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Role of WNT1 and PTCH Genes in the Diagnosis of Odontogenic Lesions – A Review

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ABSTRACT

Odontogenic lesions of the maxillofacial region constitute a complex group of lesions with diverse histopathologic types and clinical behavior. Diagnosis is the key for early identification of odontogenic lesions. Various diagnostic modalities like radiographic imaging (OPG, CT, MRI), Fine needle Aspiration cytology (FNAC) are utilized, but histopathological findings found to be the confirmatory one. Molecular level understanding of Odontogenic lesions gives exact pathogenesis and progression of the disease. Both Patched (PTCH) and WNT1 are being involved in imparting organ specific features. Any abnormalities associated with these genes results in tumour occurrence.

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I. INTRODUCTION

Odontogenic cysts and tumors constitute an unusually diverse group of lesions. This diversity reflects the complex development of the dental structures, since all these lesions originate through some alteration from the normal pattern of odontogenesis. Some of these lesions does not represent true neoplasm, but are only minor alterations in the normal process of tooth development. Despite the availability and the use of various diagnostic modalities like radiographic examinations (OPG, CT-Scan, MRI) and Fine needle Aspiration cytology, histopathological findings are found be the confirmatory one.

Molecular understanding of these lesions gives exact pathogenesis and progression of the disease and might be useful in early diagnosis. Bmp, Fgf, SHH, Wnt and Notch pathways act as major signaling pathways during development of tooth and were found to be involved in imparting organ specific features.
WNT1 the first gene of WNT family, was identified by Varmus and Nusse in 1982. It was originally named integration site 1 (Int-1) as it encodes a cysteine rich protein. It was renamed in 1987 as WNT1 because of the homology between Wingless (Dorsophilia Melanogaster) and Int-1. WNT1 (wingless protein family) is a key signal molecule that controls cell growth and proliferation.

It transfers regulatory information between cells and serves as an important role in stem cell differentiation and neural development. WNT1 gene induces phosphorylation of β catenin in the nucleus which activates the classic WNT pathways, inducing cell proliferation which helps in tooth development and inhibiting apoptosis to generate anomalous growth, resulting in tumour occurrence.

Abnormalities in these pathways induces tumor occurrence as WNT1 gene activation phosphorylates β-catenin in the nucleus to activate the classic WNT pathways, which induce cell proliferation and inhibits apoptosis to generate excessive growth.

The PTCH gene (human homolog of the Drosophila segment polarity gene PTC, patched), a tumor suppressor gene mapped to chromosome 9q22.3, in basal cell carcinoma (BCC) –the most frequent tumors in Gorlin' s syndrome.

Patched is a transmembrane protein that binds to the Sonic hedgehog (SHH) receptor to form a complex compound. PTCH gene expressions are intended to down- regulate and stop the signaling triggered by the arrival of the SHH secreted protein at the cell. PTCH gene auto-regulates to ensure limited programmed proliferation. And this auto-regulation fails if the gene is altered by deletion or mutation. It results in uncontrolled cell proliferation and also continuous and abnormal synthesis of the non- functional PTCH gene. Identification of these tumor markers might be useful in the early diagnosis of odontogenic lesions.

II. REVIEW OF LITERATURE

Several studies were done in tissue samples of Odontogenic lesions and peripheral blood using Immunohistochemistry and RT PCR for identification of WNT1 and PTCH.
Barreto et al., in 2000 conducted a study among cases with sporadic odontogenic keratocysts and nevoid basal cell carcinoma syndrome (NBCCS) to identify PTCH gene mutations. Peripheral blood was collected from both the patients and the volunteers. DNA extraction was done followed by Polymerized chain reaction (PCR) and identified PTCH gene mutations both in sporadic and NBCCS associated odontogenic keratocysts. They found that PTCH gene mutations are involved in the formation of odontogenic keratocysts.

W. Zedan et al., in 2001 compared PTCH ex pressions among odontogenic cysts associated with NBCCS and sporadic cases based on staining intensity and area of cells stained from Immunohistochemistry and stated the differentiation between syndromic and non-syndromic cysts.
In comparison of PTCH expressions among dentigerous cyst, Odontogenic keratocyst and radicular cysts by Pavelic et al., in 2001 similarity existed between odontogenic keratocyst and dentigerous cyst based on immunohistochemistry.

Kochaji et al., in 2005 evaluated PTCH expressions in Odontogenic keratocyst, dentigerous cyst and radicular cysts and found their role in pathogenesis and clinical complication of odontogenic cysts. Kawabata et al., in 2005 found higher alteration of PTCH gene in ameloblastomas using polymerized chain reaction.

T-J Li et al., in 2008 conducted study on Nevoid Basal cell carcinoma syndrome (NBCCS) associated odontogenic cysts, mutation of PTCH gene was found both in tissue samples and peripheral blood from Polymerized chain reaction.

Vered et al., in 2009 compared immunohistochemical expressions of SHH pathway signaling related proteins (PTCH, smoothened (SMO) and GLI-1, and of the SHH–induced bcl-2 oncoprotein in primary and recurrent Odontogenic keratocysts, NBCCS associated odontogenic keratocysts, solid ameloblastomas, dentigerous, radicular cysts and found more positive expression of PTCH in Odontogenic kertaocysts, dentigerous cysts and radicular cysts Kee seng chuah et al., in 2009 demonstrated increased expression of WNT1 in recurrent unicystic ameloblastomas from Immunohistochemistry of tissue specimens.
Siar et al., in 2011 demonstrated increased expression of WNT1 in different types of ameloblastoma (unicystic, solid/multicystic, desmoplastic and recurrent ameloblastomas) from immunohistochemical analysis and showed that WNT1 would be a key signaling molecule in the tumorigenesis of ameloblastoma.
L.C. Farias et al., in 2012 observed the expression of PTCH proteins in tissue samples of ameloblastoma using RT PCR
Yan-Yan Guo et al., in 2013 identified PTCH1 gene mutations in tissues and peripheral blood samples of both NBCCS and sporadic keratocystic odontogenic tumors (KCOTs) using PCR and concluded that the genetic analysis of PTCH1 gene will be useful for early diagnosis of NBCCS.

Shahram Ghanaati et al., in 2015 and found strong positive expression of PTCH in ameloblast and stellate reticulum like cells of ameloblastoma using Immunohistochemistry among west African population and suggested anti PTCH chemotherapeutics could be used as target therapy for ameloblastomas.

Sabrina-Nogueira Dutra et al., in 2017 identified the expression of WNT/ beta catenin signaling pathway in a series of ameloblastomas and calcifying cystic odontogenic tumour (CCOT) by immunohistochemistry and found epithelial expression of WNT1 and WNT5a in ameloblastoma and in Calcifying Cystic Odontogenic Tumour, WNT1 and WNT5a expressions were seen in ghost cells.

Wang et al., in 2018 compared normal mucosa with ameloblastoma and observed the changes in WNT1 expression using Immunohistochemistry and measured the protein expression by western blot and RT q(PCR) and found increased expression of WNT1 protein in ameloblastoma compared to normal mucosa
Santos et al., in 2019 compared the immunoexpressions of Regy, Wnt-1, and b-catenin in ameloblastomas, odontogenic keratocyst and adenomatoid odontogenic tumors. They found nuclear and cytoplasmic expression of Regy gene in all ameloblastomas, adenomatoid odontogenic tumor and odontogenic kertaocyst with significantly higher expression in amloblastomas. WNT1 expression was predominantly higher in cytoplasm of ameloblastomas when compared with Adenomatoid odontogenic tumors and odontogenic keratocyst

Gardenia De Matos et al., in 2019 observed the expressions of wingless type proteins (WNT1, Wnt5a, SUFU and β-catenin) in the epithelial cells of ameloblastomas and odontogenic keratocysts using immunohistochemistry

Nakano et al., in 2020 observed the expression of WNT1 and β-catenin by immunohistochemistry and found epithelial and mesenchymal expression in ameloblastic fibroma and along tumour nests in ameloblastomas. They have also found that there was no expression of WNT1 and β-catenin in odontogenic myxoma.

III. CONCLUSION

The role of molecular bio-markers are crucial in the diagnosis and prognosis of odontogenic lesions of the jaw. Further studies with larger number of samples on individual lesions helps to identify the sensitivity and specificity of the tumour markers on single specific lesion. Targeted therapies on these genes would help to eliminate the need for radical surgery and also improves the quality of life of the patients.
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