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Pathogenesis of Ameloblastoma – A Review

Nivia M[1], S K Padmakumar[2],Uma Mohan[3],Anu Andrews[4]
[1](Assistant Professor, Department of Oral Pathology and Microbiology, Government Dental College, Alappuzha, Kerala/ KUHS, India))
[2] (Professor and HOD, Department of Oral Pathology and Microbiology, Government Dental College, Alappuzha, Kerala/ KUHS, India)
[3,4] (Senoir Resident, Department of Oral Pathology and Microbiology, Government Dental College, Alappuzha, Kerala/ KUHS, India)

Abstract: *Ameloblastoma is a benign epithelial odontogenic tumour. Pathogenesis of Ameloblastoma is explained with the help of many theories. Embryologic events that initiate and control formation of human odontogenic structures through finely regulated series of inductive interaction between epithelium and ectomesenchyme. Failure of this inductive mechanism results in the formation of hamartomas, malformations and neoplasm collectively known as odontogenic tumours. Better understanding of the pathogenesis will help in developing new treatment approaches and better prognosis. An attempt is made to discuss the current concept of pathogenesis related to molecular and genetic changes.*

Keywords*: Odontogenic tumour, Pathogenesis, Ameloblastoma*

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I. Introduction

Ameloblastoma can arise either from epithelial rests of enamel organ, either remnants of dental lamina or epithelial rests of malassez, disrturbances of the developing enamel organ, epithelial lining of odontogenic cyst, particularly dentigerous cyst and odontomas, basal cells of the surface epithelium of the jaws or from the heterotrophic epithelium in other parts of the body, especially the pituitary gland.

It is likely the result of alterations or mutations in the genetic material of cells that are embryologically preprogrammed for tooth development. Environmental and individual factors like general health status also play a role in modulating the incidence of the disease. Cahn in 1993 reported ameloblastoma originating from the wall of dentigerous cyst. Stanly and Diehl found that 17% of ameloblastomas were definitely associated with an impacted teeth or dentigerous cyst. They also found that there is a marked reduction in the prevalence of such cases after the age of 30 years due to the loss of ameloblastomatous potential of the odontogenic epithelium.[3]

II. History

Ameloblastoma is a true tumour of odontogenic epithelial origin. It is the second most common odontogenic neoplasm after odontomas. The term ameloblastoma was first adopted by Ivy and Churchil. The histopathological description of ameloblastoma first given by Weld in 1853 and he called the tumour cystosarcoma or cystosarcoma adenoids. Malassez introduced the term adamantine epithelioma and Derinsky introduced the term adamantinoma in 1890.[7] It can occur centrally with in bone or peripherally without an intraosseous component. Molar angle ramus area in mandible is the most commonly affected area. It occurs overs a broad age range between 20 and 60 years.[8] Regezi etal in an analysis of 706 odontogenic tumours found the incidence of ameloblastoma to be 11%.

III. Pathogenesis

RAS (an abbreviation of "Rat sarcoma") is a family of genes that make proteins involved in cell signaling pathways that control cell growth and cell death. Mutated forms of the RAS gene like KRAS, HRAS may cause cancer cells to grow and spread in the body. Sandros etal (4) immunohistochemically compared Ameloblastoma with normal teeth for the expression of HRAS [Harvey rat sarcoma viral oncogene homolog] and KRAS [Kirsten rat sarcoma viral oncogene homolog] encoded gene products of p21RAS. p21RAS is expressed preferentially in odontogenic epithelial cells. Overexpression of p21RAS is found in ameloblastoma when compared with normal developing teeth.

Growth factors are hormone-like polypeptides that play key roles in the control of cell proliferation and differentiation. Kumamoto etal(5) studied the immunohistochemical expression of hepatocyte growth factor (HGF), transforming growth factor β (TGF β) and their receptors in ameloblastomas. HGF ia a multifunctional

agent identified as a growth factor for hepatocyte. It acts via its receptor tyrosine kinase, c-Met which is encoded by c-Met oncogene. HGF c-Met pathway is believed to to play an important role in oncogenesis, differentiation, tumour invasion and metastasis. TGF-β is found to be a potent growth inhibitor of epithelial cells and is associated with synthesis of extracellular matrix especially collagen. They found that HGF and TGF β reactivity was marked in epithelial cells near the basement membrane and their receptors were diffusely positive in most epithelial cells. These growth factors play an important role in epithelial mesenchymal interactions involved in neoplasia and they act on tumour cells via paracrine and autocrine mechanisms similar to that of a tooth germ.

Heat shock proteins (HSPs) are highly conserved proteins rapidly generated in response physical, biological and chemical stress. They act as molecular chaperones and assists in the correct folding of newly synthesized proteins. Kumamoto etal[6] studied the Immunohistochemical analysis of HSP70 and it was found to be slightly higher in ameloblastoma compared to tooth germ. Elevated levels of HSP70 protects cells from apoptotic death and might be involved in neoplastic transformation of odontogenic epithelial cells.

Enamel matrix is made from non-collagenous proteins and contains enamel proteins, such as ameloblastin. Expression of ameloblastin and MMP 20 (Enamelysin) recognized in epithelial components of odontogenic tumor suggest that aberrations of enamel-related proteins are involved in oncogenesis of odontogenic epithelium. Ameloblastin gene express a protein, AMBN which plays an important role in differentiation of ameloblast cells and epithelial mesenchymal signalling during odontogenesis. Perdigao etal **(7)** found that this protein shows high expression during differentiation of inner enamel epithelium. DNA extraction and mutation analysis of ameloblastoma and normal mucosal cells were done using PCR. The results demonstrated novel mutations in ameloblastoma, while normal mucosal cells showed the wild type of DNA sequence. MMP-20 (enamelysin) is a matrix metalloproteinase predominantly expressed in teeth. MMP-20 was found to degrade collagen XVIII which is a basement membrane component. Vaananen etal(8) found that MMP-20 and collagen XVIII were co-localised in enamel like tumour in odontogenic tumours.

Apoptosis, also known as programmed cell death has diverse roles in embryogenesis and normal homeostasis, as well as in a variety of pathologic conditions. The apoptotic processes are modulated by a large family of genes, such as the tumor necrosis factor (TNF) family. TNF plays an important role in inducing cell survival, proliferation, differentiation and apoptosis. The study done by Henderman etal(9) suggested that TNFα is expressed in ameloblastoma and it can induce Mitogen activated protein kinase which later might induce cell survival and proliferation in ameloblastoma. Both the TNF α and its receptors TNF Receptor 1 and TNF Receptor 2 were clearly expressed in ameloblastomas.

Tumour-suppressor genes normally act as regulators of cell growth, and inactivation of these genes by mutations or loss of heterozygosity (LOH) in both alleles results in tumor development. Retinoblastoma protein (RB), the product of retinoblastoma (RB) tumor-suppressor gene, acts as a signal transducer connecting the cell cycle with the transcription machinery. During the time preceding G1-phase, underphosphorylated RB binds to transcriptional regulators termed E2 promoter-binding factors (E2Fs) and represses their transcriptional activation. Kumamoto et al(10) found that the expression of retinoblastoma protein (RB) and E2 promoter-binding factor-1 (E2F-1) found to be higher in ameloblastomas than in tooth germs.

Claudins and occludins are the transmembrane component of intercellular tight junction. Claudins are essential for barrier function of epithelium and endothelium while occludins are more important for cell signalling. Bello etal(11) analyzed the distribution pattern of claudins 1, 4, 5, 7 and occludin in ameloblastomas and developing human teeth. The overexpression of claudins in the areas with microcyst formation may indicate their attempt to maintain the interepithelial cohesion of the cells.

Insulin like growth factor [IGF] and their receptor IGF-I receptor which is a transmembrane protein with tyrosine kinase activity which regulates cell growth and metabolism. Platelet derived growth factor [PDGF] seen in platelets act as a growth promoting factor for fibroblasts, smooth muscle cells and glial cells. Kumamoto etal (12) found that the expression of IGF, PDGF and their receptors in tooth germs and ameloblastic tumours suggests that the signal of these growth factors contribute to cell proliferation and survival in neoplastic odontogenic tissues.

DNA methylation is an efficient epigenetic mechanism of transcriptional repression that occurs in cytosine. The presence or absence of methyl groups in cytosines promote the remodeling of chromatin, making it less or more accessible to transcription. So the DNA methylation plays a role in development of odontogenic tumour. Moreira etal(13) investigated the methylatio status of p16, p21, p27, p53 and RB1 genes in epithelial odontogenic tumours. In ameloblastoma the highest methylated genes were found to be p16 and p21.

The matrilysins, also known as MMP-7 and MMP-26 are involved in cell proliferation, apoptosis, invasion and metastasis. Freitas etal(14) studied the immunohistochemical expression of MMP-7 and MMP-26 of ameloblastoma in epithelium and stroma. The marked expression of these matrilysins suggest their role in the process of tissue remodelling and growth. Ayoub etal(15) analysed immunohistochemically the expression of human papilloma virus (HPV) and Epstein Barr virus (EBV) in benign and malignant ameloblastoma of the

jaws. Positive staining for bening ameloblastoma found to be 40%. So HPV might be implicated in the etiology of ameloblastoma.

p53 is a tumour suppressor gene involved in cell cycle arrest. Proliferating cell nuclear antigen [PCNA] is a marker of cellular prolifareation and DNA replication and its increased expression indicates tumourigenesis. Salehinejad etal[16] immunohistochemically evaluated the expression of PCNA and p53 in ameloblastoma. They correlated the increased expression of PCNA with the clinical behaviour of these lesions and the increases expression of p53 explains the aggressive nature of ameloblastoma.

Sonic Hedgehog signalling [SHH] pathway is a key regulator of embryonic development and cell growth control. SHH act through transmambrane protein Patched [PATCH] to activate GLI transcription factors. Loss of heterozygosity [LOH] is the loss of one allele and is a common somatic hallmark of inactivation of a tumour suppressor gene. Farias etal and Kanda etal [17,18] found that ameloblastomas studied showed LOH of the PATCH gene and also an increased transcription of GLI transcription factors.

Brown etal found that mutually exclusive RAS–BRAF and FGFR2 mutations were identified in ameloblastoma with BRAF V600E being the most common. BRAF inhibitor suggests a potential role for targeted therapy . A critical step in the pathogenesis of ameloblastoma is the discovery of recurrent activating mutations in FGFR2, BRAF, and RAS leading to the dysregulation of MAPK pathway signaling pathway. [19,20]

Midkine is a heparin-binding growth factor expressed during tooth development. This protein is overexpressed in ameloblastomas. This protein upregulates the MAP kinase (MAPK) and Protein kinase B (Akt) pathways and plays a role in development and progression of the tumor.[21]

The microRNA system regulates the expression of human genes while its deregulation will result in neoplastic development. Ollara etal identified an aberrant expression of microRNAs in ameloblastoma. MicroRNAs expressed in ameloblastomas are related to neoplastic development, osteogenic process and neoplastic differentiation. They identified a microRNA (miR-489) suggestive of differentiating between solid and unicystic ameloblastomas.[22]

Ameloblastoma mostly shows osteolytic growth. Periostin is an oncogene, mainly produced by osteoblasts and their precursors cells. Periostin play an important role in bone lysis. Kang Y etal[23] showed that Periostin levels are significantly higher in patients with Ameloblastoma than in controls. Results suggested that Periostin expression promotes the proliferation of Ameloblastoma.

Liu etal[24] studied the effect of interactions between tumor cells and bone marrow stromal cells (BMSCs) on osteoclast formation in ameloblastoma. They found that increased expression of interleukin-8 and Activin A induces osteoclastogenesis in Ameloblastoma.

IV. Conclusion

Pathogenesis of Ameloblastoma is multifactorial. Thorough understanding of the pathogenesis of Ameloblastoma will help in developing advanced techniques for the early diagnosis and better prognosis. The molecules involved in pathogenesis can act as biomarkers and newer treatment options like targeted therapy will improve the overall survival rate.

MOLECULAR MARKERS IN AMELOBLASTOMA

MOLECULAR MARKER	EXPRESSION IN AMELOBLASTOMA	INDICATION
Transforming growth factor β [TGF- β]	Increased	Altered expression suggest thatTGF-beta signaling affect differentiation of neoplastic odontogenic epithelial cells.
Hepatocyte growth factor [HGF/ c-met]	Increased	Promote tumor proliferation
Heat Shock Protein 70	Elevated	Protects cells from apoptosis
Enamel proteins Ameloblastin.	Increased	Promotes the epithelial mesenchymal signalling
Retinoblastoma protein	Slightly elevated	Cell proliferation and differentiation of odontogenic epithelium.
Claudins and Occludins	Strongly expressed	
Insulin like growth factor	Increased	Cell proliferation and survival
DNA methylation	Highest methylated genes are p16 and p21	Epigenetic mechanism of transcriptional repression.
MMP-7 and MMP-26 [Matrix metalloproteinases]	Increased	MMP has a role in tissue remodelling
p53 and PCNA	Increased	Reflects the aggressiveness and clinical behaviour
GLi transcription factor	Increased	Cell proliferation
Micro RNA	Increased	Neoplastic development and differentiation
Periostin	Increased	Bone lysis, promotes proliferation of tumour
Interleukin 8, Activin A	Increased	Bone resorption in tumour

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