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Original Research Article

Bioinformatic analysis of important miRNA and Gene-Network analysis of PDGFRA gene, a key regulator of head and neck cancer

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Name of Author:
Snigdha Bhardwaz [1], Dr. Sathish Sankar [2] Dr. AS Smiline Girija [3]*

Affiliation: *[1]Undergraduate Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences Saveetha University, Chennai - 600077*
[2]Associate Professor Department of Microbiology Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences Saveetha University, Chennai - 600077
[3]Professor and Head, Department of Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, P.H. Road, Chennai, Tamil Nadu, India.

Corresponding Author:
Dr. AS Smiline Girija

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Abstract: ***Background:*** Head and neck cancer is a diverse group of cancers that arise from the squamous epithelium of the oral cavity and pharynx.This type of cancer is the ninth most common type of cancer.Despite improvements in medicine and surgery, there are more than 500 000 new cases reported each year, and the 5-year survival rate is 50%. ***Aim:*** This current study aims to analyse the PDGFRA gene related to head and neck cancer. ***Materials and methods***: Prediction of microRNA targets for PDGFRA gene in humans was carried out using Targetscan Human software program. Target mRNAs were predicted using miRDB online server program. ***Results:*** This study predicted 192 targeted by the PDGFRA gene through miRDB analysis. Of these, two miRNAs (hsa-miR-8485 and hsa-miR-4719) were selected that had a target score of <99. ***Conclusion:*** The PDGFRA mutation may be connected with squamous cell carcinoma and favourably correlated with cancer prognosis. As a result, this mutation could be used as a prognostic marker for squamous cell carcinoma. This study proved that PDGFRA expression is a significant OSCC predictor and gives insight on targeted therapy research in the future.

Keywords: PDGFRA, miRNA, Head and neck cancer, gene.

INTRODUCTION

Head and neck cancer is a diverse group of cancers that arise from the squamous epithelium of the oral cavity and pharynx. This type of cancer is the ninth most common type of cancer.Despite improvements in medicine and surgery, there are more than 500 000 new cases reported each year, and the 5-year survival rate is 50%. In poor nations, oral squamous cell carcinoma (OSCC) accounts for a large portion of HNSCC, and regrettably, the majority of patients who initially present to a health facility are already in advanced stages of the disease.(Ong *et al.*, 2018) The prognosis

and cure rate for advanced squamous cell carcinoma of the head and neck squamous cell (HNSCC) remains low, especially in the laryngeal SCC (LSCC), with survival unchanged. Current treatment options for advanced HNSCC, combination therapy (surgery, radiation therapy, and / or chemoradiotherapy), have not changed for several years. In addition, treatment options for relapsed or metastatic disease are limited. New targeted tumor treatment options are widely used in other cancer treatments, but are limited in HNSCC. (Cierpikowski *et al.*, 2018)

Platelet-derived growth factor receptor (PDGFR) is a catalytic receptor that exhibits intracellular tyrosine kinase activity. They play a role in regulating many biological processes, including embryonic development, angiogenesis, cell proliferation and differentiation.Tyrosine kinase functions as a cell surface receptor for PGFA, PDGFB and PDGFC and plays an important role in the regulation of embryonic development, cell proliferation, survival, and chemotaxis.(Lin *et al.*, 2020) The PDGFRA gene encodes a cell surface tyrosine kinase receptor that is a member of the platelet-derived growth factor family. These growth factors are mesenchymal-derived cell mitogens. The identity of the growth factor bound to the receptor monomer determines whether the functional receptor is a homodimer or heterodimer composed of both the platelet growth factor receptor alpha and beta polypeptide. Previous studies suggest that this gene is involved in organ development, wound healing, and tumor progression. Mutations in this gene are associated with idiopathic hypereosinophil syndrome, somatic and familial gastrointestinal stromal tumors, and various other cancers.(Tsao *et al.*, 2011; Lin *et al.*, 2020)

PDGFRA (Platelet-Derived Growth Factor Receptor Alpha) is a gene that encodes a protein. Diseases associated with PDGFRA include idiopathic GistPlus syndrome and eosinophilia syndrome. Related signaling pathways include apoptotic and CREB signaling pathways in synovial fibroblasts. Gene ontology (GO) annotations associated with this gene include protein homodimerization activity and protein kinase activity.PDGF is involved in angiogenesis of normal and tumor tissues.(Heldin, 2013) Dysfunction of PDGF and their associated receptors has been shown to play an important role in human carcinogenesis. Overexpression of PDGFR was associated with high-grade glioma and advanced stages of head and neck cancer. PGDFR is rarely studied at Oral Squamous Cell Carcinoma and its role has not been established.

Head and neck tumors have traditionally been considered difficult to cure beyond the very early stages of the disease. However, recent advances in the use of chemotherapy and radiation therapy and the use of ultrasplit radiation therapy have increased survival in clinical trials. However, it is not very clear to what extent the improved survival observed in clinical trials will lead to improved survival at the population level. The malignancy known as oral squamous cell carcinoma (OSCC) is varied and heterogeneous. Although the function of PDGFRA in oncogenesis and neovascularization is unknown, that of EGFR and VGFR is well documented. It is clear that the PDGFRA signalling pathway plays a part in a number of malignancies. In previous studies, the authors think that the research focused on the shared processes of carcinogenesis and development among diverse malignancies could offer a possible target for therapy.(Zhang *et al.*, 2015) This current study aims to analyse the PDGFRA gene related to head and neck cancer.

MATERIALS AND METHODS

Target scan prediction

Prediction of microRNA targets for PDGFRA gene in humans was carried out using Targetscan Human software program (https://www.targetscan.org/vert_80/). Broadly conserved, and poorly conserved miRNA family were searched for the presence of 8mer, 7mer, and 6mer sites matching each miRNA seed region. Predicted regulatory targets of the PDGFRA gene were identified using the program with default settings.
The targets of the conserved miRNA, hsa-miR-8485 miRNA with a mi TG score of ≥0.99 were identified using mirdb.org software program.Gene network analysis of PDGFRA 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 were carried out.

RESULTS

This study predicted 192 targeted by the PDGFRA gene through miRDB analysis. Of these, two miRNAs (hsa-miR-8485 and hsa-miR-4719) were selected that had a target score of <99.

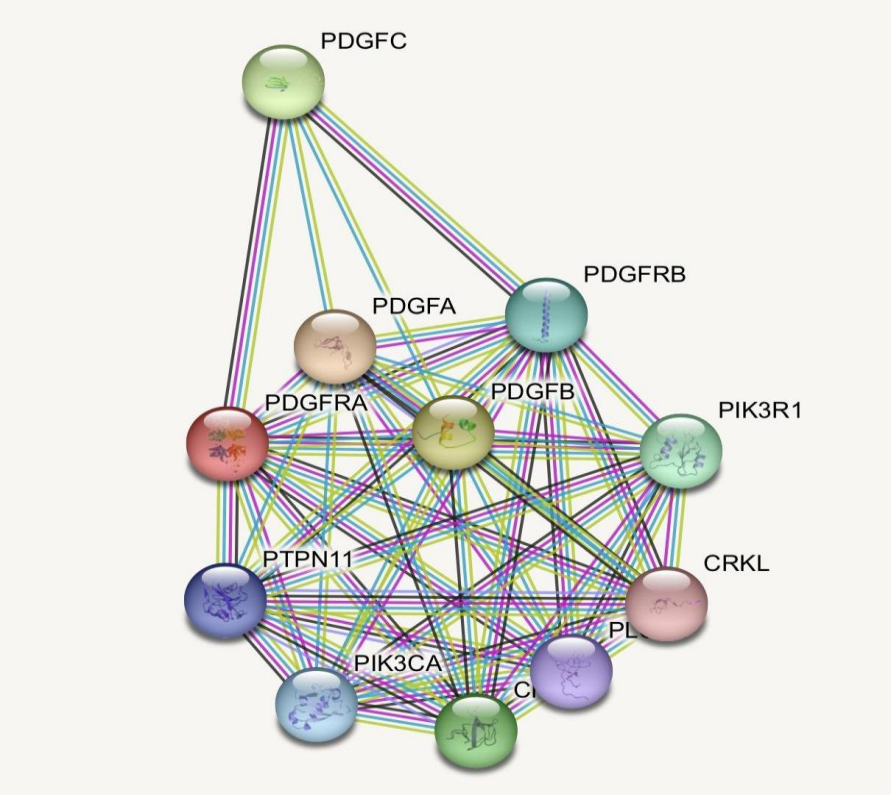
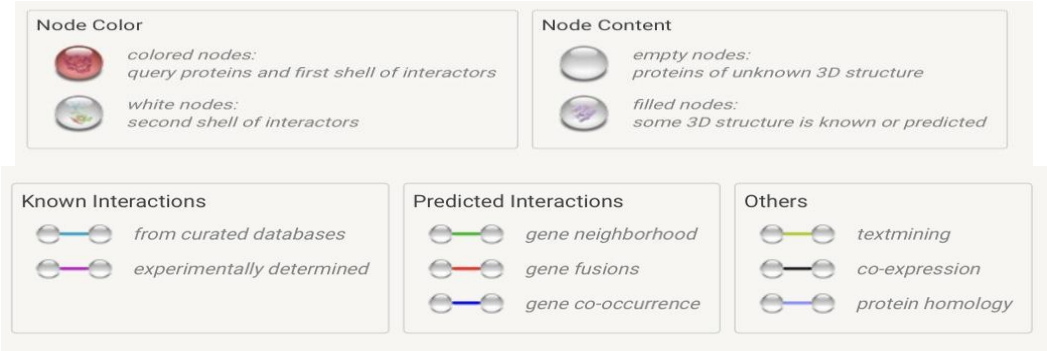


Figure 1: Gene analysis ofPDGFRA. The genes mentioned above are few genes which are co related to PDGFRA. The upregulation of PDGFRA effects the regulation of the other stated genes.



	miRNA Name	miRNA structure	Important genes
97	*hsa-miR-8485*	*5′ - cacacacacacacacguau - 3′*	**RAPGEFL1,PCK1,VAPB, PTP4A**
96	*hsa-miR-4719*	*5′ - ucacaaaucuauaaauaugcagg - 3′*	**USP37, GOLGA6L4, GOLGA6L10**
95	*hsa-miR-302b-5p*	*5′ - acuuuaacauggaagugcuuuc - 3′*	**TMEFF1, AEBP2, CCDC62, EGLN1**
95	*hsa-miR-302d-5p*	*5′ - acuuuaacauggaggcacuugc - 3*	**FNDC3A, EGLN1,**

			CCDC62, SMAECAD1
93	*hsa-miR-7850-5p*	*5′ - guuuggacauaguguggcugg - 3′*	**TNK1, CBFA2T3, CYSTM1, IIKZF2**
93	*hsa-miR-7856-5p*	*5′ - uuuuaaggacacugagggauc - 3′*	**MINDY2, SNX13, MGAT4A, UBE2A**
93	*hsa-miR-4753-3p*	*5′ - uucucuuucuuuagccuugugu - 3′*	**RBM20, PCDHA8, PCDHAC1, ONECUT2**

Figure 2: Prediction of miRNAs for PDGFRA. These are few miRNAs related to PDGFRA in which target scores of more than 93 were considered.

DISCUSSION

In previous studies it was observed that the platelet-derived growth factor receptor alpha (PDGFRA) is a tyrosine protein kinase that functions as a cell's surface receptor for PDGFA, PDGFB, and PDGFC. It is crucial for the control of embryonic development, cell proliferation, survival, and chemotaxis, stimulating or preventing cell migration and proliferation depending on the situation. It plays a crucial part in the differentiation of mesenchymal stem cells that are generated from bone marrow. Early embryonic development, necessary for proper skeleton development and cephalic closure.(International Agency for Research on Cancer and World Health Organization, 2005)

In another study, The ability of PDGFRA to heterodimerize enables it to influence other signaling components, function independently, and engage in a vicious cycle via autocrine or paracrine stimulation. It is obvious that PDGFRA contributes to a variety of cancers.(Schultz, 2011) According to one study, PDGFR stimulation can trigger the activation of many signalling receptors, such as dedifferentiation of tumour cells, as well as an increase in cell motility and tumour aggressiveness, are caused by EGFR and Notch. (Aderhold et al., 2013) Another study found that some sets of oral carcinomas expressed PDGFR, which could lead to increased activation of signalling pathways in tumour cells 7that rely on this receptor. We might propose that oral cancer cells that produce more PDGFR might behave more aggressively.(Hernandes, Pereira and Severino, 2017)(Dua et al., 2019; Gan et al., 2019)

According to some researchers, PDGFR may indirectly promote the invasion of nearby normal tissue and the spreading of carcinoma cells from the primary tumour tissue.(Markov et al., 2021)PDGFR expression and poorly differentiated tumour cells may be related, which may have an effect on cell motility and make it easier for cells to cross the basement membrane. (‘Inter-observer agreement in grading oral epithelial dysplasia – A systematic review’, 2015, ‘Apoptotic induction and anti-metastatic activity of eugenol encapsulated chitosan nanopolymer on rat glioma C6 cells via alleviating the MMP signaling pathway’, 2020)High PDGFR expression in oral squamous cell and carcinoma may contribute to decreased cell-cell adhesion and enhanced cancer cell dissemination, similar to liver and breast carcinoma.(Heldin, 2013; Hernandes, Pereira and Severino, 2017)(Aldhuwayhi et al., 2021) (Neelakantan, Grotra and Sharma, 2013; Mohan and Jagannathan, 2014; Sheriff and Santhanam, 2018; Paramasivam et al., 2020)

CONCLUSION

The PDGFRA mutation may be connected with squamous cell carcinoma and favourably correlated with cancer prognosis. As a result, this mutation could be used as a prognostic marker for squamous cell carcinoma. A better understanding of the carcinogenesis process in head and neck cancer may be possible with the aid of other interacting genes. This study proved that PDGFRA expression is a significant OSCC predictor and gives insight on targeted therapy research in the future.

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