miR-421–Mediated Epigenetic Regulation of EGFR in Head and Neck Squamous Cell Carcinoma: An In-Silico Analysis

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Abstract
Background/Objectives: Head and neck squamous cell carcinoma (HNSCC) continues to be a significant global cancer burden along with very limited therapeutic success and high rates of mortality. Unregulated epidermal growth factor receptor (EGFR) signaling plays a vital role in progression of tumor, while microRNAs (miRNAs) operate as essential post-transcriptional regulators in pathways of oncogenesis. This study aimed to investigate the epigenetic regulation of EGFR by miR-421 using in silico approaches.
Methodology: Prediction of EGFR-targeting was done using miRNAs implemtung the TargetScan database, and miR-421 was selected based on target score and biological relevance. Analysis of the expression of EGFR and miR-421 in HNSCC was assessed based on TCGA datasets using the UALCAN platform. The assessment of prognostic significance was done using Kaplan–Meier survival analysis. Protein–protein interaction networks and functional enrichment analyses were conducted using STRING and Metascape databases.
Results: EGFR and miR-421 were both significantly overexpressed in tissues of HNSCC as compared to normal samples. Their elevated expression correlated with advanced tumor stage, higher histopathological grade, metastasis, and TP53 mutation status. Survival analysis demonstrated that higher expression levels of EGFR and miR-421 were linked with poorer overall survival. Network and enrichment analyses revealed that EGFR is a central hub in key oncogenic signaling pathways.
Conclusion: miR-421 may contribute to HNSCC progression by regulating EGFR expression and its downstream oncogenic pathways. The miR-421–EGFR axis may function as a potential prognostic biomarker and therapeutic target; however, further experimental validation is required.
Keywords: HNSCC; EGFR; miR-421; epigenetic regulation; bioinformatics; TCGA; prognosis, cancer, health, education
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Introduction

Head and neck squamous cell carcinoma (HNSCC) were found to be among the sixth most frequently occurring cancers constituting 30% of all-cancer cases [1] with 800,000 new cases per year according to the GLOBOCAN database [2,3] Most Head and neck squamous cell carcinoma (HNSCC) are known to originate from the epithelium of the mucosa in the oral cavity, pharyngeal and laryngeal structures[4] with rapidly progressing malignant characteristics and extremely poor survival outcomes. The most common symptoms patients presented with included glossodynia, persistent long standing mouth sores, red or whiteish lesions occurring in the buccal mucosa; severe throat pain;persistent hoarseness; dysphagia; cervical lump; nasal congestion on one side and epistaxis[5]. Etiological effects of synergistic effect of tobacco, alcohol along with viral infections such as those

associated with human papillomavirus were considered as major risk factors for HNSCC [6] ; however most of HNSCC were associated with specific gene alterations and mutations at the molecular level which initiated tumor progression [6]. One of the most common alterations, including dysregulation of receptor tyrosine kinases namely Epidermal growth factor receptor (EGFR) exhibited an over-expression in up to 90 % of HNSCC tumors [7]

EGFR oncoprotein from the family of ErbB cell surface receptors often referred to as ErbB1 or HER1 [8] plays a significant role in rampant growth, histodifferentiation, antiapoptotic mechanism, sprouting angiogenic vascularisation and metastasis thus facilitating malignancies [9]. It is an independent prognostic marker showing features of enlarged tumor size, reduced sensitivity to radiation, and higher chance of recurrence [10 11].

The marked biological heterogeneity of HNSCC, necessitated identification of reliable diagnostic and prognostic bio markers for early detection and monitoring [12]. Traditionally used diagnostic markers for HNSCC included histopathological and immunohistochemical evaluation of cell proliferation, apoptosis, and signaling pathways, such as p53, EGFR, Ki-67, and cyclin D1[13]. Additionally, mutations like atypical DNA methylation, activation of oncogene, and tumor suppressor gene inactivation were evaluated as diagnostic markers [14].

MicroRNAs (miRNAs) have emerged as key diagnostic and therapy monitoring prognostic markers in head and neck squamous cell carcinoma (HNSCC) [15] owing to their tumor-specific expression patterns and remarkable stability in tissue and bodily fluids such as plasma, saliva or urine [16] even after long-term storage FFPE processing [17]. The function of miRNA is indicated to synchronise varied molecular processes from regulation at a cellular level to responses to stress in many diseases[18,19]. It was noted that, patient-specific and therapy-responsive circulating miRNA signatures identified in the plasma of head and neck cancer patients correlated with prognosis, supporting their utility as minimally-invasive diagnostic and prognostic biomarkers in HNSCC [20,21].

Among dysregulated miRNAs in HNSCC, miR-421 has been implicated in tumor progression through regulation of oncogenic signaling, including pathways associated with EGFR. Given the increasing role of computational approaches in elucidating miRNA–target interactions, in silico bioinformatics and molecular docking analyses imparted significant data into the regulatory potential of miR-421 in EGFR-driven HNSCC. The aim of this study was to evaluate the potential regulatory interactions between miR-421 and EGFR through a comprehensive in-silico analysis.

2. Materials and Methodology

2.1 TargetScan analysis for identification of EGFR-targeting miRNAs

TargetScan (https://www.targetscan.org) was employed for prediction of human microRNAs specifically focusing on the epidermal growth factor receptor (EGFR) gene. The analysis recognized conserved and non-conserved miRNA binding sites within the 3′-untranslated region (3′-UTR) of EGFR based on seed sequence complementarity and evolutionary conservation. The envisioned miRNAs were graded as per context++ scores, reflecting the likelihood and power of miRNA–mRNA interaction. MiR-421 was appointed for analysis due to maximum scores for prediction and significant relevance in the cancer regulation pathways.

2.2 UALCAN analysis of EGFR and miR-421 expression in HNSCC

UALCAN (https://ualcan.path.uab.edu) in levels of EGFR and miR-421 expression associated with HNSCC utilized The Cancer Genome Atlas (TCGA) dataset. Differential expression comparing tumor and normal tissues was assessed among clinicopathological parameters including-tumor stage, histopathological grading, lymph node and status of TP53 mutation. This platform provided transcriptomic data and statistical significance values from TCGA RNA-seq and miRNA-seq datasets. These analyses enabled assessment of the medical utility of EGFR and miR-421 expression in HNSCC.

2.3 Survival analysis using Kaplan–Meier plots

The analysis of Kaplan–Meier survival was conducted for assessing prognostic importance of the expression of EGFR & miR-421 in patients with head and neck squamous cell carcinoma (HNSCC) using TCGA data. Cases were subdivided into high- and low-expression groups based on median expression values. Total outcome of survival was set against one another among groups utilizing log-rank tests, followed by determining the statistical significance. This analysis was also implemented in correlating

EGFR and miR-421 expression compared with patient prognostic outcomes.

2.4 Protein–protein interaction network and functional enrichment analysis

The STRING database (https://string-db.org) has been implemented to produce the protein–protein interaction (PPI) of EGFR protein. Identification of interacting proteins was based on predicting interactions which were experimentally validated, along with application of a high confidence interaction score. Assessment of the biological function and related EGFR signaling pathways, interacting partners and functional analysis of enrichment was done implementing the Metascape platform. Gene Ontology terms and pathway enrichment analyses were employed to identify oncogenic signaling pathways associated with the EGFR network

Results

3.1 Identification of EGFR-targeting miRNAs using TargetScan

TargetScan analysis identified several microRNAs containing predicted binding sites between the 3′-UTR of the EGFR gene. Among the candidates predicted, several miRNAs demonstrated high context++ target scores, suggesting strong potential regulatory interactions with EGFR. Comparative analysis demonstrated that miR-421 was considerably augmented in HNSCC samples and showed a strong predicted interaction with EGFR. Based on its high target score, differential expression, and prognostic association, miR-421 was selected for further downstream analyses (Table 1).

miRNA targeting EGFR	Context Target Score	Expression profile in HNSCC	Normal vs HNSCC (P-value)	Prognosis Association (Yes/No)	P-value	Median survival (Months)	
						High exp	Low exp
hsa-miR-133b	60	Downregulated	9.37×10-4	Yes	0.0012	30.5	61.27
hsa-miR-133a-3p	60	Downregulated	9.79×10-4	Yes	0.0023	30.9	61.27
hsa-miR-7-5p	80	Upregulated	1.11×10-15	No	0.38	57.73	57.27
hsa-miR-148a-3p	90	Downregulated	4.06×10-2	Yes	0.0023	61.27	42.97
hsa-miR-152-3p	90	Downregulated	2.43×10-2	Yes	0.006	31.37	65.73
hsa-miR-148b-3p	90	Upregulated	9.41×10-8	Yes	0.029	65.73	48.63
hsa-mi	32	Downreg	8.96×	Yes	0.00	96.67	42.97

R-411-5p		ulated	10-3		016		
hsa-miR-455-3p	86	Upregulated	<10-12	No	0.16	85.57	48.63
hsa-miR—137	38	Upregulated	6.52×10-10	Yes	0.000111	32.83	68.8
hsa-miR-372-3p	82	Upregulated	4.56×10-2	Yes	0.00013	47.97	91.37
hsa-miR-421	80	Upregulated	1.11×10-16	Yes	0.000077	26.87	61.27

Table 1: MicroRNAs (miRNAs) targeting EGFR and their clinicopathological significance in Head and Neck Squamous Cell Carcinoma (HNSCC). The table summarizes selected EGFR-targeting miRNAs along with their target prediction scores, expression profiles in HNSCC (upregulated or downregulated), differential expression between normal and HNSCC tissues (p-value), and their association with patient prognosis. Prognostic significance is indicated along with corresponding p-values and median overall survival (months) for patients with high and low miRNA expression levels.

3.2 Expression analysis of EGFR and miR-421 in HNSCC using UALCAN

Datasets of TCGA-HNSCC analysis using UALCAN displayed elevated EGFR expression in tumor tissues in comparison with normal controls (Fig. 1). Correspondingly, miR-421 was markedly raised in HNSCC samples (Fig. 2) with stratified analysis showing that overexpression of EGFR and miR-421 could be correlated with progressive tumor staging, higher grade, lymph node metastasis, and TP53 mutation (Fig. 4)

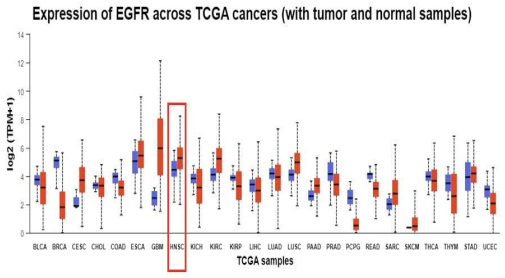

Figure 1. EGFR expression across pan-cancer samples (TCGA)
Boxplots displayed the differential expression of EGFR across multiple TCGA cancer types. EGFR expression was significantly high in numerous epithelial malignancies compared with corresponding tissues, emphasising on its role in initiation of tumorigenesis.

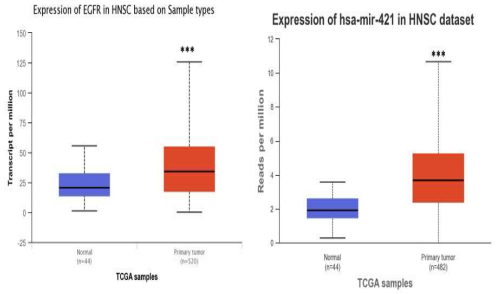

Figure 2. Differential expression of EGFR and miR-421 in HNSCC (TCGA)
UALCAN distinction between tumor vs. normal tissue demonstrated significant upregulation of EGFR and miR-421 in HNSCC thereby demonstrating remarkably higher expression in tumor tissue, supporting their role in HNSCC biology.

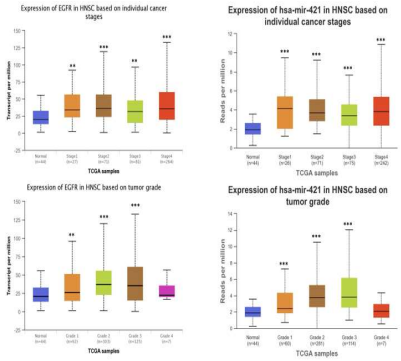

Figure 3: Clinicopathological correlation of EGFR expression in HNSCC.

The expression of EGFR was further subcategorised based on the staging of tumor, histopathological grading, metastasis of the lymph nodes, and mutation status of TP53 gene (Figure 4). Progressively elevating levels of expression and severity of disease was higher in TP53-mutated tumors. (*P < 0.05; **P < 0.01; **P < 0.001)

3.3 Prognostic significance of EGFR and miR-421 expression

Analysis of survival outcomes using Kaplan–Meier revealed that high expression of EGFR and miR-421 were strongly correlated with poorer overall longevity in HNSCC patients (Fig. 5) and the results were suggestive that both EGFR and miR-421 expression levels showed prognostic importance and may play a contributory role as negative predictors of patient outcome in HNSCC.

3.4 EGFR protein–protein interaction network and functional enrichment analysis

EGFR was recognised as a central hub with protein–protein interaction analysis done using STRING along with several proteins involved in oncogenic pathways (Fig. 5A). Functional analysis using Metascape demonstrated EGFR-associated networks were abundant in pathways related to receptor tyrosine kinase signaling, PI3K/AKT signaling, and cancer progression (Fig. 5B) emphasizing its biological importance in Head and neck cancers.

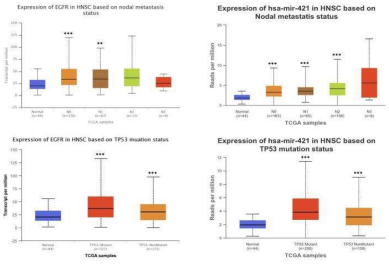

Figure 4. Clinicopathological correlation of miR-421 expression in HNSCC.

miR-421 levels distinguished across clinical subgroups (stage, grade, metastasis, TP53 mutation). miR-421 is significantly elevated in aggressive tumors, advanced grades, malignant diseases, and cases with TP53-mutations. (*P < 0.05; **P < 0.01; **P < 0.001)

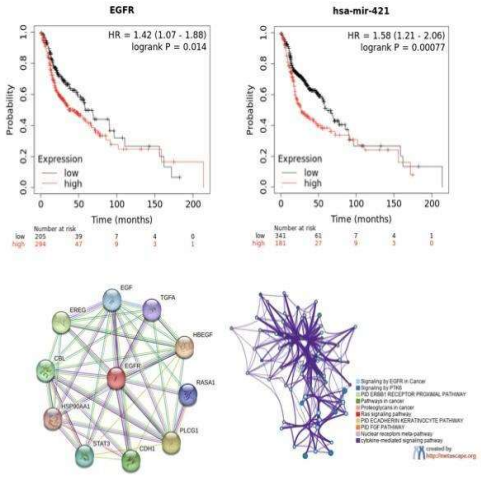

Figure 5: 5A: Prognostic significance of EGFR and miR-421 in HNSCC; 5B EGFR protein–protein interaction (PPI) network and pathway enrichment. Kaplan–Meier survival curves demonstrated total survival distinction comparing high- and low-expression groups of EGFR and miR-421 with expression of both markers showing association with reduced patient survival, confirming their negative prognostic impact.

Discussion

Head and neck squamous cell carcinoma (HNSCC) persistently remains a grave neoplastic burden on account of its rampant, invasive nature and exceedingly high rate of relapse [22] along with substandard outcomes of survival despite progressive breakthroughs and advancement in surgical procedures, radiation and chemotherapeutic drugs as treatment modalities. Moreover, these management strategies are non-selective, damaging to normal tissue with a likelihood of inducing systemic toxicity [23]. The considerable molecular and clinical variability of HNSCC led to difficulties in early diagnosis, poor prognosis and selection of treatment [24]. Increasing evidence indicated that genetic and epigenetic mutations played a vital role in initiation and proliferation of tumors accompanied with resistance to therapeutics [25]. As a result, there is an escalating necessity for identifying molecular

biomarkers and regulatory networks to enhance risk assessment and enable personalized therapeutic strategies in HNSCC.

Among the molecular drivers studied in HNSCC, epidermal growth factor receptor (EGFR) was observed to be clinically relevant. EGFR overexpression was noted in significant proportions of HNSCC cases linked with the rapidly progressing nature of the tumor, insusceptibility to radiotherapy, and poor prognosis [26]. EGFR activation brought about downstream signaling of PI3K/AKT and MAPK pathways, promoted tumor progression, survival, angiogenesis, and nodal metastasis.

EGFR overexpression in immunohistochemical and genomic studies was observed in 80–90% of HNSCC tumors [27], similarly in our TCGA-based analysis results- HNSCC tissues reported with elevated EGFR expression, with overall reduced survival, thereby supporting clinical relevance of EGFR as a prognostic marker in HNSCC. Although EGFR signaling played a central role in metastasis of HNSCC, EGFR- targeted therapies remain limited due to intrinsic and acquired resistance [9] emphasizing the need to identify upstream regulators of EGFR that may help improve treatment.

A systematic review conducted by Qiu et al, stated that aberrant microRNA expression was intrinsically connected to recurrence, metastasis, and poor survival outcomes in HNSCC [28]. Furthermore, according to Ji et al. miR-421 was part of a TCGA prognostic marker in esophageal adenocarcinoma [29] associated with poor overall survival. Dong et al. correlated advanced TNM staging, nodal metastasis, and poor prognosis in papillary thyroid carcinoma with elevated miR-421 [30] Consistent with these findings, dysregulated miRNAs and elevated miR-421 in the present study could be correlated with poorer overall survival in HNSCC, reinforcing its role as a clinically relevant prognostic biomarker across epithelial malignancies.

Increasing evidence of the contribution of microRNAs as vital post transcriptional regulators of disease associated genes and in silico approaches have widely been studied- Awadhi et al demonstrated using bioinformatics based analysis that miRNA influenced EGFR in Hepatocellular carcinoma, emphasizing the utility of computational frameworks for uncovering miRNA-EGFR signaling interactions [31]. Similarly, Bhatia et al. experimentally confirmed miR-421–mediated post-transcriptional regulation of oncogenic targets in prostate cancer [32]. Although direct experimental validation of miR-421 targeting EGFR in Head and neck carcinomas is currently lacking, evidence from other malignancies reinforced its role as biologically significant regulators of oncogenic pathways. In the present study, TargetScan analysis identified miR-421 as a predicted regulator of EGFR, while TCGA-based expression analysis demonstrated concurrent upregulation of miR-421 and EGFR in HNSCC tissues, both of which were closely linked with poorer survivorship. Collectively, the results suggested a possibility of regulatory association between miR-421 and EGFR in HNSCC that necessitated further confirmatory experimental evaluation.

Pathway-level analysis revealed that activating EGFR influenced PI3K/AKT/mTOR and MAPK pathways- critical for progression and survival of the tumor in HNSCC, along with resistance to therapeutic drugs [33]. Corroborating these findings, within protein–protein interaction networks using STRING and Metascape analysis, EGFR was identified as a central hub in oncogenic pathways which provided functional context for the predicted miR-421–EGFR interaction, suggesting that its modulation could influence downstream oncogenic signaling in HNSCC [34]. This overall integrated bioinformatics approach demonstrated an association between overexpressed EGFR in HNSCC with poor patient survival, along with prognostic relevance of upregulated miR-421. Predicting the target along with network analyses further drew a correlation with its role in progression and tumorigenesis and also provided a coherent and logical framework by establishing a link between miRNA dysregulation and EGFR-driven molecular networks in HNSCC, highlighting miR-421 as a significant prospective biomarker as well as a treatment approach [35 36].

The limitations of the present study included the absence of direct experimental validation of the miR-421–EGFR interaction, owing to its in-silico design and reliance on publicly available TCGA datasets. In addition to this, retrospective transcriptomic data was likely not able to entirely assess tumor variability or post-transcriptional modulation. Further experiments using in vitro and in vivo studies would be essential for confirmation of the functional role of miR-421 in adapting EGFR signaling in HNSCC.

Conclusion

In conclusion, miR-421 and EGFR were observed to be substantially overexpressed in head and neck squamous cell carcinoma and were attributed with severely reduced patient prognosis. Holistic and multidisciplinary bioinformatics analyses suggested that miR-421 may contribute to regulation of EGFR-associated oncogenic signaling pathways which contributed to tumorigenesis and progression of cancer. These findings indicated that targeting miR-421 might potentially be able to represent a promising therapeutic strategy in EGFR-driven HNSCC and warranted further experimental and clinical validation.

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