: faint brown stain
- Type 4 cells: dark brown stain

Scoring Criteria

Calculations of H score: H score derivation for USP22 expression was done by using the following formula:

H Score = [(1+intensity of type1 cells) x total % of type 1 cells) + (1+intensity of type2 cells) x total % of type 2 cells) + (1+intensity of type 3 cells) x total % of type 3

cells) + (1+intensity of type 4 cells) x total % of type 4 cells)].

Where the score for – The intensity of type 1 cells is 0, the intensity of type 2 cells is 1, the intensity of type 3 cells is 2 and the intensity of type 4 cells is 3

The average H score of 5 fields of each slide was considered as the final H score of that slide.

Results

Varying intensities of USP22 expression was observed in the nuclei of both peripheral Ameloblast like and central stellate reticulum like cells as shown in (fig.1) along with the nuclei of squamous metaplastic cells in Acantomatous type of Ameloblastoma as shown in (fig. 3).

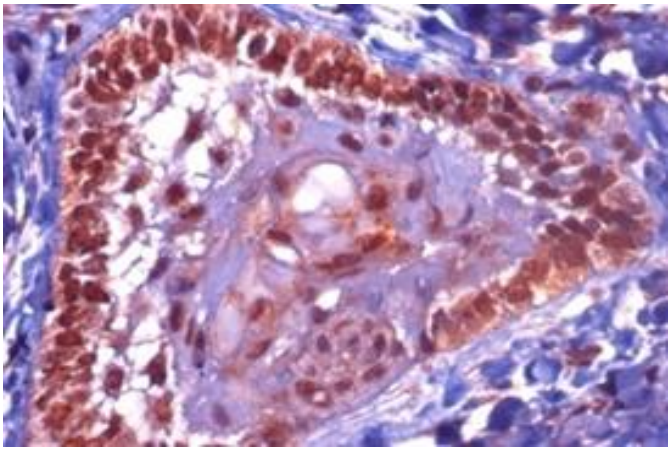

Figure 1: Usp22 expression in follicular type of ameloblastoma under 40x magnification

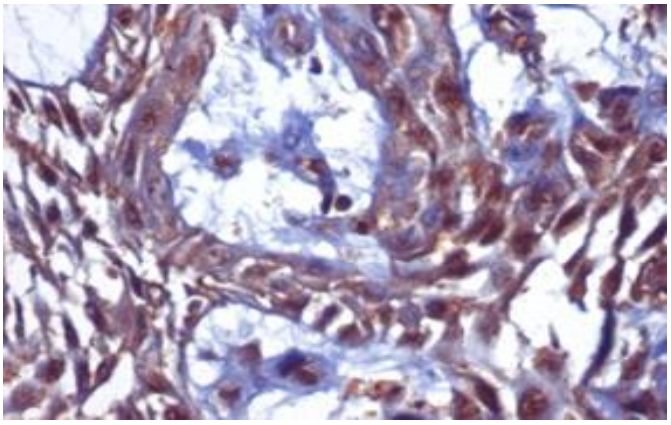

Figure 2: Usp22 expression in plexiform type of ameloblastoma under 40x magnification

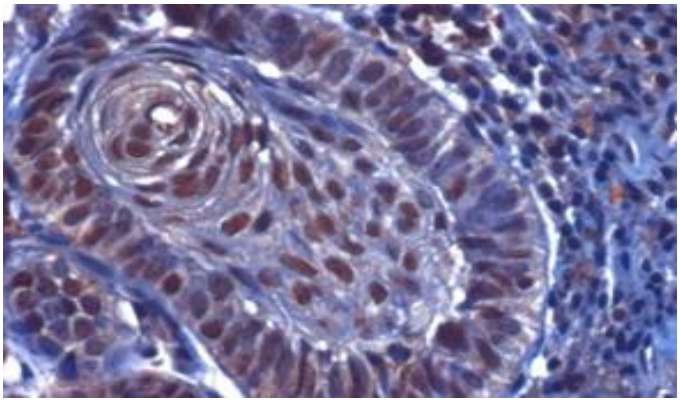

Figure 3: Usp22 expression in follicular type of ameloblastoma with squamous metaplasia under 40x magnification.

USP22 expression was observed in the nuclei of long anastomosing cords and sheets of Odontogenic Epithelium in Plexiform type Ameloblastoma with varying intensities as shown in (fig-2). Statistical analysis of mean expression of USP22 in Ameloblastoma and normal tissue was statistically significant (P= 0.041*) using Mann-whitney U test. The mean expression of USP22 values of case and control were shown in (fig-4). Statistical analysis using Mann-whitney U test showed a statistically significant difference (P=0.041) in the mean expression of USP22 in Ameloblastoma when compared to that of inflamed tissue

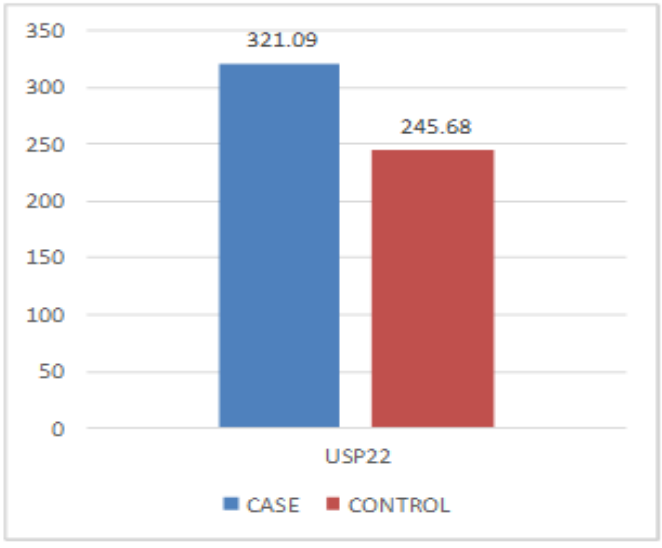

Figure 4: Graph Showing Mean USP22 Expression in Case and Control

Discussion

Ameloblastoma is a benign locally aggressive tumor characterized by high cellular proliferation and reduced apoptosis[10]. In Amelobalstoma USP22 may play a key role. USP22 upregulation has a role in cellular proliferation, migration and invasion in various tumors. Altered and over expression of USP22 facilitate premature transition of cell cycle at various stages. USP22 is involved in tumorigenesis and tumor progression. USP22 expression is positively correlated with proteins involved in cell growth and cell cycle and is negatively correlated with the tumor suppressor proteins.

Figure 5: Pathogenic Events in Ameloblastoma

The length of telomeres progressively reduces after each cell division, which eventually cause senescence and apoptosis. Through telomeric repeat binding factor 1, cancer cells are able to maintain the length of their telomeres by reactivating telomerase or a recombination-based process. Increased USP22 expression in Ameloblastoma may play a crucial role in the progression of the disease by regulating TRF-1, which preserves telomere length[11].

USP22 regulates apoptosis by altering sirtuin1 (SIRT1), a NAD+-dependent class III histone deacetylase. USP22 catalyzes the removal of poly-ubiquitin chains from SIRT1 in order to stop its degradation and boost its abundance. In turn, SIRT 1 deacetylates TP53 and prevents TP53 target genes from being transcriptionally activated. Therefore, USP22/SIRT1/TP53 regulatory pathway prevents DNA-damage-induced apoptosis.

COX-2 promotes expression of ICAM-1 and VCAM-1 adhesion molecules. The ubiquitin/proteasome pathway affects COX-2 levels by directing misfolded or damaged proteins toward the 26S proteasome for destruction by covalently attaching ubiquitin chains. Silencing of USP22 downregulates COX-2 and thus inhibits cell proliferation by controlling its ubiquitination status. COX-2 overexpression is an independent predictor of poor survival [12].

Histones are small nuclear proteins that range in size from 11 to 15 kDa play a crucial role in DNA compaction. USP22 edits the histone code as part of the mammalian SAGA (Spt-Ada-Gcn5) complex by deubiquitinating H2A and H2B. Histone deubiquitylation is closely related to cancer progression, epigenetic regulation, and transcription activation.

USP22 overexpression represses p21 and promotes early cell cycle transition through several phases, combined with enhanced Fructose-1,6 bisphosphatase1 capacity, which may enhance the proliferation of cancer cells. Cyclin-dependent kinases (CDKs) tend to proliferate when p21 is repressed, enabling injured cells to move from the G1/S state. It is also observed that USP22 overexpression facilitates the G1/S transition. USP22 overexpression was associated with reduction in p21 and p27 levels and abundance of Cyclin D1, CDK4 and CDK6, which form a complex that promotes G1 progression thus causing cell cycle progression.

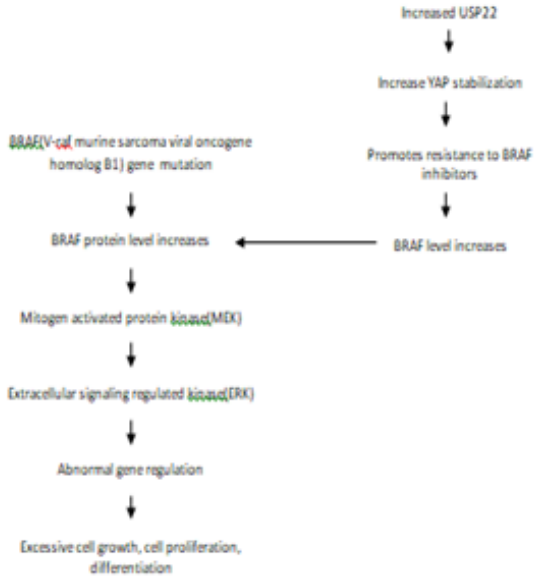

Figure 6: Pathogenic Mechanism in Ameloblastoma

- Increased expression of USP22 was associated with higher expression of Yes associated protein 1(YAP1) in patients with melanoma. Stabilization of YAP protein promote increased resistance to v- raf murine sarcoma viral oncogene homolog B1(BRAF) inhibitors thus, increasing levels of BRAF.
- Abnormal BRAF protein levels causes elevated levels of mitogen activated protein kinase(MEK).
- MEK in turn activates the extracellular signal regulated kinase causing abnormal gene regulation, finally leading to excessive cell growth, cell proliferation, differentiation.

Conclusion

The current study showed a significantly higher expression of USP22 in Ameloblastoma compared to normal oral mucosal epithelium. Having known the credential role of USP22 in various phases of cell cycle, its faulty expression could indeed be disapproving to normal cellular function. Hence its enhanced expression in Ameloblastoma could be reasoned for its aggressive nature along with other factors. Further exploration with increased sample size is needed to uncover the concealed link between USP22 and its role in pathogenesis of Ameloblastoma.

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