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Thorough Bioinformatics Examination Reveals NOC4L as a Prognostic Indicator in Lung Adenocarcinoma

Ayoob Radhi Al-Zaalan
Department of Medical Lab Technology, College of Health and Medical Technology, Southern Technical University, Basrah, Iraq

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ABSTRACT

Objective: *This study systematically investigates the prognostic significance of nucleolar complex-associated protein 4 homolog (NOC4L) in lung adenocarcinoma (LUAD) and explores its associations with clinicopathological parameters, immune microenvironment components, and molecular pathways.* ***Method:*** *A bioinformatics-based approach was applied using publicly available databases including Kaplan–Meier Plotter, GEPIA2, UALCAN, and TIMER2.0. Survival analyses encompassed overall survival (OS), disease-free survival (DFS), first progression survival (FPS), and post-progression survival (PPS). Correlations with tumor stage, nodal metastasis, histological subtypes, tumor-infiltrating immune cells, and p53 pathway genes were evaluated.* ***Results:*** *High NOC4L expression was consistently associated with poor prognosis across all survival indicators and correlated with advanced tumor stage, nodal metastasis, and aggressive histological forms. Elevated NOC4L expression showed positive correlations with immunosuppressive cells such as myeloid-derived suppressor cells and cancer-associated fibroblasts, and negative correlations with cytotoxic $CD8^+$ T cells.* ***Novelty:*** *This study identifies NOC4L as a potential prognostic biomarker in LUAD, linking its overexpression to immune suppression and tumor aggressiveness, thereby suggesting its role in cancer progression and its potential as a therapeutic target.*

INTRODUCTION

Lung cancer continues to be the leading cause of cancer-related deaths globally, with lung adenocarcinoma (LUAD) representing approximately 40% of all cases [1], [2]. Although modern therapeutic opportunities existed in the recent past, survival rates have continued to be very low, especially at an advanced level of disease [3]. LUAD has the large molecular heterogeneity that poses a serious challenge to treatment choice and prognosis [4]. Consistent clinical variables may not adequately capture tumor biology and this fact explains why there are new prognostic biomarkers that are reported to stratify patients better and improve therapeutic decisions [5].

The nucleolar proteins have received interest in cancer studies because of their functions in ribosome generation, and cell division. In addition to their roles in the canonical pathways, some of these proteins have extra-ribosomal functions that affect the oncogenic pathways [6], [7]. Nucleolar Complex Associated 4 Homolog (NOC4L) is a conserved protein that is useful in assembling ribosomal subunits and has shown a tumor-suppressive effect in gastric disease because it favors p53 acetylation and apoptosis [8]. According to the nucleolar proteins, however, transcription in relation to cancer types may differ significantly. The p53 mutational status is also a greatly variable

factor that can dictate the role of these proteins as tumor suppressors or oncogenic drivers [9].

The role of NOC4L in LUAD, in which mutations in p53 happen in half the instances, is unexplored. Ribosome biogenesis and cancer development have a complicated and context-based relationship. The role of elevated ribosome production in promoting tumor growth may vary depending on tumor types although this is usually supported by protein demands of the fast-dividing cells because of the need to meet protein synthesis demands [10]. Also, the tumor microenvironment, in particular, the composition of the immune cells, varies considerably across tissue sources and can markedly decrease the formation of the disease [11]. It is the indication of the above finding, which implies that the activity of NOC4L in LUAD may not be similar to the same activity, which plays a role in gastric cancer.

The fundamental aim of the research was to describe the expression of NOC4L and to use them in clinical practice fully through the venerable bioinformatics analysis. To be exact, we compared patterns of NOC4L expression between cancer types, evaluated patterns that were most related to clinical pathologic features (tumor stage, nodal metastasis, histological subtypes), prognostic prognostic associations were assessed across 4 or more independent cohorts, correlations between NOC4L and immune cell response interests, and correlations between NOC4L and 25 major molecular pathways such as the p53 signaling cascade.

RESEARCH METHOD

Gene expression analysis

NOC4L expression levels in LUAD and other cancer types were analyzed using the Gene Differential Expression module of TIMER2.0 (http://timer.cistrome.org), which integrates TCGA gene expression data. Expression differences between tumor and normal tissues were evaluated using the Wilcoxon rank-sum test, with $p<0.05$ considered statistically significant [12].

Survival analysis

Two independent platforms were utilized in order to evaluate the prognostic importance of NOC4L. The Kaplan-Meier Plotter database (https://kmplot.com/analysis) was utilized in order to assess the relationship between the expression of NOC4L (218860 probe at) levels and First Progression Survival (FPS), Post-Progression Survival (PPS), and Overall Survival (OS) in lung cancer patients [13]. GEPIA2 (http://gepia2.cancer-pku.cn) was used to validate the association between the expression of NOC4L and OS, Disease Free Survival (DFS) in TMC LUAD cohort [14]. Median values were used to stratify the patients into high and low expression grouping and the log rank test was used to determine the difference in survival between the analyzed groups.

Analysis of NOC4L expression in relation to clinic pathological characteristics

The UALCAN web portal (http://ualcan.pathuab.edu/profile) was used to examine links between the expression of NOC4L and clinic pathological dimensions of

patients with LUAD in TCGA [15]. Such parameters as tumor stage (stages 1-4), the presence of nodal metastasis (N0-N3), histological subtypes, sex of patients, race, and smoking history were examined. Statistical comparisons done using student t-test with $p<0.05$ being the significance limit.

Analysis of immune cell infiltration

TIMER2.0 has been used on the NOC4L expression to investigate its relationship with immune cell infiltration in 594 LUAD patients in TCGA. Five immune cell populations were analyzed: Cancer-Associated Fibroblasts (CAFs), Common Lymphoid Progenitors (CLPs), Common Myeloid Progenitors (CMPs), CD8+T cells, and Myeloid-Derived Suppressor Cells (MDSCs). Spearman's rank correlation was used to assess the relationship between NOC4L expression and immune infiltration scores. Combined survival analysis was performed to evaluate the joint prognostic impact of NOC4L expression and MDSC infiltration [12].

Functional enrichment assessment

Co-expressed genes with NOC4L were identified using GEPIA2 based on Pearson correlation analysis in TCGA-LUAD dataset. The top 1,000 correlated genes were subjected to Gene Ontology (GO) and pathway enrichment analysis using Enrichr (http://amp.pharm.mssm.edu/Enrichr). The top five enriched terms in Biological Process, Cellular Component, and Molecular Function categories, as well as the top ten Reactome pathways, were identified using Fisher's exact test with Benjamini-Hochberg correction [16]. Additionally, correlations between NOC4L and six p53 pathway genes (CCNB1, CCNB2, CDK1, CHEK1, GTSE1, and RRM2) were assessed using Spearman's correlation in TIMER2.0 [12].

Statistical analysis

All statistical analyses were performed using the built-in functions of the respective platforms. Continuous variables were compared using Student's t-test or Wilcoxon rank-sum test as appropriate. Survival analyses were done by using the Kaplan-Meier method with log-rank tests. Cox proportional hazards regression was used to determine hazard ratios and 95% confidence intervals. A two-tailed p-value less than 0.05 was deemed to be statistically significant.

RESULTS AND DISCUSSION

Results

NOC4L is overexpressed in LUAD and multiple cancer types

The TCGA data analysis using TIMER2.0 showed that NOC4L mRNA expression level was highly increased in tumor tissues relative to adjacent normal tissues in various types of cancers. NOC4L was found to be significantly overexpressed in tumor tissues compared to normal lung tissue in lung adenocarcinoma (LUAD) ($p<0.001$) (Figure 1), indicating its possible involvement in the tumorigenesis process.

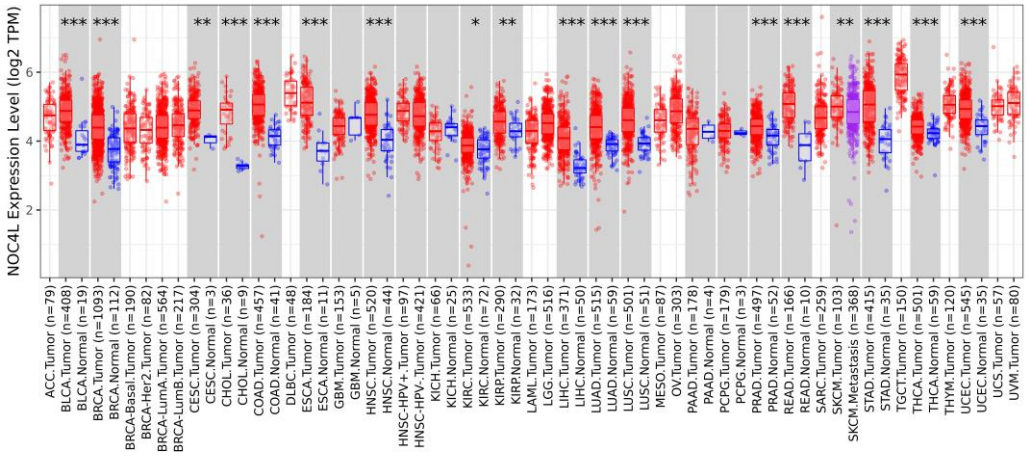

Figure 1. The levels of NOC4L in the various forms of cancer. Compared to normal tissue (blue), the differential expression of NOC4L mRNA in tumor tissues (red) versus normal tissues in several types of cancer in the TCGA database. LUAD is overexpressed significantly (***p<0.001). Data analyzed using TIMER2.0.

NOC4L expression and patient survival outcomes

Kaplan-Meier Plotter database showed that elevated NOC4L expression was strongly linked with unfavorable prognosis among LUAD patients, such as decreased First Progression Survival (FPS: HR= 1.33, p= 2.5x10^{-6}), Post-Progression Survival (PPS: HR= 1.41, p= 0.0011), and Overall Survival (OS: HR= 1.19, p= 0.04) (Figures 2a- Nevertheless, GEPIA2 validation analysis of TCGA data on NOC4L expression demonstrated no significant correlation with either OS (HR= 1.1, p= 0.73) or Disease-Free Survival (DFS: HR= 0.89, p= 0.44) (Figures 2D-E). This difference could be as a result of differences in patient cohorts, sample size, and methodologies of analysis on the two platforms.

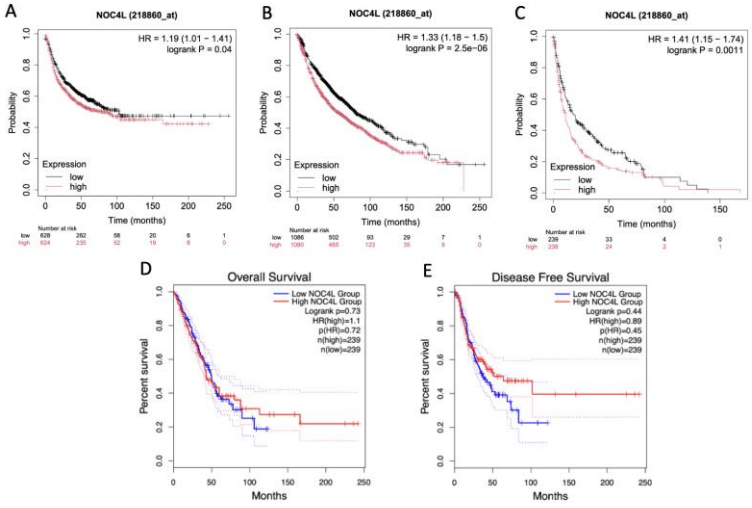

Figure 2. Survival analysis of NOC4L expression in LUAD patients. Kaplan-Meier survival curves showing the association between NOC4L expression and patient outcomes. (A) First Progression Survival (FPS), (B) Overall Survival (OS), and (C) Post-Progression Survival (PPS) from Kaplan-Meier Plotter database. (D) Overall Survival and (E) Disease-Free Survival from GEPIA2 database using TCGA-LUAD cohort. High expression group shown in red, low expression group in black.

NOC4L expression correlates with aggressive clinic pathological features

Using UALCAN, we examined the relationship between NOC4L expression and clinic pathological characteristics in TCGA-LUAD patients. NOC4L expression was significantly elevated in tumor tissues across all examined subgroups compared to normal tissue. Importantly, NOC4L levels increased progressively with advancing tumor stage, with stages 2-4 showing significantly higher expression than stage 1 (Figure 3A). Similarly, NOC4L expression was elevated in tumors with nodal metastasis, particularly in N2 compared to N0 stage (Figure 3E). Demographic analysis revealed higher NOC4L expression in male patients compared to females (Figure 3C), in Caucasian and Asian patients compared to African-Americans (Figure 3B), and in smokers compared to non-smokers (Figure 3D). Among histological subtypes, Clear Cell and Solid Pattern Predominant carcinomas exhibited the highest NOC4L expression (Figure 3F).

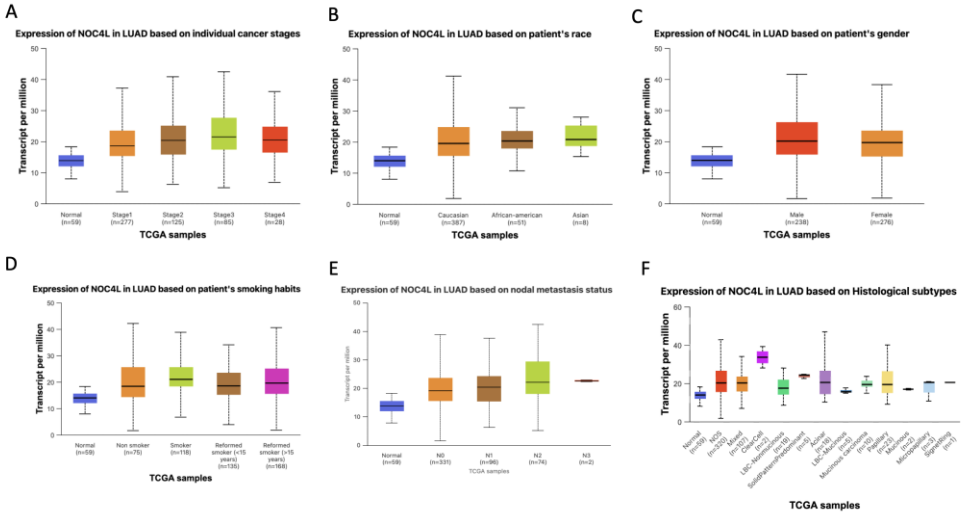

Figure 3. Association between NOC4L expression and clinicopathological features in LUAD. Box plots showing NOC4L expression levels stratified by (A) tumor stage (stages 1-4), (B) race/ethnicity, (C) patient sex, (D) smoking history, (E) nodal metastasis status (N0-N3), and (F) histological subtypes. Data from TCGA-LUAD cohort analyzed via UALCAN. * p<0.05, ** p<0.01, *** p<0.001.

Statistical validation confirmed these associations (Table 1). NOC4L expression was significantly elevated in all tumor stages versus normal tissue (p<0.001), with stage 3 showing higher expression than Stage 1 (p=0.0195). N2 tumors demonstrated significantly higher expression than N0 tumors (p=0.0135). Clear Cell carcinoma showed significantly higher NOC4L levels compared to multiple other subtypes (p<0.05 for all comparisons).

Table 1. Statistical analysis of NOC4L expression across clinicopathological parameters in LUAD.

Comparison	Statistical significance
Individual cancer stage	
Normal-vs-stage1	1.62447832963153E-12
Normal-vs-stage2	1.62447832963153E-12

Normal-vs-stage3	1.62903024403249E-12
Normal-vs-stage4	3.6087000000018E-05
Stage1-vs-stage3	1.951780E-02
Patient race	
Normal-vs-Caucasian	1.62436730732907E-12
Normal-vs-AfricanAmerican	6.69630018101941E-10
Normal-vs-Asian	2.043000E-03
Gender	
Normal-vs-Male	<1E-12
Normal-vs-Female	1.62436730732907E-12
Smoking habit	
Normal-vs-Non smoker	1.28820000222518E-08
Normal-vs-Smoker	<1E-12
Normal-vs-Reformed smoker1	3.33066907387547E-16
Normal-vs-Reformed smoker2	1.62447832963153E-12
Non smoker-vs-Smoker	1.437640E-02
Non smoker-vs-Reformed smoker1	3.026100E-04
Non smoker-vs-Reformed smoker2	4.504200E-02
Nodal metastasis status	
Normal-vs-N0	<1E-12
Normal-vs-N1	1.65578661892596E-12
Normal-vs-N2	1.97619698383278E-14
Normal-vs-N3	1.90089999996257E-06
N0-vs-N2	1.349980E-02
Tumor histology	
Normal-vs-NOS	<1E-12
Normal-vs-Mixed	<1E-12
Normal-vs-LBC-NonMucinous	8.696800E-03
Normal-vs-SolidPatternPredominant	2.344100E-02
Normal-vs-Acinar	2.057700E-03
Normal-vs-LBC-Mucinous	2.416800E-03
Normal-vs-Mucinous carcinoma	1.357700E-03
Normal-vs-Papillary	2.780400E-04
Mixed-vs-ClearCell	9.617800E-03
ClearCell-vs-LBC-NonMucinous	3.898300E-02
ClearCell-vs-LBC-Mucinous	9.418100E-03
ClearCell-vs-Mucinous carcinoma	7.616000E-03
ClearCell-vs-Papillary	3.029800E-02

NOC4L expression associates with immunosuppressive microenvironment

Analysis of immune cell infiltration using TIMER2.0 revealed significant correlations between NOC4L expression and immune cell composition in LUAD. NOC4L showed strong positive correlation with Myeloid-Derived Suppressor Cells (MDSCs) (Rho= 0.459, p= 4.20×10^{-27}) and weaker positive correlation with Cancer-Associated Fibroblasts (CAFs) (Rho = 0.167, p= 2.01×10^{-4}) (Figures 4A, E). Conversely, NOC4L

expression negatively correlated with CD8+ T cells (Rho= -0.199, p= 8.21×10^{-6}) and Common Myeloid Progenitors (Rho= -0.095, p=0.0357) (Figures 4C, D). No significant correlation was observed with Common Lymphoid Progenitors (Figure 4B). Combined survival analysis demonstrated that patients with both high NOC4L expression and high MDSC infiltration experienced significantly worse OS compared to those with high NOC4L but low MDSC infiltration (HR= 1.96, p= 0.0088) (Figure 4F), indicating a synergistic negative prognostic effect.

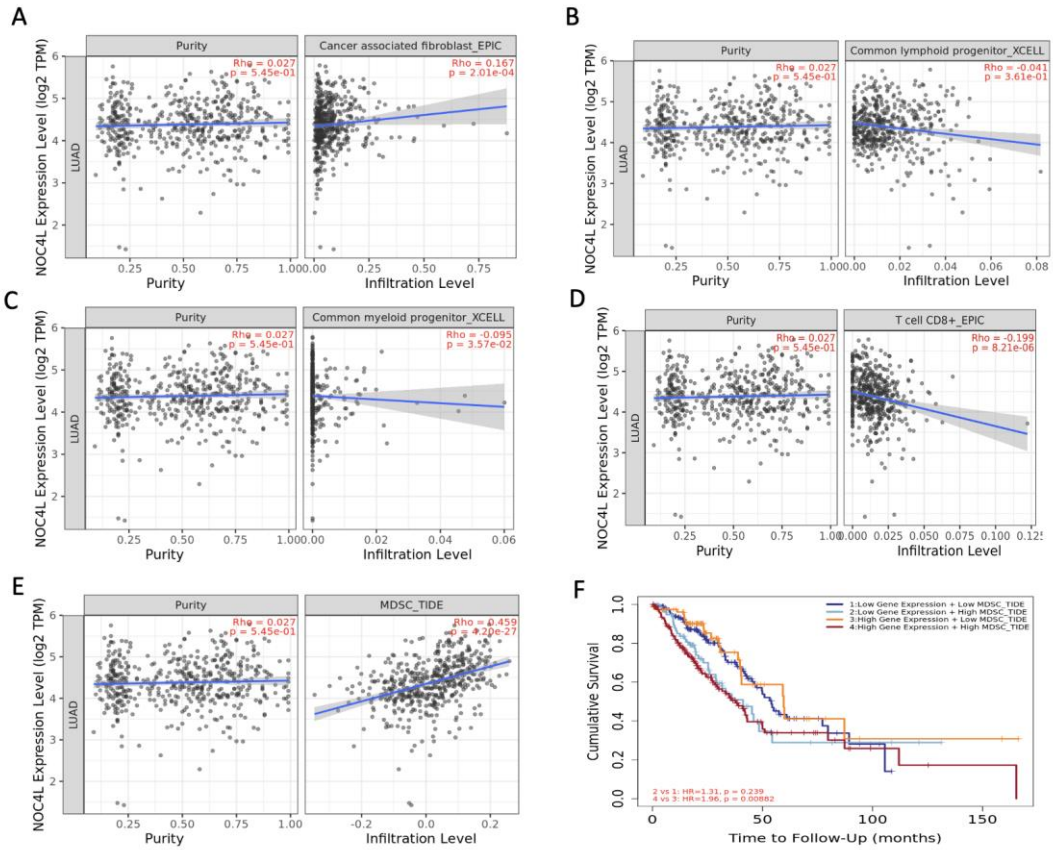

Figure 4. Correlation between NOC4L expression and immune cell infiltration in LUAD. Scatter plots showing Spearman correlations between NOC4L expression and infiltration levels of (A) Cancer-Associated Fibroblasts (CAFs), (B) Common Lymphoid Progenitors (CLPs), (C) Common Myeloid Progenitors (CMPs), (D) CD8+ T cells, and (E) Myeloid-Derived Suppressor Cells (MDSCs) in TCGA-LUAD cohort (n=594). (F) Combined survival analysis stratified by NOC4L expression and MDSC infiltration levels. Analysis performed using TIMER2.0.

Functional enrichment implicates NOC4L in cell cycle and RNA metabolism

Analysis of gene ontology of gene co-expressed with NOC4L identified that there were substantial biological processes enriched with RNA processing, DNA repair, and regulation of the Mitotic Cell Cycle (Figure 5A). The analysis of cellular components revealed that it was majorly localized in the Nucleus and Nucleolus (Figure 5B), whereas the molecular function showed that snoRNA and snRNA binding activities were enriched (Figure 5C). The analysis of reactome pathways revealed that the association between NOC4L and both Metabolism of RNA and Cell Cycle pathways (Figure 5D) was

strong and indicated that NOC4L is involved in the key cellular processes that are fundamental to cell proliferation.

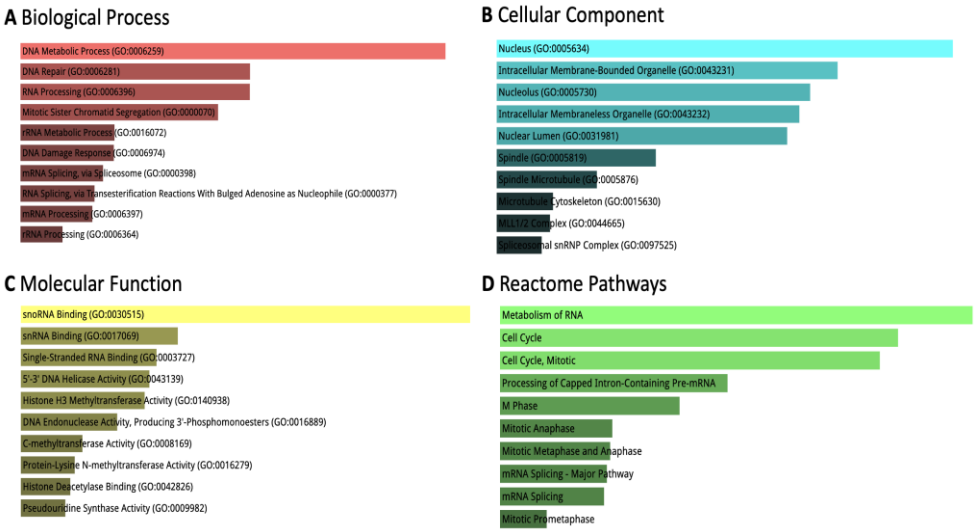

Figure 5. Functional enrichment analysis of NOC4L co-expressed genes. Enrichment analysis of the top 1,000 genes co-expressed with NOC4L in LUAD. Bar plots showing significantly enriched terms in (A) Gene Ontology Biological Process, (B) Cellular Component, (C) Molecular Function, and (D) Reactome Pathways. Analysis performed using Enrichr database.

NOC4L expression correlates with p53 pathway regulators

We examined correlations between NOC4L and six key genes in the p53 pathway. Strong positive correlations were observed with all examined genes: CHEK1 (Rho= 0.519, p= 8.15×10^{-37}), CCNB2 (Rho= 0.423, p= 8.93×10^{-24}), CCNB1 (Rho= 0.426, p= 4.20×10^{-24}), CDK1 (Rho= 0.339, p= 2.83×10^{-15}), RRM2 (Rho = 0.387, p= 8.20×10^{-20}), and GTSE1 (Rho= 0.319, p= 9.39×10^{-14}) (Figure 6A). Survival analysis demonstrated that high expression of each gene was significantly associated with poor OS: GTSE1 (HR= 1.37, p= 5.75×10^{-4}), CDK1 (HR= 1.30, p= 0.0033), RRM2 (HR= 1.31, p= 0.0024), CCNB2 (HR= 1.23, p= 0.0188), CHEK1 (HR= 1.22, p= 0.0255), and CCNB1 (HR= 1.21, p= 0.0168) (Figure 6B). These findings suggest NOC4L functions within a regulatory network that promotes cell cycle progression and may contribute to p53 pathway dysregulation in LUAD.

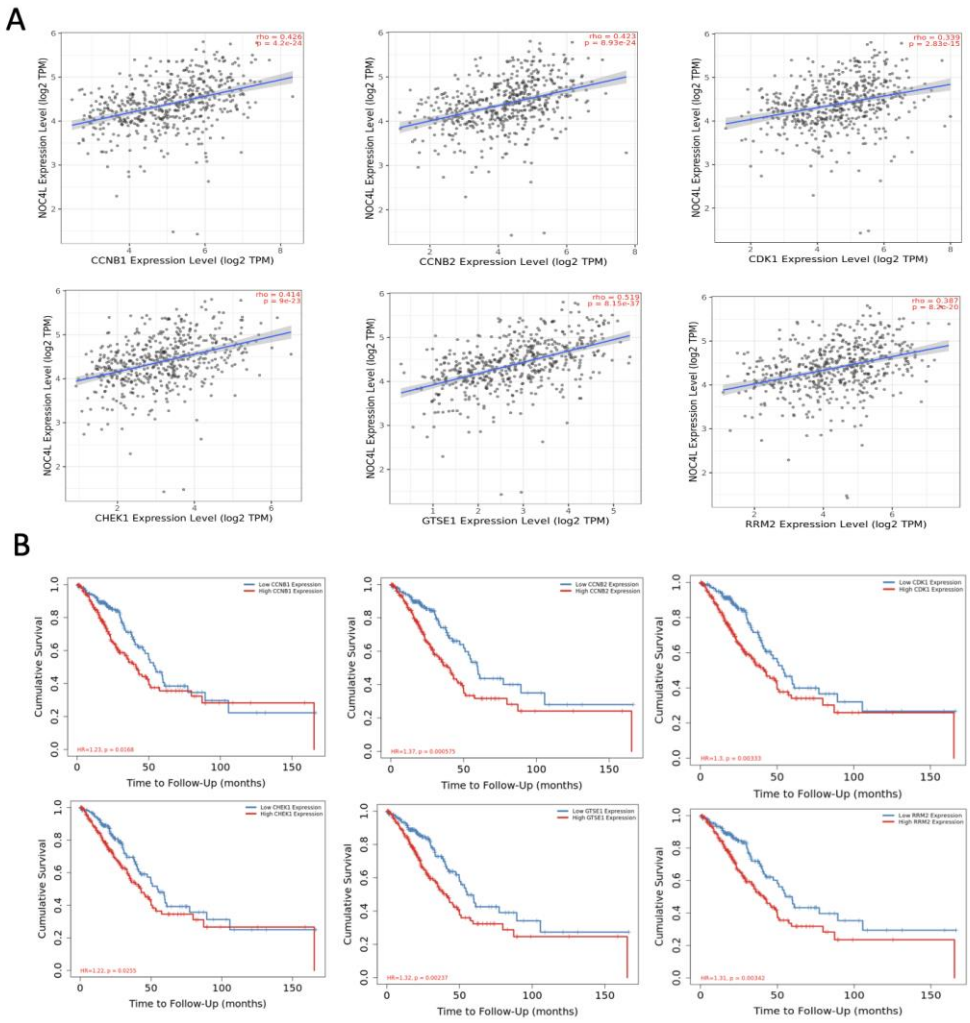

Figure 6. Correlation between NOC4L and p53 pathway genes in LUAD. (A) Scatter plots showing Spearman correlations between NOC4L expression and six key p53 pathway genes (CCNB1, CCNB2, CDK1, CHEK1, GTSE1, RRM2) in TCGA-LUAD cohort. (B) Kaplan-Meier survival curves demonstrating the prognostic significance of each gene in LUAD patients. Analysis performed using TIMER2.0 and Kaplan-Meier Plotter.

Discussion

We conducted an overall bioinformatics analysis in this study to examine the prognostic role and oncogenic potential of NOC4L in lung adenocarcinoma (LUAD). The total results we obtained indicate that high levels of NOC4L expression are a resultant feature of a low prognosis in LUAD patients and a complex interconnection with diverse clinicopathological traits, immune cell infiltration, and the p53 signaling pathway. The findings are congruent with the recent literature that has explained that nucleolar proteins and ribosome biogenesis are crucial in cancer development [10], [11], [12], [13], [14], [15], [16], [17].

Contradicting results regarding the prognostic value of NOC4L were made through survival analyses. A log Ramulation Kaplan-Meier Plotter analysis showed that a great proportion of NOC4L was strongly correlated with negative age, state of shorter First

Progression Survival (FPS: HR= 1.33, p= 2.5 × 10^{-6}), post progression survival (PPS: HR= 1.41, p= 0.0011) and overall survival (OS: HR= 1.19, p= 0.04) among LUAD patients. Nonetheless, the association between the NOC4L expression and the Overall Survival (OS: HR= 1.1, p= 0.73) or Disease-Free Survival (DFS: HR= 0.89, p= 0.44) did not imply any statistically significant outcome after the validation analysis using GEPIA2 with the help of TCGA data. This difference in bioinformatics tools is no anomaly, and it might be explained by a number of factors, such as the dissimilarity of sample size, of cohorts of patients, algorithms of data processing and the very choice of methodologies used to conduct a survival analysis [18], [19]. Variations in probe selection for microarray platforms versus RNA-sequencing approaches, differences in data normalization methods, and heterogeneity in patient cohorts across databases can all contribute to divergent survival associations for the same gene. Despite these variations, the consistent trend across both platforms points towards NOC4L as a marker of poor prognosis, consistent with recent pan-cancer evidence demonstrating that elevated ribosome biogenesis activity is associated with tumor aggressiveness and reduced patient survival [20].

Analysis of clinicopathological features showed that NOC4L expression was significantly elevated in LUAD tissues compared to normal tissues and correlated with advanced tumor stage and nodal metastasis, suggesting a potential role in tumor progression and spread. It is notable that of the particular histological subtypes, such as clear cell and solid pattern predominant carcinomas, the expression of NOC4L was the highest, which suggests that it could serve as a subtype specific biomarker in cancer. The results may be related to the known role of the ribosome biogenesis to promote the high pace of metabolism and proliferation of cancer cells [10]. Though the ribosome biogenesis process has historically been viewed as a housekeeping task, recent studies also indicate that this process might be selective toward the process of protein synthesis [21]. By selectively regulating this, the cancer cells might receive a survival benefit and keep abiding by the tumor microenvironment to support the development of the disease.

Tumor immune microenvironment analysis was performed, revealing the potentially existing processes between NOC4L and LUAD development. Intrusion of cancer-related fibroblasts (CAFs) as well as myeloid derived suppressive cell Cover (MDSCs) that respectively have been linked with the creation of an immunosuppressive tumor microenvironment had strong positive connections with the expression of BLC4L. Conversely, they were also observed to be associated with the CD8+ T cells that play an important part in anti-tumor immunity in a negative correlated way. This implies that that induced occurrence of high expression of NOC4L that might contribute to an immune-evasive attachment and consequently enable tumor growth and metastasis. The combined survival analysis that revealed that patients with a strong expression of NOC4L and MDSC infiltration also proved this hypothesis. The presented findings align with the previous investigations according to which the interactions between ribosome biogenesis and immune control are complicated [21].

The survey of gene enrichment indicated that NOC4L plays a role in basic and maintenance cellular activities, such as RNA processing, repair of DNA, cell division control, etc. The high associations of NOC4L with essential elements of the p53 pathway (CCNB1, CCNB2, CDK1 and CHEK1) imply the existence of a mechanistic relationship between NOC4L and cell cycle deregulation. The p53 pathway is one of the most essential tumor suppressor pathways which are commonly silenced in cancer cells. The surging relationship between NOC4L and these proliferating cell cycle genes results in the possibility that NOC4L can be affiliated to the circumvention of brain cycle inquiry phenomena as present in p53; hence being inclined to unreserved expansion. This aligns with the rest of the findings of Jia *et al.,* who showed that NOC4L has the capacity to foster the development of gastric cancer by inhibiting p53 deacetylation in favor of SIRT1 [8].

It has a number of limitations to this study. To begin with, our results are correlational in nature since they are an in silico analysis, which relies on publicly available databases and, therefore, cannot prove causality. The given associations of NOC4L expression with clinical outcomes have to be confirmed by experimental studies. Second, the difference in the prognostic associations regarding survival in the Kaplan-Meier Plotter and GEPIA2 databases reveals the ability of bioinformatics to vary and stressed the importance of cautioning in the interpretation of associations with prognostic factors. Such variance can be due to variation in the populations of patients, data processing techniques, and use of a microarray or RNA-sequencing platform. Third, analysis was only conducted on levels of mRNA expression, which does not necessarily indicate protein levels or activity of NOC4L. Proteins are also open to post-transcriptional as well as post-translational modifications which may drastically modify the levels and activity including being underrepresented in transcriptomic studies. Fourth, there are potential pressure or selection biases due to their retrospective design in primary analysis based on TCGA scriptures, and potential control over such factors as treating regimens and comorbid status cannot be monitored either. Fifth, we have identified the signs of the expression of NOC4L and immune cells invasion, but the ways to obtain how strongly associations are possible are hard as these associations are yet to be functionalized.

Irrespective of these limitations, our in-depth bioinformatics analysis allows us to make practical information on the possible role of the NOC4L in the development of LUAD and preconditions of future experiment researches. It shall be essential in the ongoing research of transcriptomic and proteomic research, in combination with experiments on the functionality to establish the precise molecular pathways of how NOC4L reduces tumor invasion and immune regulation. Moreover, the identification of the prognostic meaning of NOC4L in the large independent groups of patients with standardized and high-quality methods will play a critical role in describing its clinical utility as a biomarker and as a potential therapeutic target.

CONCLUSION

Fundamental Finding : This bioinformatics analysis identifies NOC4L as a potential prognostic biomarker for lung adenocarcinoma (LUAD). Elevated NOC4L expression is associated with advanced disease stage, nodal metastasis, and higher histological grade. Furthermore, its correlation with an immunosuppressive tumor microenvironment—characterized by increased myeloid-derived suppressor cells (MDSCs), reduced CD8+ T-cell infiltration, and dysregulation of the p53 pathway—suggests that NOC4L may contribute to immune evasion and uncontrolled cell proliferation. **Implication :** These findings imply that NOC4L could serve as a promising molecular marker for disease progression and prognosis in LUAD, as well as a potential therapeutic target for modulating tumor immunity and proliferation pathways. **Limitation :** Despite these insights, variations in survival outcomes across bioinformatics platforms highlight the limitations of data heterogeneity and underscore the need for biological validation. **Future Research :** Further experimental studies using independent patient cohorts and in vivo or in vitro models are essential to clarify the molecular mechanisms of NOC4L, validate its prognostic value, and assess its potential as a therapeutic target in lung adenocarcinoma.

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*__Ayoob Radhi A-Zaalan (Corresponding Author)__
Department of Medical Lab Technology, College of Health and Medical Technology, Southern Technical University, Basrah, Iraq
Email: ayoob.r.tuama@stu.edu.iq