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Bioinformatic analysis of important miRNA and Gene network analysis of CDKN2A gene: a key regulator of head and neck cancer

Javith I and Sathish Sankar*
Department of Microbiology, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600 077
Email: javithsyed14@gmail.com.

ABSTRACT:
BACKGROUND: CDKN2A/p16 is a known tumour suppressor gene with a homologous deletion in oral squamous cell carcinoma. CDKN2A/p16 is inactivated in >80% of a wide range of solid tumours and OSCC. Molecular alterations of CDKN2A/p16 during the course of OSCC are important prognostic tools for squamous cell carcinoma. **AIM:** To find key miRNAs and other genes that are strongly linked to the CDKN2A gene. **METHODS:** Target scan prediction of microRNA targets for CDKN2A gene in humans was carried out using portal.gdc.cancer.gov. Broadly conserved, conserved and poorly conserved mRNA family were searched for the presence of RFXAP, STXBP1, SCN2A, NDST3, SPSB1, SMAD2 sites matching each miRNA seed region, predicted regulatory targets of the CDKN2A gene were identified using the program with default settings. The targets of the conserved mRNA. hsa-miR-617 miRNA with a miR score of ≥0.99 were identified using the mirdb.org software program. Gene network analysis of CDKN2A was carried out by STRING database online server program. Important gene interactions with a combined score of >0,99 were considered and listed. **RESULTS:** In this study it was observed that 44 miRNAs were targeted by the CDKN2A gene through miRDB analysis. Of these, miRNAs (hsa-miR-617) were selected that had a target score of >99. RFXAP, STXBP1, SCN2A, NDST3, SPSB1, SMAD2 were some of the genes found to have interactions with the BRAF gene. **CONCLUSION:** Our research discovered key miRNAs that may have a role in head and neck cancer. Other interacting genes might help researchers better understand the carcinogenesis process in head and neck cancer.
KEYWORDS: Head and neck cancer, CDKN2A gene, miRNAs, gene analysis

Introduction

MicroRNAs (miRNAs) are considered a class of non-coding RNAs whose expression patterns have been shown to be tissue- and cancer-type specific. miRNAs can be detected not only in cells but also in various biological fluids such as plasma and serum, follicular fluid, i.e. extracellular miRNAs (ECmiRNAs) (Aldhuwayhi et al. 2021). Circulating miRNAs from tumour cells have attracted the attention of researchers for their diagnostic and prognostic potential if they could prevent new opportunities for cancer early prediction and treatment (Aldhuwayhi et al. 2021; Dua et al. 2021). It is noteworthy that miRNAs can regulate target genes by inducing miRNA degradation or abrogating miRNA translation (Gan et al. 2019). Aberrant expression levels of miRNAs have been found to be associated with the initiation and progression of many types of cancer in tissues and cell lines which includes Osteosarcoma (OS) (Gan et al. 2019; Khoury, Sultan, and Sultan 2022). miRNAs can regulate 90% of protein-coding genes (Li et al. 2020; Neelakantan, Grotra, and Sharma 2013). Mature miRNAs may play important roles in the pathogenesis of OS as oncogenic agents or tumour suppressors, as changes in miRNA regulation appear to be positively associated with cell proliferation, adhesion, invasion, migration and metastasis, and apoptosis. often fulfil . As a result, these molecules can be viewed as good strategies for developing prognostic markers for various malignancies. It is worth noting that a given miRNA may have different miRNA targets. On the other hand, it should be considered that some miRNAs can regulate specific miRNA targets. Nonetheless, the interactions between miRNAs and target genes are complex when the complex interactions have not been revealed in a clear manner.

Head and neck cancer is the sixth most common type of cancer and the fifth most common cause of cancer-related deaths worldwide. More than 90% of these tumours are squamous cell carcinomas (HNSCC) and arise in the epithelial mucosa of the upper aerodigestive tract (oral and nasal cavities, oropharynx, hypopharynx, and larynx). The global incidence of HNSCC is not entirely clear, but may be associated with increased prevalence of risk factors such as smoking, alcohol consumption, and high-risk human papillomavirus (HPV) infection. has been increasing for decades. In the United States alone, there were an estimated 63,030 new cases and 13,360 deaths from head and neck cancer in 2017. Despite an appropriate combination of therapeutic modalities such as surgical resection, chemotherapy and radiotherapy, local or distant recurrence rates remain high in HNSCC patients. Due to early-stage symptoms and lack of effective screening techniques, the majority of HNSCC patients are diagnosed at advanced stages. Recurrent, distant failure, and advanced cancer are very aggressive diseases with very low survival rates, indeed HNSCC has less than 50% of his 5-year survival rate. Therefore, there is an urgent need for more effective and reliable biomarkers for early screening, diagnosis, and identification of risk of recurrence and subsequent death, which are of critical importance for improving prognosis. .

HNSCC develops in a multistep process that involves undergoing different molecular alterations including the accumulation of multiple genetic and epigenetic changes with tumour progression. As one of the most important epigenetic alterations, hyper methylation in the promoter region frequently associated with transcriptional silencing, may serve as a crucial mechanism to inactivate tumour suppressor genes(TSGs) in several cancers, including breast, liver, oesophageal, and thyroid cancer. Aberrant methylations are believed to be early events in cancer, which may serve as biomarkers for cancer diagnosis and prognosis. Cyclin-dependent kinase inhibitor 2A (CDKN2A) located on chromosome 9p21, encodes two functionally distinct tumour suppressor genes, p141* and p16 NKta, which play active roles in p53 and retinoblastoma (RB) tumour suppressive pathways. CDKN2A is involved in tumorigenesis by the regulation of cell division and apoptosis, and maintenance of cellular homeostasis by decelerating cell cycle progression at G1 S phase. Hypermethylation of the CDKN2A promoter has been shown to be responsible for its loss of expression in numerous cancers, including hepatocellular carcinoma, cervical cancer, oral squamous cell carcinoma and non-small cell lung cancer.

Recently, many researchers have studied the association between CDKN2A and HNSCC or clinicopathological features of patients. However, due to small sample sizes or errors among different studies, the results have been inconsistent. Additionally, the role of CDKN2A in HNSCC carcinogenesis, and its clinical application for HNSCC diagnosis remain less intensely investigated. Therefore, to obtain more reliable and systematic results, we performed a bioinformatic analysis of important miRNA and Gene network analysis of CDKN2A for head and neck cancer.

Materials and methods

Target scan prediction of microRNA targets for CDKN2A gene in humans was carried out using portal.gdc.cancer.gov. Broadly conserved, conserved and poorly conserved mRNA family were searched for the presence of RFXAP, STXBP1, SCN2A, NDST3, SPSB1, SMAD2 sites matching each miRNA seed region, predicted regulatory targets of the CDKN2A gene were identified using the program with default settings. The targets of the conserved mRNA. hsa-miR-617 miRNA with a miR score of ≥0.99 were identified using the mirdb.org software program. Gene network analysis of CDKN2A was carried out by STRING database online server program. Important gene interactions with a combined score of >0,99 were considered and listed.

miRDB prediction

Target mRNAs were predicted using miRDB online server program. miRNA targets with a target score of more than >90 were considered for further analysis. The target details and the predicted genes for the miRNAs http://mirdb.org/cqi-bin/mature_mir.cgi?name=hsa-miR-6507-5p were carried out.

Gene network analysis:

Gene network analysis of CDKN2A was carried out by STRING database online server program. This software was used in order to determine the various links that CDKN2A has with other genes. This database allows the user to filter out the desired gene links for the user's benefit

Results

systematically evaluated the patterns of CDKN2A family and tumor immune microenvironment characteristics of HNSCC patients by clustering the expression of 44 members of CDKN2A family. We identified them with distinct clinical and immune characteristics in HNSCC and constructed a risk scoring system based on the expression profile of CDKN2A family genes.

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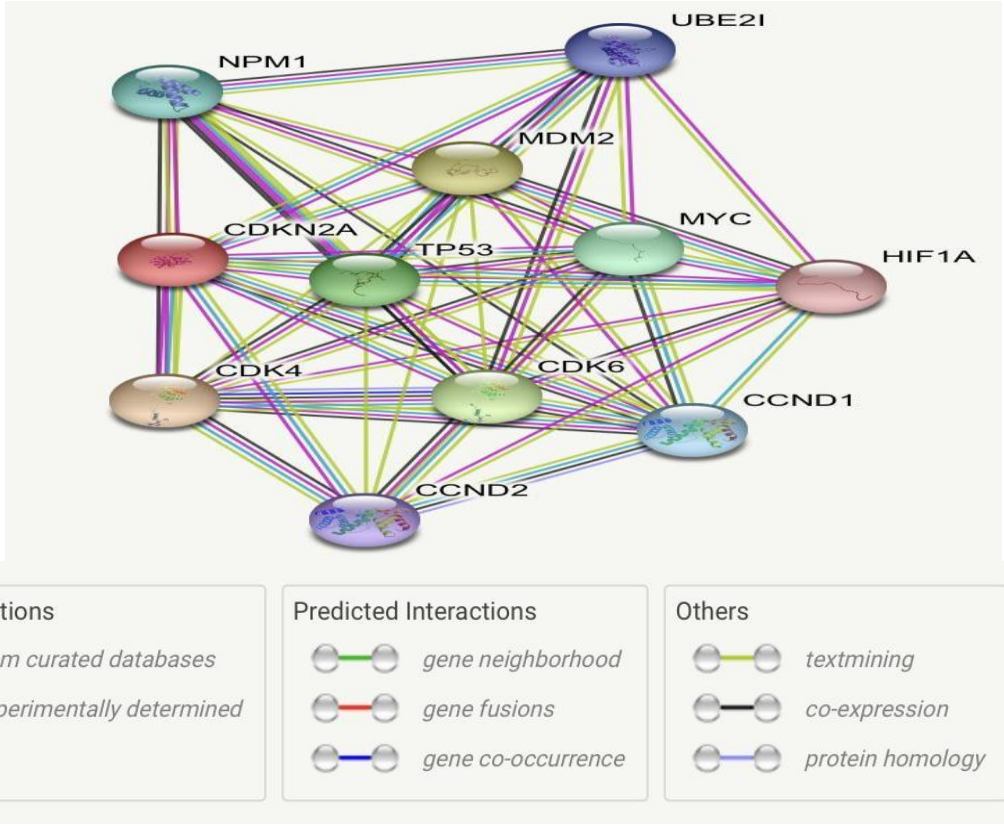
Target Rank	Target Score	miRNA Name	Gene sequence	Important gene
1	88	hsa-miR-617	5' - **agacuucccauuugaagguggc** - 3'	RFXAP, STXBP1
2	86	hsa-miR-1257	5' - **agugaaugauggguucugacc** - 3'	SCN2A, NDST3
3	84	hsa-miR-5011-5p	5' - **uauauauacagccaugcacuc** - 3'	SPSB1, SMAD2
4	82	hsa-miR-3714	5' - **gaaggcagcagugcuccccugu** - 3'	OSBPL3, TENM1
5	80	hsa-miR-153-5p	5' - **ucauuuuugugauguugcagcu** - 3'	CHMP2B, COBLL1



From the figure 2 we could see that CDKN2A gene is associated with various other genes such as CDK4, TP53, CCND2, CCND1, HIF1A, MYC, CDK6, NPM1, UBE1, MDM2 and their associations could be briefly explained.

Some important Genes that are linked with TNF is discussed below

CCND2

G1/S-specific cyclin-D2; Regulatory component of the cyclin D2-CDK4 (DC) complex that phosphorylates and inhibits members of the retinoblastoma (RB) protein family including RB1 and regulates the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complex and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylated RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenic and anti mitogenic signals.

NPM1

Nucleophosmin; Involved in diverse cellular processes such as ribosome biogenesis, centrosome duplication, protein chaperoning, histone assembly, cell proliferation, and regulation of tumour suppressors p53/TP53 and ARF. Binds ribosomes presumably to drive ribosome nuclear export. Associated with nucleolar ribonucleoprotein structures and bind single-stranded nucleic acids. Acts as a chaperonin for the core histones H3, H2B and H4. Stimulates APEX1 endonuclease activity on apurinic/apyrimidinic (AP) double- stranded DNA but inhibits APEX1 endonuclease activity on AP single-stranded RNA.

UBE1

SUMO-conjugating enzyme UBC9; Accepts the ubiquitin-like proteins SUMO1, SUMO2, SUMO3 and SUMO4 from the UBLE1A-UBLE1B E1 complex and catalyses their covalent attachment to other proteins with the help of an E3 ligase such as RANBP2, CBX4 and ZNF451. Can catalyse the formation of poly-SUMO chains. Necessary for sumoylation of FOXL2 and KAT5. Essential for nuclear architecture and chromosome segregation. Sumoylates p53/TP53 at 'Lys-386'; Belongs to the ubiquitin-conjugating enzyme family

Discussion

Previous study had shown an increased expression of a specific miRNA with BRAF gene associated with tumour aggression. Other studies have shown the importance of miRNA in methylated CDKN2A of Head and neck cancer. Our study has identified important miRNAs that could potentially play a vital role in

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the head and neck cancer biology. The *CDKN2A* gene provides instructions for making several proteins. The most well-studied are the p16(INK4A) and the p14(ARF) proteins (*The P16 Pathway in Breast Cancer and Senescence Control* 1999). Mutations in the *CDKN2A* gene are found in up to one-quarter of head and neck squamous cell carcinomas (HNSCC) (Siddique et al. 2020). This type of cancerous tumour occurs in the moist lining of the mouth, nose, and throat (Mohan and Jagannathan 2014). *CDKN2A* gene mutations associated with this condition are acquired during a person's lifetime and are found only in tumour cells (Janani et al. 2020); these changes are known as somatic mutations (Khoury, Sultan, and Sultan 2022). Most of these mutations lead to production of little or no functional p16(INK4A) protein (Mohan and Jagannathan 2014; Hochi et al. 2023; Werning 2011). Without p16(INK4A) to regulate cell growth and division (proliferation), cells can continue to grow and divide without control, which can lead to tumour formation (Arvind Tr and Dinesh 2020). A different type of alteration involving the *CDKN2A* gene can result in reduced amounts or an absence of the p16(INK4A) or p14(ARF) protein (Qiu et al. 2023; Wilcox et al. 2023). This alteration, known as promoter hypermethylation, turns off the production of p16(INK4A) or p14(ARF) (Li et al. 2020). Without one of these tumour suppressors, cells can grow and divide unchecked, leading to the development of cancer (Markov et al. 2021). Methylated CDKN2A is a promising biomarker for the diagnosis and prognosis of head and neck cancer. It is associated with the carcinogenesis and metastasis of head and neck cancer (Markov et al. 2021; Mohan and Jagannathan 2014). CDKN2A/p16 frequently alters in oral cancer progression with a deletion/loss of function in the recurrent cases displaying its role in aiding several molecular events for the malignant transformations occurring throughout disease progression (Qiu et al. 2023). Previous research concludes that Hereditary oral squamous cell carcinoma is associated with CDKN2A germline mutation. It is important to consider CDKN2A mutation testing in familial HNSCC and young patients without obvious risk factors.

Conclusion

Our study concludes that miRNAs may have a role in head and neck cancer. Other interacting genes that may help researchers better understand the carcinogenesis process in head and neck cancer. These findings imply that miNAs collaborate to promote tumour development.

Future scope

This study could help to develop miRNA targeted therapy and study the tumour genesis process of head and neck cancer.

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CONFLICT OF INTEREST: The authors declare that there are no conflicts of interest in the present study.

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