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# Ameloblastoma: Where do we stand

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**Abstract**
Ameloblastoma is the most common odontogenic tumor in India and is the second most common in the world. It is most commonly seen in the mandibular posterior region. The exact mechanism is not dully understood. In this review we have compiled all the exisiting data on the molecular pathogenesis of Ameloblastoma.

**Keywords:** Ameloblastoma, odontogenic, tumor

## Introduction

Ameloblastoma is an odontogenic tumor of epithelial origin which arises from the epithelium of the dental lamina, and is characterized by its local aggressive behavior and a high recurrence rate. It accounts for about 1% of all oral tumors and about 9–11% of odontogenic tumors. (1, 2) It is generally a slow-growing but locally invasive tumor. Its peak incidence is in the third to fourth decades of life and the male: Female ratio is 1:1. Its incidence was 0.6 cases/million, and of 0.31 cases/million in a white population of South Africa. Ameloblastoma accounted for 60.3% of all odontogenic tumors in Indian population, with a mean age of presentation of 30.2 years. A slight male predilection and major occurrence in the mandibular molar-ramus area were elicited. They are classified as unicystic, multicystic or solid, 86% of cases are multicystic ameloblastomas. Ameloblastoma in the mandible can progress to great size and cause facial asymmetry, displacement of teeth, malocclusion, and pathologic fractures.

## Molecular pathogenesis

A series of genetic and molecular alterations appear to promote the development and progression of tooth via sequence of biological events. Although the etiology and pathogenesis of odontogenic tumors especially Ameloblastoma remains unknown, recent studies have identified various molecular alterations responsible for their development and progression.

**Fig 1:** Molecules responsible in pathogenesis of Ameloblastoma are

| Molecules involved in Tumorigenesis and/or differentiation of Ameloblastoma | Molecules involved in cell adhesion and migration | Molecules involved in progression of Ameloblastoma |
|---|---|---|
| Clonality<br>Stem cell related molecules<br>Cell cycle proliferation/ Cell cycle regulators<br>Regulators of tooth development<br>Apoptosis related factors<br>Oncogenes<br>Oncogenic virus | Syndecan (CD138) | Cell adhesion molecules<br>Matrix degrading proteinases<br>Angiogenic factors<br>Osteolytic cytokines |

## Molecules involved in Tumorigenesis and/or differentiation of Ameloblastoma

### Clonality

The etiology of Ameloblastoma has not yet been clarified. Determination of clonality pattern is essential for understanding pathogenesis of tumor. Most of the odontogenic tumor including Ameloblastoma are monoclonal in nature. Although molecular alterations were found in Ameloblastoma, the sequence of events is still not known [7].

### Stem Cell Related Molecules

Kumamoto *et al.* (2010) [29] analysed expression of stem cell related molecule in Ameloblastic tumor and tooth germ-Bmi1,CD133, ATP binding cassette subfamily G member2 (ABCG2) [8]

**Fig 2:** CD133& Bmi1

| Kumamoto *et al.* (2010) [29] | Showed positive expression in odontogenic epithelial cells adjacent to basement membrane in tooth germs, Ameloblastoma, Metastasizing Ameloblastoma and Ameloblastic carcinoma. Ameloblastic carcinoma>Ameloblastoma >Tooth germ |
|---|---|

**Fig 3:** ABCG2

| Kumamoto *et al.* (2010) [29] | Expression is evident in Ameloblastic tumors whereas it is absent in tooth germs. Ameloblastic carcinoma>Ameloblastoma> tooth germ |
|---|---|

Cell cycle proliferation/ cell cycle regulators

Cell proliferation index of Ameloblastoma has been studied since 1995. Cell proliferation shows an orderly progression through the cell cycle, which is governed by numerous factors including retinoblastoma protein, cyclins, Cyclin Dependent Kinases, Cyclin Dependent Kinase inhibitors and other critical regulators. Cell cycle phase or cell proliferation markers-PCNA, Ki67, DNA topoisomerase II alpha, histone H3- reflect proliferation activity and malignant potential [9, 10].

**Fig 4:** Ki67

| Florescu *et al.* 2012 [9] | Observed increased expression of Ki67 in peripheral cells of tumor islands when compared with central cells suggesting that the peripheral cells are more proliferative. |
|---|---|
| Nafarzadeh (2013) [10] | Ki67 index is similar in unicystic and solid ameloblastoma with difference in few types. Luminal types of UA showed higher value which can be attributed to presence of less number of stellate reticulum like cells and most of the cells are basal or parabasal cells which are usually positive. |

**PCNA**

Increased in Unicystic ameloblastoma than in solid ameloblastom [7, 10, 11, 13, 14].

**Fig 5**

| Funaoka *et al.* | Higher PCNA labelling index in follicular ameloblastoma than in plexiform ameloblastoma |
|---|---|
| Ueno *et al.*(1989) Reichart (1995) [1] | Higher PCNA labelling index in follicular ameloblastoma explains high rate of recurrence |
| Salehinejad *et al.* (2011) [11] | Highest mean index labelling for PCNA in acanthomatous ameloblastoma |
| Lie *et al.* and Shear *et al.* | Ki67 and PCNA, markers for recurrence and aggressive behaviour of tumors Unicystic Ameloblastoma >Plexiform Ameloblastoma >follicular Ameloblastoma >Ameloblastic carcinoma |

**Fig 6:** Cyclin D1

| Kumar *et al.* (2011) [12] | Nuclear and cytoplasmic expression of cyclin D1 was predominantly seen in both peripheral cells and stellate reticulum like tissue suggesting their role in proliferation in peripheral cells and differentiation in central cells. |
|---|---|

**Telomerase**

Telomerase is a specialized reverse transcriptase that synthesizes telomeric DNA at the ends of chromosomes and compensates for its loss with each cell division, participating in cell immortalization [14, 15, 16].

**Fig 7**

| | **On TRAP assay and IHC ameloblastoma tumor cells were consistently positive for telomerase activation- Telomerase activation is associated with tumorigenesis of ameloblastoma.** |
|---|---|
| Kumamoto *et al.* (2001) [29] | Expression of c-Myc protein is similar to TERT, suggested that c-Myc might induce telomerase activity in Ameloblastoma. |
| Zhong *et al.* (2004) [16] | High expression of Human telomerase RNA and hTERT was closely related to the clinical behaviour of Ameloblastoma and regulated by p53. |

**Growth factors**

Growth factors are hormone like polypeptides that play key roles in the control of cell proliferation and differentiation, and many growth factors are identified. [EGF, PDGF, IGF, HGF, FGF, VEGF, TGF]. Growth factors transmit signals by binding to specific high affinity subsequent signalling molecules.

EGF, TGF-alpha and receptors- Most commonly located in odontogenic epithelial cells. Ameloblastoma shows expression of TGF alpha and tooth germ shows expression of EGF and TGF alpha. Ameloblastoma and OKC shows higher expression of EGFR than epithelium of other odontogenic cysts

TGF beta and receptors- Plays an important role in cell differentiation and matrix formation via regulation or dysregulation of EMI in Ameloblastoma and Ameloblastic fibroma.

HGF and receptor (c-Met) - Affects EMI in developing teeth and also in neoplastic odontogenic tissues. Increased expression seen in Ameloblastic Carcinoma and Clear cell odontogenic Carcinoma which shows that it associated with malignant potential of epithelial odontogenic tissues. Thus, presence of increased expression in Ameloblastoma is an indicator of malignant transformation.

FGF1, 2 and receptor type 2&3- shows similar staining in Ameloblastoma and normal dental follicle. In cultured ameloblastoma cells, there was intense staining in the cytoplasm of the tumor cells. High expression of FGF1 seen in both basal and stellate reticulum like cells and FGF2 in basement membrane of Ameloblastoma.

IGF and PDGF as well as TGF and FGF are stored in bone matrix and participate in local regulation of bone metabolism. IGF and PDGF along with its receptor expression was seen in Ameloblastic tumors which affects the interactions with bone microenvironment. Sulzbacher *et al.* (2008) - Somatic mutation in PDGF receptor gene was evident in an ameloblastoma case.

PDGF levels in Ameloblastic Carcinoma was more than that in Ameloblastoma.

PDGF and receptors might participate in malignant transformation of odontogenic epithelium.

Ras/MAPK and PI-3K/Akt pathways- function downstream to growth factor receptor and regulate cell proliferation and Differentiation. Expression of ERK, a classic MAPK showed higher expression in Ameloblastoma than in dental follicles. Ameloblastoma shows increased expression of PI3K&& Akt and decreased expression of PTEN.

Thus, dysregulation of growth factor, growth factor receptor or signalling molecules might result in tumorigenesis and malignant transformation of Ameloblastoma [13, 14, 17, 19].

Tumor Suppressor Gene

Tp53- most widely mutated gene across all cancer. Aberration of p14, MDM-p53 cascade strongly correlates with neoplastic transformation [7, 13, 14].

**Fig 8**

| **Kumamoto *et al.* (1999) [29]** | **Nomutations in Tp53 were evident in Ameloblastoma and concluded that it plays minor role in neoplastic change of odontogenic epithelium** |
|---|---|
| Kumamoto *et al.* (2004) [29] | Elevated expression of p14, MDM2-p53 in benign and malignant Ameloblastoma am suggested that alteration of p14, MDM2-p53 cascade leads to oncogenesis or malignant transformation of odontogenic epithelium and is also associated with tissue structuring and cytodifferentiation of Ameloblastoma. |

Rb- first suppressor gene found in malignant tumors of the retina in childhood, located on chromosome13.

**Fig 9**

| **Kumamoto *et al.*(2006) [29]** | **Increased expression of Rb and Phosphorylated Rb in Ameloblastoma more Than That in tooth germ. Rb might have a role in cell proliferation and differentiation of odontogenic epithelium.** |
|---|---|
| Lim and Ahn *et al.* (2006) | Found contradictory results, conducted study using DNA microarray and RT-PCR and found that Rb1 is downregulated in Ameloblastoma in comparison to Dentigerous cyst. Role of this gene in pathogenesis of Ameloblastoma is unclear. |

PTEN- negative regulator of PI3K/Akt pathway, which is considered an important molecule in pathogenesis of Ameloblastic tumors.

**Fig 10**

| | |
|---|---|
| | There is decreased expression of PTEN in Ameloblastic tumors than in Dental follicles. Ameloblastic tumors shows high frequency of allelic loss of PTEN. PTEN/KT/mTOR pathway are negative regulators for aggressiveness of Ameloblastoma. P16- downregulated in relation to dentigerous cyst |
| | Higher methylation of p21 in Ameloblastoma than normal Dental follicles. |

APC gene- in normal development, APC gene or protein causes down regulation of beta-catenin, an essential product of Wnt signalling pathway for nor al development and differentiation of cells. In deficiency of Wnt signalling pathway, APC results in degradation of beta-catenin, repressing it's accumulation in cytoplasm [7, 13, 14].

**Fig 11**

| | |
|---|---|
| | Beta-catenin is expressed in cell membrane and cytoplasm of benign as well as Ameloblastic Carcinoma were as it is only expressed in nucleus of Ameloblastic Carcinoma. Both decreased APC and increased beta-catenin are expressed in Ameloblastoma and odontogenic Carcinoma. APC causes dysregulation of proliferation of cells which affects the cytodifferentiation and oncogenesis of epithelium of odontogenic origin. |

Regulators of Tooth Development

Tooth development is under strict genetic control of regulators that determine the position and shape of teeth (Msx-1, Msx-2, Dlx-2, Barx1, Pax9 or that involved in morphogenesis and cytodifferentiation of teeth (SHH, BMP, Wnt, HGF, FGF).

HGF and BMP mediates EMI in Ameloblastic tumors.

Notch receptors and ligands are expressed by ameloblastoma and are important for modulating cell fate decision. Notch signalling might control cell differentiation and proliferation in Ameloblastoma [7, 13, 14, 20, 28, 29].

**Fig 12**

| | |
|---|---|
| Ruhin Poncet (2009) | Distinct pattern of expression of Msx and Dlx is seen in Ameloblastoma: Msx2- epithelial cells of Ameloblastoma and some peripheral tumor cells. Dlx3- exclusively in epithelial cells. |
| Barreto *et al.* | Ameloblastoma shows under expression of PTCH and benign and metastasizing Ameloblastoma shows Shh reactivity predominantly in malignant tumor cells. |
| Kumamoto *et al.* (2004) [29] | SMO and Gli1 are expressed in neoplastic and stromal cells of benign and Metastasizing Ameloblastoma. Gli more in neoplastic epithelial cells than in stromal cells |

Regulators of tooth development are involved in oncogenesis and cytodifferentiation of odontogenic tumor.

**Fig 13:** BMP

| **Gao *et al.* (1997)** | **Positive expression in ameloblasts un tooth germs but not expressed in tumor cells of Ameloblastoma** |
|---|---|
| Kumamoto and Ooya (2006) [29] | BMP-4 and BMP-7 and BMP receptor I and II showed expression in basal cells of Ameloblastoma which plays a role in differentiation of neoplastic odontogenic epithelium. |
| | Strong positive reactivity of BMP-7 in keratinising cells of Ameloblastoma suggests an association with cell death in neoplastic epithelium. |

**Ameloblastin and Enamel matrix proteins**

Ameloblastin is the most important protein involved in dental cytodifferentiation and is highly expressed during differentiation of the Inner Enamel Epithelium [7, 13, 14, 20].

**Fig 14**

| | **Ameloblastin protein, enamelin and sheathlin protein are not expressed in Ameloblastoma, suggesting that tumor cells do not attain functional maturation as secretory phase ameloblasts.** |
|---|---|
| | Ameloblastin null mice developed odontogenic tumor of epithelial origin. The tumor expressed amelogenin, enamelin, tuftelin. |
| Gomes *et al.* (2010) | Over expression of ameloblastin protein inhibits proliferation of human Ameloblastoma cell lines that lacked ameloblastin. Ameloblastin confers protection against Ameloblastoma development. |

**Apoptosis related factors**

In odontogenic tumors, apoptotic cells can be seen by:

1. Terminal deoxynucleotidyl transferase (TdT) mediated dUTP biotin nick end labelling (TUNEL) assay used to perceive those cells which undergo apoptosis.
2. IHC using single stranded DNA antigen, which led to the conclusion that death of cell assumes paramount part in oncogenesis and cell differentiation in odontogenic epithelium [7, 13, 14, 20, 2].

**Fig 15**

| | |
|---|---|
| Kumamoto *et al.* (2004) [29] | Apoptosis bodies were distinguished in typical and malignant epithelial cells of odontogenic origin disconnected from basement membrane. |
| | Immuno-reactivity for ssDNA was more in granular cell Ameloblastoma, especially in granular cells than in other neoplastic cells. Apoptotic bodies combative with anti-ssDNA antigen identified as minute circular specks on the nuclei of both normal and malignant odontogenic epithelial cells. Scattered ssDNA expression was seen in tooth germ, chiefly in the stratum intermedium and the expression shows transition from outer cuboidal or columnar cells to central polyhedral cells in plexiform and follicular ameloblastoma. |
| | Increased reactivity of ssDNA seen in acanthomatous ameloblastoma especially in the keratinising cells and numerous apoptotic bodies. Basal cell ameloblastoma and desmoplastic ameloblastoma comparable to follicular ameloblastoma and negligible apoptotic bodies in Ameloblastic Carcinoma. |
| Kumamoto *et al.* (2010) [29] | Normal and neoplastic odontogenic epithelial cells show immunoreaction for Fas and FasL. Ameloblastic Carcinoma shows significant Downregulation of Fas and upregulation of FasL expression in comparison with benign ameloblastoma signified the release from death of cells attacked by immune cells. Basal cell ameloblastoma showed lower expression whereas desmoplastic ameloblastoma showed higher expression of Fas and caspase-3. |
| | Expression of TNF-α in dental follicles controls progression included in tooth eruption. |
| Sandra *et al.* (2001) | Most of the normal and neoplastic odontogenic tissue displayed expression of TRAIL and receptor which relatively recurred in epithelial component of tooth forming apparatus, paralleled with TNF-α expression and also in the cells near basement membrane in ameloblastoma and tooth germ. Low TRAIL expression in acanthomatous ameloblastoma predominantly in the keratinising cells. High expression of TRAIL in granular cell ameloblastoma in the granular cells. |
| | Bcl2 expression in tooth germ, during normal tooth development. In ameloblastoma Bcl2 is predominantly expressed in basal cells. |
| Mitsuyasu *et al.* | Bcl2 expressed in basal cells of ameloblastoma and in basal cell ameloblastoma, all the cells expressed Bcl2. |
| Kumamoto *et al.* | Found expression of Bcl2 and Bclx and inhibitors of apoptotic protein (IAP), survivin and XIAP in basal cells of |

| | |
|---|---|
| (1992 and 2004) [29] | ameloblastoma suggesting their role in suppression of apoptosis. |
| Kumamoto *et al.* (2005) [29] | Expression of apoptotic protease activating factor-1, cytochrome C, apoptosis inducing factor and caspase9 in tooth germ and ameloblastoma suggested that apoptotic death of normal and neoplastic odontogenic epithelium is by mitochondria mediated apoptotic pathway. Increased apoptotic cell death in keratinising cells in acanthomatous ameloblastoma, granular cells in granular cell ameloblastoma and malignant cells in Ameloblastic carcinoma. This describes a role in cytodifferentiation and malignant transformation of odontogenic epithelium. |
| Luo *et al.* (2006) | Studied expression of Fas/FasL and concluded that it might have a role in the disposal of terminally differentiated or degenerative tumor cells in ameloblastoma. |
| | Studies on apoptosis demonstrated that anti-apoptotic proteins (Bcl2) and cell proliferation markers (Ki67) expressed in basal cells of ameloblastoma. it is believed to contribute to progression of ameloblastoma. |

Molecules involved in cell adhesion and cell migration

Cellular invasion requires disintegration of the basement membrane and surrounding ECM, followed by the growth and proliferation of cells. Thus, decreased intercellular adhesion and changes in basal membrane composition influence the growth of malignant neoplasias. Regarding that cell- to-cell adhesion must be indispensable for the regulation of cellular behavior, a number of cell adhesion molecules have been identified in ameloblastoma.

**Syndecan (CD138)**

Regulated odontogenesis and is suggested to participate in WNT induced tumorigenesis of odontogenic epithelium [24].

**Fig 16**

| | |
|---|---|
| | Loss of Syndecan-1 expression demonstrated in malignant epithelial neoplasm is associated with tissue invasion, metastasis and poor prognosis. |
| | Syndecan-1 expression is inversely proportional to Ki67 staining. |
| | Loss of Syndecan-1 expression is an unfavourable prognostic indicator in different benign and malignant epithelial neoplasm. It could explain the aggressive behaviour of solid Ameloblastoma or its malignant transformation. |

**Molecules involved in progression of Ameloblastoma**

**Osteoclastic markers**

The most controversial character of ameloblastoma is its invasiveness into surrounding bone via osteoclastic bine destruction, despite its benign nature.

**Fig 17**

| | |
|---|---|
| Kumamoto and Ooya (2006) [29] | Expression of parathyroid hormone related peptide (PTHrP), osteoclastic differentiation factors (ODF) or RANKL and osteoclastogenesis inhibitory factor (OCIF)/ OPG in ameloblastoma and tooth germs. They found that it may contribute to the local regulation of bone dynamics in both. |
| Sandra *et al.* (2001) | Evidence that ameloblastoma could induce osteoclastogenesis by secreting RANK and RANKL and TNF-α providing space for ameloblastoma to expand the bone. |
| Abdel Syed *et al.* (2004) | Increased expression of PTHrP in ameloblastoma shows role in local bone resorption. This gives an explanation for infiltrative growth and destructive behaviour of ameloblastoma. |

**Matrix degrading Enzymes**

The MMPs are important in matrix degradation during tumor growth, invasion and induction of angiogenesis. MMP-2 has na important function as it degrades type IV collagen. It is suggested to promote tumor invasion and metastasis [20, 27].

**Fig 18**

| | |
|---|---|
| | RT-PCR done on dental follicles and ameloblastoma showed high expression of MMP-2, TIMP-2 and MMP-14 RNA. This is suggested to contribute to local invasive characteristic of ameloblastoma. |
| | TIMPs and MMP-14 is significantly higher in recurrent and solid ameloblastoma than primary and unicystic ameloblastoma, contributing to its invasive capacity. |
| | Inhibition of MMP2 activity using TIMP2 leads to suppression of invasive activity. |
| Ribero *et al.* (2009) | Expression of MMP- 1,2 and 9 in ameloblastoma. The aggressive behaviour is due to active participation of stromal cells and products. (MMPs). |
| Shen *et al.* (2010) | IHC expression of osteonectin or secreted protein acidic and rich in cysteine (SPARC) and MMP-1, 2, 9. SPARC and MMP9 in ameloblastoma regulate tumor invasion. MMP2 and 9 degrade type IV collagen component of the basement membrane. |

**Angiogenesis factors**

Angiogenesis is an essential part of a variety of physiological and pathological process, including embryogenesis wound healing, inflammation and tumor progression. It is controlled by numerous different molecules.

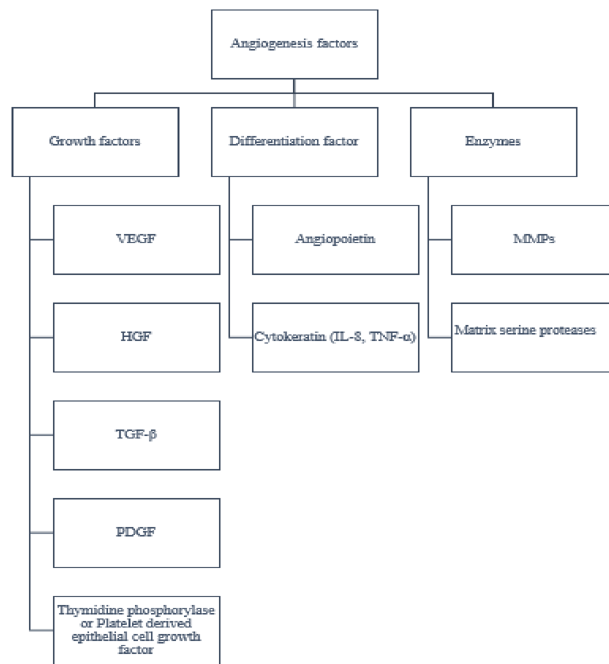


**Fig 1:** Various angiogenic factors that play role in tumor angiogenesis

**Fig 19**

| | |
|---|---|
| | Immunohistochemical evaluation of microvessel density using vascular endothelial marker, CD 34 has higher vascularity in ameloblastoma than in tooth germ. |
| | Increased expression of VEGF, TP/PD-ECGF in amelobastoma |
| | The levels of angiopoietin-1 shows variations:<br>Ameloblastic carcinoma> Ameloblastoma> Tooth germ |

Thus, angiogenic factor play an important role in mediators of tumor angiogenesis or malignant transformation of odontogenic tumor epithelium.

[Molecular and genetic aspects in the etiopathogenesis of ameloblastoma: An update. JOMFP. 2016: 20(3)]

Other signalling molecules

PTCH- encodes a transmembrane receptor for Sonic Hedgehog. It represses function of smoothened gene which inhibits proliferation. When SHH binds to PTCH releases SMO, activating the GLI transcription factor inducing proliferation of the cells.

SHH regulates the growth and determines shape of the tooth but doesnot play a role in differentiation of ameloblasts odontoblasts. Dysregulation of genes involved in odontogenesis plays a role in Ameloblastoma histogenesis.

**Fig 20**

| | |
|---|---|
| | IHC studies have shown increased expression of SHH, SMO and GLI |
| | PTCH protein was highly expressed in Ameloblastoma more than in tooth germ. |
| | PTCH expression showed 7.7 times increased risk of Ameloblastoma development in Patients with homozygous genotype associated with a high PTCH1 production. |
| | SHH underexpressed and PTCH is overexpressed. |

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[Kumamoto H, Ohki K, Ooya K. Expression of Sonic hedgehog (SHH) signaling molecules in ameloblastomas. J Oral Pathol Med 2004; 33: 185–90.]

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