Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 05, pp.69479-69482, May, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

REVIEW ARTICLE

SIGNAL PATHWAYS SIGNALLING AMELOBLASTOMA

[1]Dr. Chethan Aradhya, [2,*]Dr. Frankantony. P. Britto, [3]Dr. Varsha R Shetty J. and [4]Dr. Sachin Naik

[1] Asst., Professor, Department of Oral Pathology, Century International Institute of Dental Sciences, Poinachi, Kasargod Kerala
[2]Asst. Professor, Department of Oral Pathology, SJM dental College and Hospital, Chitradurga, Karnataka
[3]Assistant Professor, Department of Oral Pathology, Srinivas Institute of Dental Sciences, Mukka Surathkal, Mangalore
[4]Reader, dept. of Public Health Dentistry, SJM dental College and Hospital, Chitradurga, Karnataka

ARTICLE INFO

Article History:
Received 25th February, 2018
Received in revised form
10th March, 2018
Accepted 20th April, 2018
Published online 30th May, 2018

Key words:
Ameloblastoma,
Molecular Mechanism,
Signaling Pathways.

ABSTRACT

Odontogenic tumors are the lesions that are derived from the tooth-producing tissues or their remnants that remain entrapped either within the jawbones. The assumption of being Odontogenic in origin derives from the fact that they are only found in the jaws having a relation to teeth and teeth-bearing tissues. Further their relationship to the teeth is fairly clear-cut, both histologically and radiographically. The pathogenetic mechanism of Odontogenic tumors is closely related to the developmental processes of teeth. As a result, the molecular signaling mechanisms for normal enamel organs and Odontogenic tumors have been closely compared. With advances in the elucidation of molecular signaling mechanisms in cells, the cytodifferentiation of epithelial tumor cells in ameloblastomas can be identified using different biomarkers. Therefore, it is suggested that comprehensive pathological observation including molecular genetic information can provide more reliable information for the propagation and prognosis of ameloblastomas. This article is aimed to review the current concepts of ameloblastomas and to discuss their clinico-pathological features relevant to tumorigenesis and prognosis.

Corresponding author:

Citation: Dr. Chethan Aradhya, Dr. Frankantony .P. Britto, Dr.Varsha R Shetty J. and Dr. Sachin Naik. 2018. "Signal pathways signalling ameloblastoma." *International Journal of Current Research*, 10, (05), 69479-69482.

INTRODUCTION

Ameloblastoma is a slow growing Odontogenic epithelial tumor of the jaw and accounts for about 1% of all oral tumors and about 18% of Odontogenic tumors. It is primarily seen in adults in the third to fifth decades of life, with almost equal sex predilection (Suk Keun *et al*., 2013). They most commonly occur in the mandible, particularly around the angle of the mandible. Radiographically, it appears as an expansile radiolucency with thinned and perforated cortices, frequently causing root resorption (Hong Zhang Huang, 2009; Tao, 2009).

Clinico-pathological classification of ameloblastoma: According to the World Health Organization (WHO), ameloblastomas are classified into the following types depending on the origin of tumorigenesis: Solid/Multicystic, Extraosseous/Peripheral, Desmoplastic and Unicystic.

The most common solid/multicystic/conventional (48.9%) ameloblastomas arise from enamel epithelial rests in jaw bone, while Unicystic ameloblastomas (25.3%) arise from the epithelium of odontogenic cysts. Desmoplastic ameloblastomas exhibit active stromal proliferation, while Peripheral ameloblastomas (3.1%) arise from dental lamina rests and oral mucosa epithelium. These tumor types differ in biological behavior and rate of recurrence eg: The recurrence rate for conventional ameloblastomas (17.1%) was significantly higher than for the unicystic type (9.1%). Therefore each type of ameloblastoma requires different forms of treatment (Anthony Pogrel, 2006; Sinem Gümgüm, 2005).

Molecular mechanisms of ameloblastoma: The molecular and genetic characteristics of ameloblastomas are poorly understood and the origin of the tumor is still unclear. The cloning and characterization of expression of the Ameloblastin and Amelogenin genes in these tumors suggests that

ameloblastoma arise from the Odontogenic apparatus or cells that are potentially capable of forming dental tissue. The potential sources for this tumor are the cell rests of the enamel organ (cell rests of Malassez and cell rests of Serre), epithelial odontogenic cysts (dentigerous cysts), basal cells of the surface epithelium of the jaws and heterotrophic epithelium in other parts of the body. Every cellular change, including proliferation, differentiation, senescence, tumorigenesis etc occurs through the activation or inactivation of related molecular signaling pathways. Identification of specific new signaling pathways involving ameloblastoma, whereby the expression and relationships among the molecules are mediated, may provide an opportunity to afford efficient prevention and develop new treatment therapies (Suk Keun Lee, 2013; Nadeem Jeddy *et al*., 2013).

Signaling pathways involved

Sonic hedgehog (SHH) pathway: Sonic hedgehog is a protein that in humans is encoded by the SHH ("sonic hedgehog") gene and is one of three proteins in the mammalian signaling pathway family called Hedgehog. It controls cell division of adult stem cells and has been implicated in the development of some cancers. PTCH1 is a member of the patched gene family and is the receptor for sonic hedgehog, This gene functions as a tumor suppressor. The PTCH1 gene product is a transmembrane protein that suppresses the release of transcription protein called smoothened (SMO) and when sonic hedgehog (SHH) binds PTCH1, smoothened is released and signals cell proliferation (Lee *et al*., 2006). A high expression of SHH, SMO and GLI protein was reported in ameloblastoma (Suk Keun Lee, 2013; Nadeem Jeddy *et al*., 2013)**.**

Wnt signaling pathways: Are a group of signal transduction pathways made of proteins that pass signals from outside of a cell through cell surface receptors to the inside of the cell. Three Wnt signaling pathways have been characterized: the canonical Wnt pathway, the noncanonical planar cell polarity pathway and the noncanonical Wnt/calcium pathway. The canonical Wnt pathway leads to regulation of gene transcription, the noncanonical planar cell polarity pathway regulates the cytoskeleton that is responsible for the shape of the cell and the noncanonical Wnt/calcium pathway regulates calcium inside the cell. All three Wnt signaling pathways are activated by the binding of a Wnt-protein ligand to a Frizzled family receptor, which passes the biological signal to the phosphoprotein Dishevelled which is a cytoplasmic transcription factor present inside the cell. The canonical Wnt pathway (or Wnt/β-catenin pathway) is the Wnt pathway that causes an accumulation of β-catenin in the cytoplasm and its eventual translocation into the nucleus to act as a transcriptional coactivator of transcription factors that belong to the TCF/LEF (Lymphocyte Enhancing Factor) family. Without Wnt signaling, the β-catenin would not accumulate in the cytoplasm since a destruction complex would normally degrade it. This destruction complex includes the following proteins: Axin, adenomatosis polyposis coli (APC) (Bryan, 2009). During tooth development WNT-3, -4, -6, -7b, -10a and -10b are encountered in the epithelium only whereas WNT -5a is expressed in both the epithelium and mesenchyme. Syndecan-1, (CD138) is a cell adhesion molecule, which is known to regulate many biological processes; including odontogenesis and plays a role in the WNT induced tumorigenesis of odontogenic epithelium. β catenin is associated with cell-cell adhesion and signal transduction in neoplastic odontogenic epithelium. The loss of Syndecan-1 indicates unfavorable prognosis in epithelial tumors due to increased transcriptional activity of accumulated β catenin. The decreased expression of Syndecan-1 was seen in ameloblastomas which could attribute to the aggressive behavior of the tumor (Nadeem Jeddy *et al*., 2013; Yi Zhong *et al*., 2011).

Akt/PKB (Protein Kinase B) signaling pathway: Is a pathway in cell signaling leading to cell survival by blocking apoptosis. It is activated by binding of growth factor protein ligand with its receptors which activates phosphoinositide 3-kinase (PI3K) which in turn activates Akt/PKB (protein kinase B). Akt indirectly activates mTOR (mammalion target of rapamycin) that regulates cell growth, cell proliferation, cell motility and Akt also inactivates pro-apoptotic factor Bad promoting cell survival.

Phosphatase and tensin homolog (**PTEN**): Is a protein that, in humans, is encoded by the *PTEN* gene. It acts as a tumor suppressor gene by the removing phosphate groups from the inositol phospholipids through the action of its phosphatase. Thus inhibiting Akt/PKB pathway and promoting apoptosis. Deficiency of *PTEN* therefore facilitates inappropriate functioning of the cell cycle, through generation of prolonged inositol phospholipid signals after growth factor stimulation. Its expression was reduced in ameloblastomas compared with teeth germs (Kenneth, 2001; Scheper *et al*., 2008).

Notch signaling pathway: Is a highly conserved cell signaling system present in most multicellular organisms. Notch is present in all mammals possess four different notch receptors, referred to as NOTCH1, NOTCH2, NOTCH3, and NOTCH4. The notch receptor is a single- transmembrane receptor protein. It is a hetero-oligomer composed of a large extracellular portion, which associates in a calcium-dependent, non-covalent interaction, a single transmembrane-region and a small intracellular region**.** The receptor is normally triggered via direct cell-to-cell contact, in which the transmembrane proteins of the cells in direct contact form the ligands that bind the notch receptor. The Notch binding allows groups of cells to organize themselves, once the notch extracellular domain interacts with a ligand, an ADAM-family metalloprotease called ADAM10, cleaves the notch protein just outside the membrane. This releases the extracellular portion of notch, which continues to interact with the ligand. The ligand plus the notch extracellular domain is then endocytosed by the ligand-expressing cell. After this first cleavage, an enzyme called γ-secretase cleaves the remaining part of the notch protein just inside the inner leaflet of the cell membrane of the notch-expressing cell. This releases the intracellular domain of the notch protein, which then moves to the nucleus, where it can regulate gene expression by activating the transcription factor CSL (Emma, 2011). Notch activity affects the implementation of differentiation, prolifereation, and apoptotic programs to control a broad spectrum of developmental processes, such as neurogenesis, somitogenesis, hematopoiesis, vasculogenesis, keratinocyte, growth/differentiation and craniofacial development, including tooth development. Notch signaling pathway plays an essential role in tooth development. Aberrant Notch has been detected in the Plexiform and Follicular ameloblastoma. These findings suggest that Notch receptors

and their ligands may play differing roles during the development of ameloblastoma with Notch4 probably playing a greater role in the acquisition of tissue-specific cellular characteristics in the ameloblastoma. Expression of Notch receptors and ligands in tooth germs and ameloblastomas suggests that Notch signaling might control cell differentiation and proliferation of normal and neoplastic odontogenic epithelium (Muraki *et al*., 2011; Kumamoto, 2008).

TGFB /SMAD signaling pathway: The transforming growth factor beta (TGFB) signaling pathway is involved in many cellular processes in both the adult organism and the developing embryo including cell growth, cell differentiation, apoptosis, cellular homeostasis and other cellular functions. The TGF beta superfamily of ligands include: Bone morphogenetic proteins (BMPs), Growth and differentiation factors (GDFs) and TGF beta family that includes TGFβ1, TGFβ2, TGFβ3. Signaling begins with the binding of a TGF beta super family ligand to a TGF beta type II receptor. The type II receptor is a serine/threonine receptor kinase, which catalyzes the phosphorylation of the Type I receptor. The ligand receptor complex then phosphorylates receptor-regulated SMADs (R-SMADs) which can now bind the coSMAD. SMADs are transcription factors that transduce extracellular TGF-β superfamily ligand signaling from cell membrane bound TGF-β receptors into the nucleus where they activate transcription TGF-β target genes. R-SMAD/coSMAD complexes accumulate in the nucleus where they act as transcription factors and participate in the regulation of target gene expression. The TGF-β/Smad signaling pathway regulates diverse cellular functions, including tooth development and is involved in numerous pathological processes such as tumorigenesis of Ameloblastoma, Calcifying cystic odontogenic tumor, and Adenomatoid odontogenic tumor (Long Zhang, 2013; Karathanasi *et al*., 2013).

Note: TGF-β may also trigger apoptosis via the death associated protein 6 (DAXX adapter protein). DAXX has been shown to associate with and bind to the type II TGF-β receptor kinase.

In Cell cycle: TGF-β plays a crucial role in the regulation of the cell cycle. TGF-β causes synthesis of p15 and p21 proteins, which block the cyclin: CDK complex responsible for Retinoblastoma protein (Rb) phosphorylation. Thus TGF-β blocks advance through the G1 phase of the cycle. In doing so, TGF-β suppresses expression of c-myc, a gene which is involved in G1 cell cycle progression.(note: The TGF beta superfamily of ligands include: Bone morphogenetic proteins (BMPs), Growth and differentiation factors (GDFs) promote cell mitosis and differentiation but in different cells eg. Action of BMP in bone promotes osteogenesis). Therefore TGF-β acts as tumor suppressor gene and prevents tumor formation especially in premalignant phase. On the other hand, cancer cells that have lost this inhibitory growth response exploit the ability of TGF- β to modulate processes such as cell invasion, angiogenesis, immune regulation,or interactions between tumor cells and their microenvironment that make them more malignant. Endoglin is the one which is responsible for this switch on or off of required pathway.

Conclusion

Further molecular studies should be encouraged to clarify the essence of the molecules involved in the tumor pathogenesis and invasion of ameloblastoma. The key breakthroughs may come from establishing stable, reliable ameloblastoma immortalized cell lines and animal models. The proper understanding of the pathogenetic mechanism involved in ameloblastoma and its proliferation aids in constituting proper treatment of choice at an early stage thereby preventing morbidity associated with extensive therapy. Further the molecules involved in the pathogenesis can serve as markers in long term follow-up to predict recurrence.

REFERENCES

Anthony Pogrel, M., Brian L., Schmidt, Chad G. Robertson. Clinical Pathology: Odontogenic and Non odontogenic Tumors of the Jaws. CHAPTER 23,Page 490 – 5.

Bryan T. MacDonald, Keiko Tamai, and Xi He. Wnt/β-catenin signaling: components, mechanisms, and diseases;*Dev Cell. 2009 July; 17(1): 9–26.*

Emma R. Andersson, 2011. Rickard Sandberg and Urban Lendah. Notch signaling simplicity in design, versatility in function, *Development, 138, 3593-3612*

Hong Zhang Huang, Qian Tao, Dan Chen, 2009. Studies on the Invasiveness of Ameloblastoma, *The Chinese Journal of Dental Research Volume 12, Number 2.*

Karathanasi V, Tosios KI, Nikitakis NG, Piperi E, Koutlas I, Trimis G, Sklavounou ATGF-β1, Smad-2/-3, Smad-1/-5/-8, and Smad-4 signaling factors are expressed in ameloblastomas, adenomatoid odontogenic tumors, and calcifying cystic odontogenic tumors: an immunohistochemical study. *J Oral Pathol Med.,* 2013 May;42(5):415-23.

Kenneth M. Yamada and Masaru Araki, Tumor suppressor PTEN: modulator of cell signaling,growth, migration and apoptosis. *Journal of Cell Science 114, 2375-2382.*

Kumamoto H, Ohki K.J. 2008. Detection of Notch signaling molecules in ameloblastomas. *Oral Pathol Med., Apr;37(4):228-34.*

Lee L. Rubin and Frederic J. de Sauvage. 2006. Targeting the Hedgehog pathway in cancer *Nature reviews | drug discovery december, VOLUME 5.*

Long Zhang, Fangfang Zhou and Peter ten Dijke, 2013. Signaling interplay between transforming growth factor-b receptor and PI3K/AKT pathways in cancer. *Trends in Biochemical Sciences, December Vol. 38, No. 12.*

Muraki, E., Nakano, K., Maeda, H., Takayama, M., Jinno, M., Kubo, K., Yoshida, W., Hasegawa, H., Kawakami. T. 2011. Immunohistochemical Localization Of Notch Signaling Molecules In Ameloblastomas. *Eur J Med Res., 16: 253-257*

Nadeem Jeddy, Jeyapradha T., Ananthalakshmi R., Sathiya Jeeva, P. Saikrishna, P. Lakshmipathy, 2013. The molecular and genetic aspects in the pathogenesis and treatment of ameloblastoma. *Journal of Dr. NTR University of Health Sciences, 2(3): 157-161.*

Scheper MA, Chaisuparat R, Nikitakis NG, Sauk JJ. 2008. Expression and alterations of the PTEN / AKT / mTOR pathway in ameloblastomas. *Oral Dis.*, Sep; 14(6):561-8.

Sinem Gümgüm, 2005. Clinical and Radiologic Behaviour of Ameloblastoma in 4 Cases, *J Can Dent Assoc., 71(7):481–4.*

Suk Keun Lee,Yeon Sook Kim, 2013. Current Concepts and Occurrence of Epithelial Odontogenic Tumors: I. Ameloblastoma and Adenomatoid Odontogenic Tumor; *The Korean Journal of Pathology, 47: 191-202.*

Tao Q *et al*. 2009. Immortalization of ameloblastoma cells via reactivation of telomerase function: Phenotypic and molecular characteristics. *Oral Oncol.*

Yi Zhong, Wei Guo, Li Wang, and Xinming Chen. 2011. Molecular markers of tumor invasiveness in ameloblastoma: An update. *Ann Maxillofac Surg. 2011 Jul-Dec; 1(2): 145–149.*

****