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Bioinformatic Analysis of Genes Involved In The Pathogenesis Of Ameloblastoma And Human Tooth Germ

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ABSTRACT

Background: Pathogenesis of most odontogenic tumors is not well established. It is important to identify various genetic deregulations and molecular alterations. Common signaling pathways between ameloblastoma and human tooth germ is yet to be well established. This study aimed to investigate, through bioinformatic analysis, the possible genes involved in the pathogenesis of ameloblastoma (AM) and human tooth germ.

Aim: To analyze the genes commonly expressed in human tooth germ and ameloblastoma for better understanding the molecular pathogenesis of ameloblastoma.

Materials and methods: This is an in-silico study. GeneCards database was used for this study. The database was used to identify important genes expressed in the formation of human tooth germ and ameloblastoma. The potential candidate genes were then mapped using an online program STRING (version 11.5). This identified the interaction of networks between the protein-coding genes. The genes which showed a high degree of confidence were included and their direct and indirect interactions were evaluated. Each gene interaction was scored to produce an overall association score. The genes which displayed the highest WNL score were mentioned as leader genes.

Results: GeneCards and STRING analysis showed a final count of 10 genes that were commonly expressed in ameloblastoma and human tooth germ were included. These were : IGF1 , STAT1 , TLR2 , BRAF , IGF2 , ERK2 , ERK1 , NFkappaB , MEK2 and MEK1. From the WNL analysis, ameloblastoma, the highest WNL values were identified in genes BRAF V600E, MAPK, STAT1 and NFKappaB, The most relevant WNL values for human tooth germ are IGF1, IGF2, TLR1, TLR2 , STAT1 and NKKappaB1.

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Conclusion: STAT 1 and NFKappaB together help in tumor cell proliferation and cell survival. Numerous targeted therapies have been produced against these genes. Further in vitro molecular analysis such as microarray are needed for proper application of these therapies.

Keywords: *Analysis, Germ, potential, human*

INTRODUCTION

Odontogenic tumors are a group of oral lesions which develop from the tissues that form the tooth structure(Philipsen and Reichart 2002). These develop centrally within the mandibular and maxillary regions or peripherally in the oral mucosa and can affect people of different ages(Adebayo, Ajike, and Adekeye 2002)(Pradeep and Senior Lecturer, Department of Conservative Dentistry and Endodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University 2021)(Ramani, Krishnan, Pandiar, Behera, et al. 2022). The tumors predominantly cause regional swelling or facial enlargement. Asymptomatic lesions can occasionally be found incidentally during routine radiographs(Mosqueda-Taylor 2008)(Pandiar et al. 2022). The tumorigenesis of various odontogenic tumors is still ambiguous. Numerous studies were carried out to identify significant genetic dysregulations and alterations in molecular pathogenesis in an effort to comprehend the mechanisms underlying tumorigenesis, differentiation, and progression.(Gomes et al. 2010)(Ramani, Pandiar, et al. 2022).

Ameloblastoma is a benign tumor that affects the maxillo-mandibular complex and develops in the odontogenic epithelium. It is an asymptomatic lesion with more frequent recurrences and locally invasive behavior(Morgan 2011)(Pradeep and Associate Professor, Department of Oral And Maxillofacial Surgery, Saveetha Dental college & Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University 2021). The mandible is the most typical site of presentation for ameloblastoma, which most frequently affects people between the ages of 30 and 60. In the maxillary region, the desmoplastic ameloblastoma variant is frequently observed(Siar, Lau, and Ng 2012)(Ramani, Krishnan, Pandiar, and Thamilselvan 2022). Children who develop ameloblastoma are thought to have a rare condition, with unicystic ameloblastoma being the most common type.The most prevalent initial symptom of ameloblastoma is a slowly growing, painless swelling of the maxilla or mandible. The ameloblastoma significantly enlarges as it advances buccolingually. Pain is a rare symptom of ameloblastoma, but it may appear if there has been bleeding inside the tumor or nearby(Rizzitelli et al. 2015).

Despite efforts to understand its pathogenesis, the true impact of molecular pathways and gene deregulations in ameloblastoma is poorly understood. In silico techniques, such as bioinformatic gene analysis have been used to look into interactions between significantly expressed proteins, gene expression, microRNA prediction models and signaling pathways, in order to better understand the pathological mechanisms of ameloblastoma.(Orlando, Bragazzi, and Nicolini 2013)(Yanar et al. 2022)(Shen et al. 2022)(L. Yang et al. 2022).

The aim of this study is to analyze and evaluate the genes commonly expressed in human tooth germ and ameloblastoma for better understanding the molecular pathogenesis of ameloblastoma. This is a first of its kind study as no in silico research has been done till date to analyze the commonly expressed genes in ameloblastoma and its normal counterpart human tooth germ.

MATERIALS AND METHODS

This is an in-silico study. GeneCards database was used for this study. The database was used to identify important genes expressed in the formation of human tooth germ and ameloblastoma.

The nomenclature used to identify genes in the database was excerpted from the Human Genome Organization (HUGO). The keywords used according to Medical Subject Headings (MeSH)

were, “ameloblastoma and gene expression” and “human tooth germ and gene expression”.

Consequently, a list of potential genes linked to human tooth germ and ameloblastoma were created. The potential candidate genes were then mapped using an online program STRING (version 11.5). This identified the interaction of networks between the protein-coding genes. The genes which showed a high degree of confidence were included and their direct and indirect interactions were evaluated.

New genes connected to ameloblastoma and the human tooth germ could be discovered using this method. Each gene interaction was scored to produce an overall association score. The genes which displayed the highest WNL score were mentioned as leader genes. The genes which showed no known relationships were not included in this analysis.

A literature review of genes associated with pathogenesis of ameloblastoma was done. Results from literature reviews were used to verify the obtained bioinformatics information. The question reviewed was "What are the genes that have been associated with ameloblastoma pathogenesis and human tooth germ formation ?" The primary search was conducted in the database MEDLINE/PubMed. The following keywords were used: "ameloblastoma and gene expression" and "human tooth germ and gene expression." The data obtained was used to corroborate with the data obtained from the STRING analysis.

RESULTS

The GeneCards and String databases were searched, and the results included 7200 genes related to ameloblastoma and 63,825 genes related to human tooth germ. Based on previous literature, the genes were filtered and a final count of 10 genes that were commonly expressed in ameloblastoma and human tooth germ were included. These were : IGF1 , STAT1 , TLR2 , BRAF , IGF2 , ERK2 , ERK1 , NFkappaB , MEK2 and MEK1. Figure1 shows the gene interactions among the major genes among the 10 selected and Figure2 shows the gene interactions among other prominently associated genes.

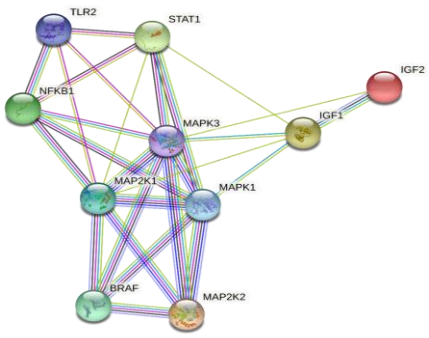

FIGURE 1: Figure shows the gene interactions among the major genes among the 10 selected genes from the literature.

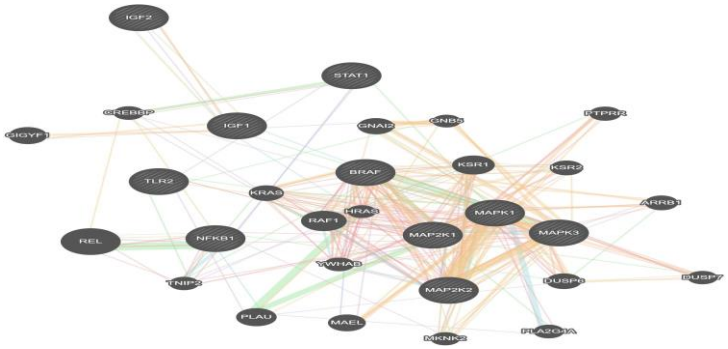

FIGURE 2: Figure shows the gene interactions among other prominently associated genes.

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According to the analysis, the number of genes in the main cluster is found to be one for ameloblastoma and one for human tooth germ. From the WNL analysis, ameloblastoma, the genes with highest WNL values were identified in BRAF V600E, MAPK, STAT1 and NFKappaB, The most relevant WNL values for human tooth germ are IGF1, IGF2, TLR1, TLR2 , STAT1 and NKKappaB1. The possible pathways associated with these genes in human tooth germ are anatomical structure formation in morphogenesis, epithelial cell proliferation and neural crest cell development.The possible pathways associated with these genes in ameloblastoma are Signaling by MAP2K pathway, suppression of apoptosis, signaling by high kinase activity BRAF mutants and osteopontin signaling.

STAT1 and NFKappaB showed significant co-expression. The possible role of STAT1 and NFKappaB in human tooth germ include the canonical NF-κB signaling pathway which participates in the regulation of dental epithelial stem cells differentiation, which is through upregulating SMAD7 expression. STAT1 helps in induction of mesenchymal stem cells and helps in the formation of tooth germ. The possible role of STAT1 and NFKappaB in ameloblastoma include up regulation of NFKappaB and STAT1 in ameloblastoma which helps in increased cell survival and decreased inflammation.

DISCUSSION

The majority of the time, odontogenic tumors have an indolent clinical course, meaning that the patient only notices them when there is change in size that impairs swallowing or phonation, or when there is a significant affection of the maxilla or mandible on radiological examination(Trosman and Krakovitz 2015). Surgery is an option for treatment when this happens. Enucleation is considered as conservative approach, while excision with local reconstruction is considered as a radical approach(Zhang et al. 2022)(Kim, Nam, and Yoon 2017). While the conservative approach preserves the bone's integrity, it is associated with a high rate of recurrence ranging from 55-90%. Its recurrence is a common side effect of conservative treatment.(Troiano et al. 2017)(Y.-C. Yang et al. 2021). Total bone resection with a safety margin, primarily with partial or subtotal maxillectomy for the maxilla and segmental or marginal mandibulectomy for the mandible, has been considered a suitable option for decreasing these recurrences.(Silva et al. 2018)(Awadalkreem and Abdoun 2020). However, because of the extremely drastic interventions, this therapy results in psychological issues for the patient as well as facial complications like aesthetic and functional deformity. This reduces the overall quality of life for the patient(Chatra et al. 2011)(Guo, Zhang, and Zhou, n.d.).

Better clinical, prognostic, and follow-up decisions may be made with the help of factors associated with surgical recurrence and knowledge of histology, cellular biology, and/or molecular biology. It is challenging to link the different types of ameloblastoma with their pathogenesis or prognosis using histopathological analysis. The development of molecular technology, particularly large-scale assays like DNA microarray and bioinformatic analysis, may lead to an improvement in our understanding of ameloblastoma(Mony and Priya Veeraraghavan 2022). Our bioinformatic findings confirm that several genes, including STAT1, IGF1, IGF2 and NFKappaB, are involved in the pathogenesis of ameloblastoma. We discovered two prominent genes that could be linked to tumor development using our bioinformatic analysis, namely STAT1 and NFKappaB.

STAT1 is an essential component of the transcription factor complex in IFN signaling pathways(Au-Yeung, Mandhana, and Horvath 2013). The STAT molecules are phosphorylated by receptor-associated kinases, resulting in activation, dimerization, and translocation to the nucleus to function as transcription factors(Jenkins 2014)(Arumugam, George, and Jayaseelan 2021). STAT1 can be activated by a variety of ligands, including interferon alpha (IFN), interferon gamma (IFN), epidermal growth factor (EGF), platelet derived growth factor (PDGF), interleukin 6 (IL-6), and interleukin 27 (IL-27)(Darnell, Kerr, and Stark

1994)(Paramasivam 2022)(Ramesh and Professor, Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and technical Sciences, Saveetha University, Chennai, India. 2021)(Sasikumar et al. 2020). Type I interferons (IFN-, IFN-ß) tend to bind to receptors, activate kinases, and phosphorylate and activate the Jak kinases TYK2 and JAK1, as well as STAT1 and STAT2. STAT molecules then form dimers and bind to ISGF3G/IRF-9, which is a complex of Interferon stimulated gene factor 3 and Interferon regulatory Factor 9(Horvath et al. 1996)(Han et al. 1996)(Sarode et al. 2021)(Jayaraman et al. 2022). STAT1 is then able to enter the nucleus. STAT1 is crucial for numerous gene expressions which regulate cell viability, survival, or pathogen response(Wagner and Siddiqui 2012)(Schindler and Darnell 1995)(Alexander et al. 2019)(Sivakumar et al. 2022). STAT1 mutations can result in either gain of function (GOF) or loss of function (LOF) . Both can result in distinct phenotypes and symptoms(Deschamps et al. 2016).

The protein nuclear factor kappa-light-chain-enhancer of activated B cells (NFKappaB) regulates cytokine production, DNA transcription and cell survival("TNFR1-Induced NFkappaB Signaling Pathway," n.d.). NFKappaB is a fast acting primary transcription factor, which is present in cells in an inactive state and does not require new protein synthesis to become activated. It is crucial for controlling cellular responses. NFKappaB regulates genes involved in cell survival and proliferation in eukaryotic cells.(Ogasa 2003)(Mithra and Department of Oral and Maxillofacial Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University 2021)(Elumalai, Ezhilarasan, and Lakshmi 2022). As a result, an increased number of tumors show dysregulated NFKappaB(Sorriento, Gambardella, and Iaccarino 2021). Active NFKappaB activates gene expression, which maintains cell proliferation and protects it from conditions that would otherwise induce apoptosis. The proteins that regulate NFKappaB signaling are mutated or overexpressed in cancer, resulting in poor coordination between the malignant cells and the normal tissue(Peng et al. 2022)(Lin et al. 2022).

STAT 1 and NFKappaB together help in tumor cell proliferation and cell survival. Numerous targeted therapies have been produced against these genes(Mirzaei et al. 2022)(Frobel, n.d.). Further in vitro molecular analysis such as microarray are needed for proper application of these therapies.

CONCLUSION

Bioinformatics uses theoretical analysis to generate relevant data and emerging knowledge by utilizing public databases, gene databases, and scientific publishing databases. These theoretical findings are well supported by research on the role of genes in the pathogenesis of ameloblastoma. As a result of the bioinformatics findings and literature review, extensive studies should be carried out to better understand the function of networks of genetic interactions in the pathogenesis of ameloblastoma.

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