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Original Article

Correlating the Genetic Alterations and Expression Profile of the *TRA2B* Gene in HNSCC and LUSC

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Abstract

Introduction: Transformer (*TRA2B*) is a serine/arginine-rich (SR)-like protein family that regulates the alternative splicing of several genes in a concentration-dependent manner. Amplification of the *TRA2B* gene, which codes for *TRA2B*, occurs in several malignancies, including those of the lung, cervix, head and neck, ovary, stomach, and uterine.

Materials and methods: The present study design follows a computational approach to predict the molecular mechanisms underlying TRA2B alterations in two cancer phenotypes, viz., lung and head and neck squamous cell carcinoma. The genetic alteration in the *TRA2B* gene was identified using the cBioportal database. The gene expression pattern in both the cancer types and their survival pattern concerning the expression profile was demonstrated using UALCAN. The microRNA targets of the *TRA2B* gene were identified using the miRDB database.

Results: Genetic alteration was found to be 27% and 48% in HNSCC and LUSC datasets, respectively. The alterations included gene amplification, missense, nonsense, and splice site mutations. The gene expression profile of *TRA2B* correlated well with the gene amplification demonstrated by patients in both groups. However, the upregulation of *TRA2B* did not correlate well with the survival profile in LUSC patients. The downregulation of *TRA2B* markedly affected the survival of HNSCC patients, which can be attributed to the functions of microRNAs targeting *TRA2B* transcripts.

Conclusion: Although *TRA2B* was found to be a potential diagnostic marker exhibiting a differential expression pattern for HNSCC, the employability of this gene as a prognostic marker needs more experimentation. Also, the influence of microRNAs on dysregulated gene expression should be considered to gain a better understanding of the underlying molecular mechanisms precipitating the disease.

Keywords

cancer, genetics, gene alterations, gene expression, microRNA

INTRODUCTION

Head and neck squamous cell carcinomas (HNSCCs) originate from the mucosal epithelium in the oral cavity, pharynx, and larynx.[1] The incidence of HNSCC varies between nations and ethnic groups, but it has typically been linked to exposure to carcinogens derived from opium consumption, tobacco smoke, binge drinking, or both.[2] An increasing number of oropharyngeal tumors have been associated with past exposure to oncogenic strains of the human papillomavirus (HPV), mainly HPV-16 and, to a lesser degree, HPV-18 and other strains.[3] Lung squamous cell carcinoma is yet another cancer type exhibiting a greater prevalence and incidence rate. There were several common risk factors associated with both cancer types.[4]

The alterations in the DNA sequence can dramatically affect the functions of the protein encoded by the gene. Gross chromosomal abnormalities such as deletions, translocations, inversions, and insertions have been linked to numerous syndromes, developmental disorders, metabolic, infectious diseases, and cancer.[5] Whilst the smallest change of nucleotide substitution is reported in hereditary disorders such as sickle cell anemia, hemophilia, etc.[6] Cancer is a polygenic disorder with a complex interplay between the genetic and epigenetic components. Gain or loss of function of protooncogenes or tumor suppressor genes is a common baseline alteration in several cancer types. The secondary incidence for hypopharyngeal, oropharyngeal, and laryngeal cancers was 41.2%, 28.6%, and 25.5%, respectively, after definitive treatment modalities. The risk factors most commonly associated with such presentation are smoking and alcohol consumption, which induces further genetic abnormalities in tumor cells.[7] Hence, accumulating knowledge about these genetic alterations and their impact on the proteins encoded can aid in a proper understanding of the mechanisms underlying the disease phenotype.

Recent research has unraveled numerous epigenetic mechanisms that are directly or indirectly associated with cancer. In this context, miRNAs have been explored to a more considerable extent and were found to play a significant role in controlling cell division, apoptosis, and growth in several physiological and pathologic processes.[8] Numerous miRNAs that function as tumor inhibitors or tumor promoters have reportedly been reported to be either increased or decreased in the tumor tissues of HNSCC[9] and LUSC patients.[10] These dysregulated miRNAs may also be effective biomarkers and targets for anticancer therapies. Thus, a deeper understanding of genetic and epigenetic marks in HNSCC and LUSC holds enormous potential for creating novel therapeutic approaches.

AIM

In line with these facts, the present study has been designed to dissect the role of the *TRA2B* gene, transformer-2 protein homolog beta (*TRA2B*), a member of the serine/arginine-rich protein family, in 2 closely similar cancer types viz., HNSCC and LUSC. Many diseases, including cancers, are linked to the dysregulation of *TRA2B*. It is expected to find *TRA2B* over-expression in various cancers, such as lung, prostate, and ovarian cancers. Through its modulation of cancer cell growth and invasion, *TRA2B* contributes to the malignant progression of cancers. *TRA2B* has been found to have pro-oncogenic splicing targets, namely CD44, HipK3, and Nasp-T.[11,12]

MATERIALS AND METHODS

Sample dataset

This study analyzed the sample datasets for HNSCC (head and neck squamous cell carcinoma) and LUSC (lung squamous cell carcinoma). The dataset consisted of 528 HNSCC patients acquired from TCGA (The Cancer Genome Atlas) Firehose legacy. The majority of patients were found to be smokers and alcohol consumers. The LUSC dataset consists of 511 samples from LUSC patients, among which 178 had information about the copy number variations and mutations. The mutation count was much higher in HNSCC. The disease's onset age was higher in LUSC than in HNSCC. The complete demographic details of the patients are given in **Tables 1, 2**.[13,14]

Table 1. Demographic details of the HNSCC dataset (TCGA, Firehose Legacy) used for analysis

Gender	**Male (n = 386)** **Female (n = 142)**
Mutation count	6-3181
Diagnosis age	19-90 years
Smoking status	Smokers: 515 Data not available: 12 Unknown: 1
Alcohol history	Yes: 352 No: 165 Data not available: 11
Neoplasm histologic grade	Grade 1: 63 Grade 2: 311 Grade 3: 125 Grade 4: 7 Grade GX: 18 Data not available: 4
Race category	White: 452 African: 48 Asian: 11 American Indian or Alaska native: 2 Data not available: 15

Table 2. Demographic details of LUSC dataset (TCGA, Firehose Legacy) used for analysis

Gender	Male: 373 Female: 131 Unknown: 7
Age	<50 - 85 years
Race	White: 351 Black or African: 31 Asian: 9 Not available: 120
Mutation count	<25 - >475
Cancer type	Non-small cell lung carcinoma
Smoking Status	Category 1: 18 Category 2: 134 Category 3: 83 Category 4: 252 Not available: 19

Oncoprint data analysis

The cBioportal database (http:// cbioportal.org) is a platform that contains clinical and molecular data from various cancer types submitted by different groups. This portal can be used to analyze genetic alterations such as mutations, copy number variations, and survival for the expression. By selecting an appropriate dataset, one can query for genetic modifications of a specific gene or a list of genes. In addition, a detailed description of the mutations in candidate genes was obtained via a lollipop plot. This mutation plot provided information on the frequency of mutations and their type, the domain in which they occur, and their consequence.[13,14]

In silico analysis of missense mutations

Various computational tools, such as SIFT, PolyPhen, and PROVEAN, were used to analyze the consequences of mutations identified in the *TRA2B* gene. SIFT (Sorting Intolerant from Tolerant) differentiates between sequences or elements that exhibit various tolerance levels or intolerance to mutations or genetic variations (https://sift.bii.a-star.edu.sg/). A score below 0.05 indicates a state where the mutations/variants are predicted to be potentially damaging or intolerant.[15] The PolyPhen predicts the potential impact of amino acid substitutions on the functional properties of human proteins. The interpretation of results based on scores is categorized as benign (0.0 - 0.15), probably damaging (0.15 - 0.85), or possibly damaging (0.85 - 1.0).[16] The PROVEAN (Protein Variation Effect Analyzer) is another tool designed to predict the effect of mutations upon mutation. A score less than -2.5 is considered potentially deleterious, and a score above -2.5 is deemed to have a benign or neutral impact (http://provean.jcvi.org/index.php).[17]

Gene expression and survival analysis

The UALCAN web portal helps to analyze and interpret cancer omics data, including transcriptomics, proteomics, and patient survival information. The portal uses data acquired from the Cancer Genome Atlas (TCGA) as the primary dataset for analysis. It allows users to visualize the expression profile of protein-coding genes, non-coding genes, and epigenetic factors such as methylation. You can access the portal through this website: http://ualcan.path.uab.edu.[18]

miRNA expression analysis

MicroRNAs are a type of RNA that do not code for proteins but instead regulate the process of gene expression. They bind to specific mRNA targets and break them down, leading to the downregulation of the targeted genes. Predicting which miRNAs target differentially expressed genes is crucial for understanding the role of epigenetic factors in carcinogenesis. To identify microRNAs that target genes identified from the hub, researchers use the miRDB database, which can be found at http://mirdb.org.[19, 20]

Protein-protein interaction analysis

The latest version of the STRING tool, version 10.5, gathers, evaluates, and combines all publicly accessible sources of protein-protein interaction data and analyzes them utilizing computational tools. The evidence of association present in the STRING database is classified into gene neighborhoods, gene fusions, gene co-occurrence, co-expression, experiments, databases, and text mining. You can find more information about this tool at https://string-db.org/.[21] Metascape is a user-friendly interface that builds networks and performs functional enrichment analysis to define biological pathways (https://metascape.org/gp/index.html#/main/step1).[22]

RESULTS

Oncoprint analysis

The oncoprint data for the *TRA2B* gene in the HNSCC dataset demonstrated gene amplification in 20% of the patients; the other 1% gene alteration comprised of X286_splice (splice-site mutation), M1? (nonstart mutation), R45H, R277L and R111P (missense mutation) **(Fig. 1a)**. On the other hand, the oncoprint data for LUSC patients revealed 47.7% of gene amplification, one patient presented with a missense mutation (R219L) in addition to gene amplification and A145S missense mutation **(Fig. 1b)**.

In silico analysis of missense mutations

The SIFT, PolyPhen, and PROVEAN predictions demonstrated that two out of five mutations, R111P (arginine to

Figure 1a. Oncoprint data demonstrating gene alterations in the *TRA2B* gene in (**a**) HNSCC and (**b**) LUSC datasets.

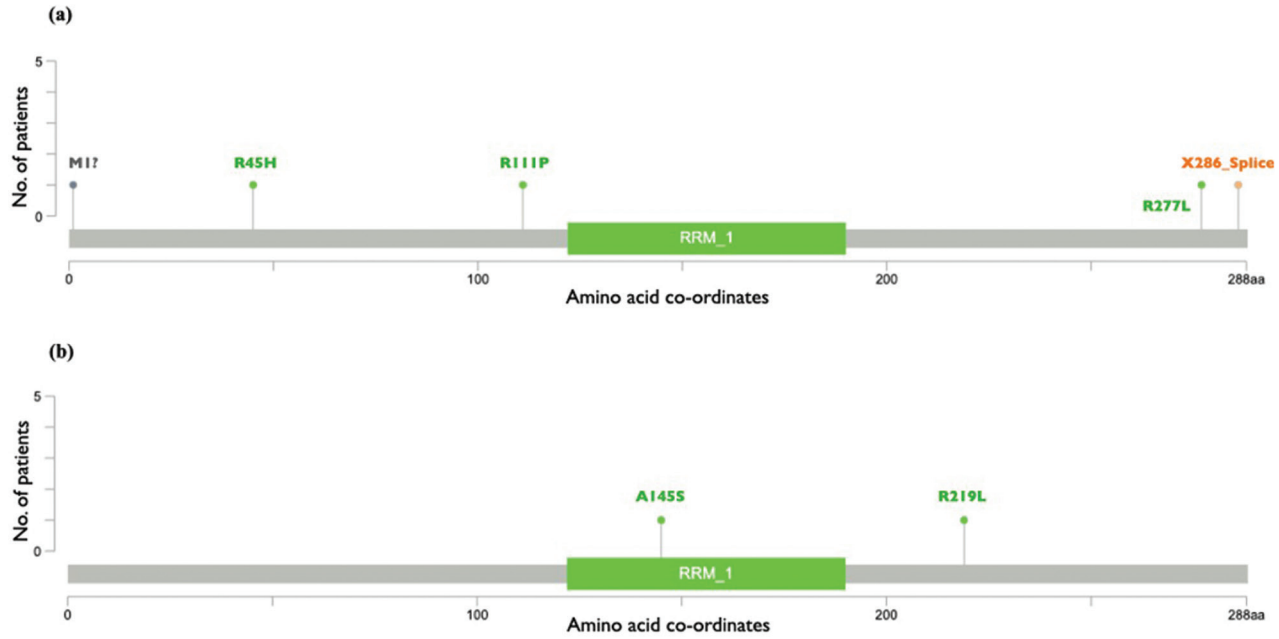

Figure 1b. Lollipop plot demonstrating mutations in the *TRA2B* gene in (**a**) HNSCC and (**b**) LUSC datasets.

proline) and R277L (arginine to leucine), had a deleterious effect on the proteins. The other mutations were benign and tolerated with neutral impact, except for the R219L (arginine to leucine) mutation, which was predicted to be deleterious with PROVEAN alone **(Table 3)**. Four out of five substitutions were found to replace arginine residue with another type of amino acid. Arginine is an amino acid with a charged side chain, whereas leucine is an amino acid with a hydrophobic side chain.

Table 3. SIFT, PolyPhen, and PROVEAN predictions for the missense mutations identified in the *TRA2B* gene in both datasets

Mutations	SIFT	PolyPhen	PROVEAN
R45H	Tolerated	Benign	Neutral
R111P	Affect protein function	Probably damaging*	Deleterious
A145S	Tolerated	Benign	Neutral
R219L	Tolerated	Benign	Deleterious
R277L	Affect protein function	Possibly damaging@	Deleterious

@: Score 0.642; *: Score 1.000

Gene expression and survival analysis

Gene amplification or duplication events generally increase RNA transcripts. The gene expression among the normal, HNSCC, and LUSC primary tumor groups showed a significant change in the transcript levels (p-value $<10^{-12}$) **(Fig. 2)**. The presentation agreed with the copy number variation observed in the oncoprint data. However, comparing survival analysis data of 2 groups concerning the *TRA2B* gene expression returned a significant result for HNSCC alone. The patients in the high-expression group were found to have a better prognosis when compared to the low/medium-expression group **(Fig. 3)**.

miRNA expression analysis

The HNSCC patients with increased expression of *TRA2B* survive longer when compared to patients with low/medium expression. The epigenetic components, such as miRNAs, can markedly affect the gene expression levels. While investigating the non-coding RNAs targeting *TRA2B*, we could identify 181 microRNAs. Since analyzing all the microRNA targets is out of the scope of this study, the top 10 targets were chosen for further expression and survival analysis. There were four microRNAs viz., *hsa-miR-570, hsa-miR-3619, hsa-miR-214,* and *hsa-miR-335,* which were found to be upregulated **(Table 4)**.

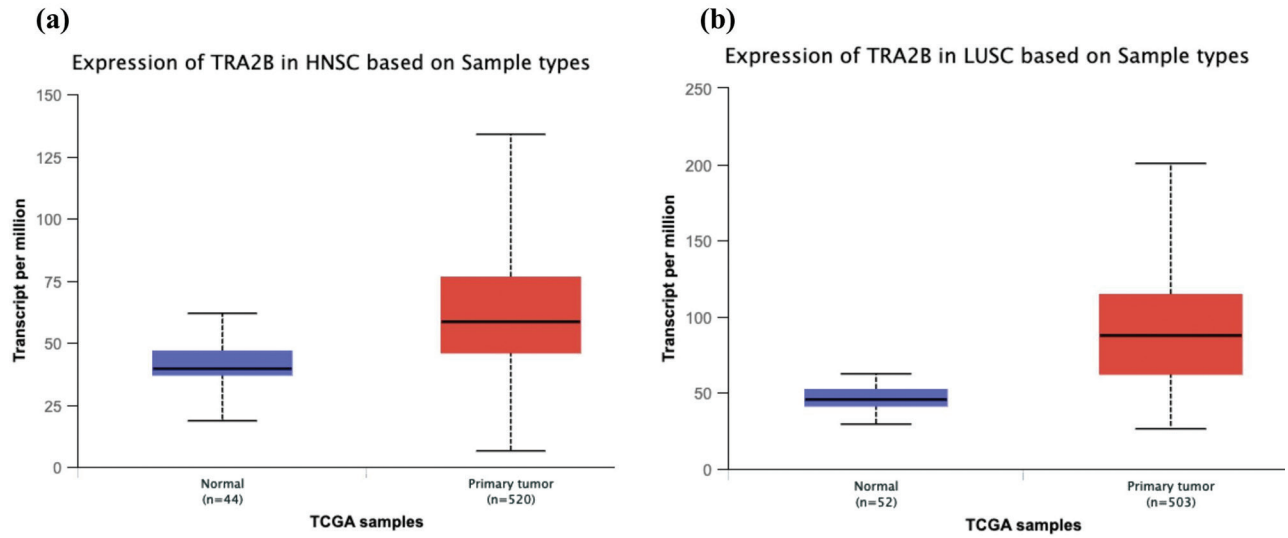

Figure 2. Box Whisker plot demonstrating the gene expression profile of *TRA2B* gene (**a**) HNSCC and (**b**) LUSC datasets. The gene expression between the normal and the HNSCC primary tumor group showed a significant change in the transcript levels (p-value $<10^{-12}$). The gene expression profile was statistically significant between the normal and LUSC primary tumors (p-value $<10^{-12}$). A p-value less than 0.05 is considered significant.

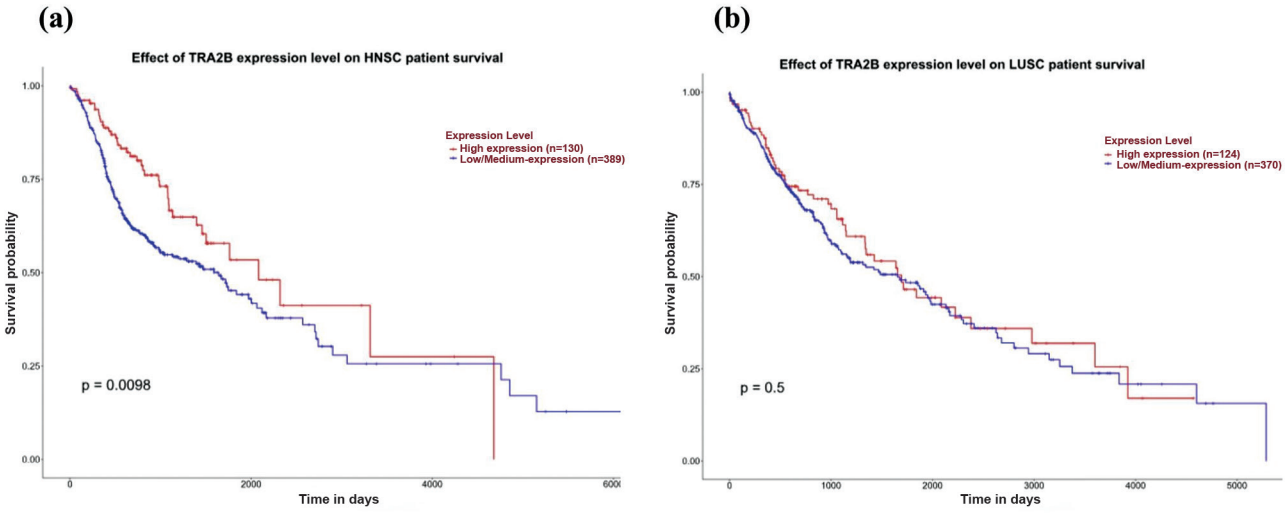

Figure 3. Kaplan Meier plot demonstrating survival probability of patients exhibiting high and low levels of *TRA2B*. A statistically significant change in survival was observed with *TRA2B* expression (p=0.0098) in HNSCC. There was no statistically significant association between the gene expression levels and survival of LUSC patients (p=0.5). A p-value less than 0.05 is considered significant.

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Table 4. List of miRNAs that target TRA2B transcripts

Target score	miRNA name	Gene expression in HNSCC (*p*-value)	Expression pattern	Survival (*p*-value)	Gene expression in LUSC (*p*-value)	Expression pattern	Survival (*p*-value)
98	hsa-miR-570	2.177×10^{-5}	Upregulation	0.79	1.624×10^{-12}	Upregulation	0.86
97	hsa-miR-587	NA	NA	NA	NA	NA	NA
96	hsa-miR-3619	$<10^{-12}$	Upregulation	0.27	1.624×10^{-12}	Upregulation	0.2
95	hsa-miR-214	4.722×10^{-3}	Upregulation	0.55	7.055×10^{-12}	Upregulation	0.49
95	hsa-miR-761	NA	NA	NA	NA	NA	NA
94	hsa-miR-1468	1.977×10^{-8}	Downregulation	0.67	1.174×10^{-2}	Downregulation	0.87
93	hsa-miR-335	2.626×10^{-4}	Upregulation	0.32	1.409×10^{-6}	Upregulation	0.8
93	hsa-miR-1-1	2.001×10^{-3}	Downregulation	0.1	NA	NA	NA
93	hsa-miR-206	2.035×10^{-3}	Downregulation	0.1	2.418×10^{-2}	Downregulation	0.087
92	hsa-miR-613	NA	NA	NA	NA	NA	NA

Protein-Protein interaction analysis

The protein-protein interaction network of TRA2B revealed the following proteins to interact with *SRSF1, SRSF2, SRSF3, SRSF6, SRSF7, SRSF9, SRSF10, RBMX, HNRNPC,* and *HNRNPH1*. Most proteins belong to mRNA processing machinery; hence, *TRA2B* can be considered a key protein that can regulate the gene expression of several candidate genes **(Fig. 4)**. The Metascape gene enrichment analysis revealed crucial pathways related to squamous cell carcinoma of lungs, which further supports this protein's key role in the carcinogenesis process **(Fig. 5)**.

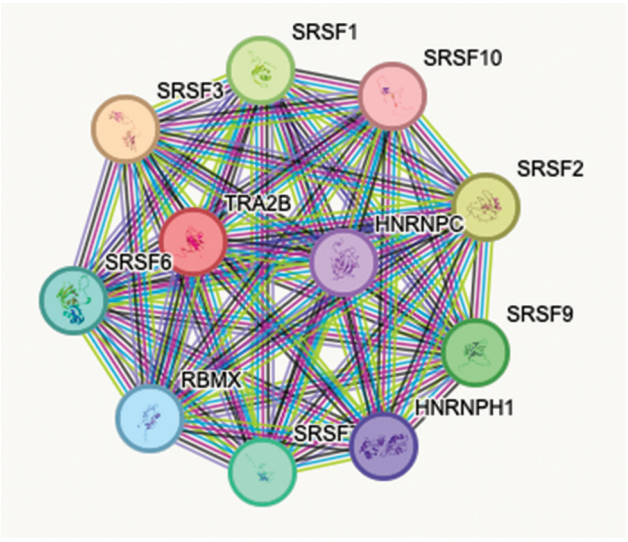

Figure 4. Protein network interactions of *TRA2B* gene.

DISCUSSION

Alternative RNA splicing is an essential process that regulates gene expression in cells. It plays a crucial role in creating different versions of the same gene, known as transcript isoforms, produced at different times in specific cells. Defects in alternative splicing are common in human tumors, and RNA splicing regulators have recently been identified as a new class of oncoproteins or tumor suppressors.[23] Tumor-associated changes in RNA splicing can occur due to mutations in splicing-regulatory elements or changes in splicing machinery components.[24] A study conducted by Ji and the team demonstrated the expression of *TRA2B* employing immunohistochemical assays and Western blot methods. The experiments revealed that the expression was higher in NSCLC tissues when compared to the surrounding non-tumor cells. The Kaplan Meier survival analysis produced results exhibiting the fact that high expression of *TRA2B* correlated with poor prognosis of the patients. The knockdown of the *TRA2B* gene was found to inhibit cell proliferation and induce apoptosis of NSCLC cells.[25] A similar study provided substantial evidence to support the fact that *TRA2B* was markedly higher in high-grade gli-

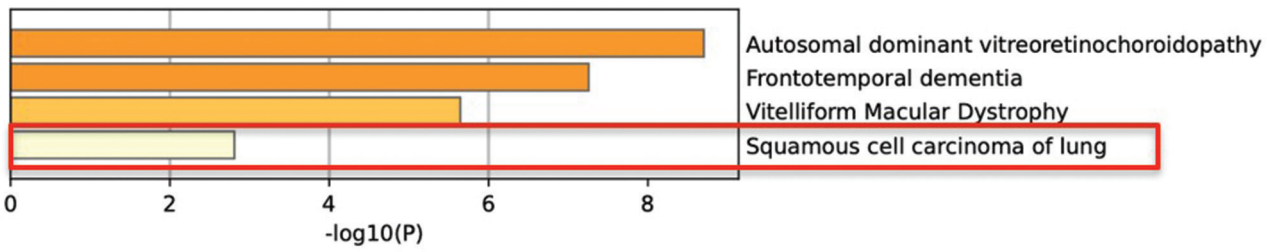

Figure 5. Gene enrichment analysis demonstrating the diseases associated with *TRAB2* network.

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omas than in low-grade gliomas. A positive correlation was also observed between *TRA2B* and Ki-67, which was also associated with a poor clinical outcome. As with the previous observation, this study also demonstrated the suppression of cell proliferation and cell cycle arrest in the G0/G1 phase upon knockdown of the *TRA2B* gene.[26]

A similar study reported the over-expression of *TRA2B* in the endometrial carcinoma cells, as assessed by RT-qPCR and Western bot technique. The dysregulation of this gene inevitably conferred viability and proliferative advantage to the cells. The treatment of such EC cells with siRNA-TRAB2 dramatically affected the proliferative ability of the cells. The inhibition of invasiveness and acceleration of apoptosis was also observed.[27] A study by Zhang and team investigated the role of *TRA2B* in the progression of osteosarcoma. The team observed that exosomes derived from bone marrow mesenchymal stem cells transported miR-206 to osteosarcoma cells, thereby inhibiting its proliferation, migration and invasive properties. The potential target of the miR-206 was found to be *TRA2B*. The study thus elucidated the molecular mechanisms underlying the inhibition of tumor progression in osteosarcoma.[28] The TRA2B-mediated alternative splicing mechanism was tightly associated with cell cycle, apoptosis and several other hallmarks of cancer. An investigation in ovarian cancer (OC) cells showed elevated expression of *TRA2B* with increasing grade of malignancy, and aggressiveness, which led to poor prognosis in OC patients.[29] Several studies have been conducted earlier employing computational approaches to identify the candidate genes from a family of genes[30], gene interaction networks[31], and genes selected through extensive data-mining processes.[32] Such studies provided primary data about the putative role of key genes concerning the specific cancer type. The results could be further validated to gain more insights into the possible mechanisms, modifiers and regulators of gene pathways, which will prove to be a valuable source of information for the development of theragnostics.

The present study is the first of its kind to identify the correlation between alterations observed in the *TRA2B* gene with the impact of these alterations on gene expression and survival of HNSCC and LUSC patients. The observations clearly showed that despite the high expression of *TRA2B* in HNSCC patients, the prognosis was reasonable compared to the low/medium expression group. The observations presented here contradict the findings reported by researchers in various other cancer types. The presentation thus requires further experimentation to gain more insight into the role of *TRA2B* as a tumor suppressor rather than an oncogenic protein in HNSCC cases. In addition, the role of non-coding RNA, miRs, was also elucidated in consonance with the same expression profile in both datasets. The downregulation of *TRA2B* could be affected by microRNAs that target this gene. In this regard, four miRNAs were identified as differentially upregulated in the HNSCC tumor. Although these miRNAs did not return any significant correlation with the survival of patients, they can be considered potential candidates for studying gene expression and regulation of the *TRA2B* gene.

CONCLUSION

The results accumulated through the present study gave a clear understanding of the convergent pathways associated with two closely related cancer phenotypes viz., HNSCC and LUSC. The epigenetic targets and gene expression patterns were similar in both cancer types. The employability of the *TRA2B* gene to HNSCC as a diagnostic or a prognostic marker has to be further investigated using experimental procedures to gain concrete evidence on the role of this gene in establishing HNSCC.

Conflict of Interest

The authors hereby declare that there is no conflict of interest in this study.

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Корреляция генетических изменений и профиля экспрессии гена *TRA2B* при HNSCC и LUSC

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Резюме

Введение: Transformer (*TRA2B*) – это семейство белков, богатых серином/аргинином (SR), которое регулирует альтернативный сплайсинг нескольких генов в зависимости от концентрации. Амплификация гена *TRA2B*, который кодирует *TRA2B*, происходит при нескольких злокачественных новообразованиях, включая опухоли лёгких, шейки матки, головы и шеи, яичников, желудка и матки.

Материалы и методы: В настоящем исследовании используется вычислительный подход для прогнозирования молекулярных механизмов, лежащих в основе изменений *TRA2B* в двух фенотипах рака, а именно, плоскоклеточный рак лёгких и головы и шеи. Генетическое изменение в гене *TRA2B* было идентифицировано с использованием базы данных cBioportal. Паттерн экспрессии генов в обоих типах рака и их паттерн выживаемости относительно профиля экспрессии были продемонстрированы с использованием UALCAN. Цели микроРНК гена *TRA2B* были идентифицированы с использованием базы данных miRDB.

Результаты: Было обнаружено, что генетические изменения составляют 27% и 48% в наборах данных HNSCC и LUSC соответственно. Изменения включали амплификацию гена, миссенс, нонсенс и мутации места сплайсинга. Профиль экспрессии гена *TRA2B* хорошо коррелировал с амплификацией гена, продемонстрированной пациентами в обеих группах. Однако повышение регуляции *TRA2B* не очень хорошо коррелировало с профилем выживаемости у пациентов LUSC. Понижение регуляции *TRA2B* заметно повлияло на выживаемость пациентов HNSCC, что можно отнести к функциям микроРНК, нацеленных на транскрипты *TRA2B*.

Заключение: Хотя было обнаружено, что *TRA2B* является потенциальным диагностическим маркером, демонстрирующим дифференциальный паттерн экспрессии для HNSCC, возможность использования этого гена в качестве прогностического маркера требует дополнительных экспериментов. Кроме того, следует рассмотреть влияние микроРНК на дисрегулируемую экспрессию гена, чтобы лучше понять основные молекулярные механизмы, ускоряющие заболевание.

Ключевые слова

рак, генетика, изменения генов, экспрессия генов, микроРНК