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LincRNA-p21, a Potential Regulator of the Cell Cycle, Is Downregulated in Gastric Cancer

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ABSTRACT

Background & Objective: Gastric cancer (GC) represents a major global health concern, often diagnosed at advanced stages, with limited effective biomarkers for early detection. Long intergenic non-coding RNA p21 *(lincRNA-p21)* has been implicated in many cancers, yet its role in GC is not fully understood.

Materials & Methods: In the current case–control design, we analyzed the expression of *lincRNA-p21* in 40 matched pairs of tumor tissues and their adjacent non-tumor counterparts, as well as in a panel of cancer and stem-like cells, including gastric (AGS, MKN45) and esophageal adenocarcinoma (FLO-1, OE-19) cell lines, the human embryonal carcinoma line (NTERA2), human induced pluripotent stem cells (hiPSCs), and mesenchymal stem cells (MSCs). This approach was designed to explore whether *lincRNA-p21* expression is associated with stemness and tumorigenic potential. Total RNA was extracted, followed by cDNA synthesis and qPCR analysis. Additionally, TCGA data were assessed via the UALCAN platform to evaluate the expression pattern of key cell cycle related genes (*CDKN1A, STAT3, CDK2* and *E2F1*) in GC samples with differing *TP53* mutation statuses.

Results: A significant reduction in *lincRNA-p21* expression was identified in tumor tissues compared to non-tumor samples ($P = 0.01$), and its reduced expression was consistent across various malignancy grades. Likewise, GC and stem-like cell lines exhibited lower *lincRNA-p21* levels relative to normal controls, suggesting a role in suppressing stemness and tumor progression. Furthermore, TCGA analysis revealed significantly elevated *STAT3, CDK2*, and *E2F1* expression in both *TP53*-mutated and wild-type gastric tumors, implicating dysregulation of the *lincRNA-p21*–p21–p53 axis in GC pathogenesis.

Conclusion: The reduced levels of *lincRNA-p21*, along with elevated STAT3, CDK2, and E2F1, indicate disrupted cell cycle control in GC. Consistent *lincRNA-p21* downregulation across malignancy stages suggests its potential as an early prognostic biomarker for GC detection.

Keywords: Gastric Cancer, *lincRNA-p21*, Cancer Stem Cells, p21-p53 Axis, Cell Cycle Control, Biomarker

1. Introduction

Gastric cancer (GC) remains among the most significant causes of cancer mortality on a global scale. According to estimates from the Global Cancer Observatory (GLOBOCAN, 2020), GC was ranked as the fifth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality, with more than 1.1 million new cases and nearly 800,000 deaths each year. Despite advancements in GC treatment, late-stage diagnosis remains prevalent, partly due to the lack of reliable and accessible biomarkers for early detection (1, 2). Long non-coding RNAs (lncRNAs), which exceed 200 nucleotides in length, are essential for regulating gene expression at both the transcriptional and post-transcriptional levels. Aberrant lncRNAs expression contributes to the initiation, progression, and treatment resistance of tumors (3, 4).

Emerging transcriptomic analyses of gastric tumors have underscored the involvement of p53-regulated lncRNAs in cancer progression and clinical outcomes **(5)**. Among the p53-responsive lncRNAs, *lincRNA-p21* stands out for its role in the negative regulation of p53-induced genes **(6)**.

Directly activated by tumor suppressor p53, *lincRNA-p21* is involved in both transcriptional and post-transcriptional regulation of genes that promote cell proliferation and tumorigenesis **(7)**. *LincRNA-p21* is positioned 15 kb upstream of p21 related gene (*CDKN1A*), which acts as a crucial regulator of the cyclin-dependent kinase complex, thereby affecting cell-cycle control and the DNA damage response **(8, 9)** (Figure 1A and 1B).

Additionally, *LincRNA-p21* participates in the epigenetic control of pluripotency-associated genes and inhibits epithelial–mesenchymal transition (EMT) and reprogramming processes (Figure 1C) **(6, 10)**.

Furthermore, *lincRNA-p21* negatively regulates protumorigenic pathways such as JAK2/STAT3 **(11)** and Wnt/β-catenin **(12)** signaling cascades, thereby attenuating cancer stem cell expansion and metastatic potential (Figure 1D). The downregulation of *lincRNA-p21* has been observed across a broad spectrum of human malignancies, including hepatocellular, prostate, colorectal, and bladder cancers, where its decreased expression is frequently linked to a worse clinical outcomes and increased tumor malignancy **(13)**.

In light of the cancer stem cell hypothesis, our previous investigation in gastric adenocarcinoma demonstrated a notable downregulation of reprogramming-inhibiting genes, particularly p21, in tumor tissues **(14)**. Building on our previous findings regarding the downregulation of p21 expression in GC, the present study primarily focused on evaluating the *lincRNA-p21* expression profile in gastric adenocarcinoma tissues of varying tumor grades, to assess its potential association with tumor progression. Additionally, we examined its expression across a range of stem cell lineages, including mesenchymal stem cells (MSCs), human induced pluripotent stem cells (hiPSCs), and embryonic carcinoma cells (NTERA2) as comparative reference for stemness-related expression. This comparison allowed us to assess whether *lincRNA-p21* is differentially expressed between cancer cells and stem cell populations, thereby providing insight into its potential role in regulating stemness and tumorigenicity. A complementary analysis using The Cancer Genome Atlas (TCGA) dataset was also conducted to explore transcript-level correlations between *lincRNA-p21* and cell cycle–associated genes (*CDKN1A*, *STAT3*, *CDK2*, and *E2F1*).

Altogether, this integrative approach was designed to characterize *lincRNA-p21* expression across clinical and stem-like cellular contexts, aiming to shed further light on its role in GC and to suggest its potential as a biomarker.

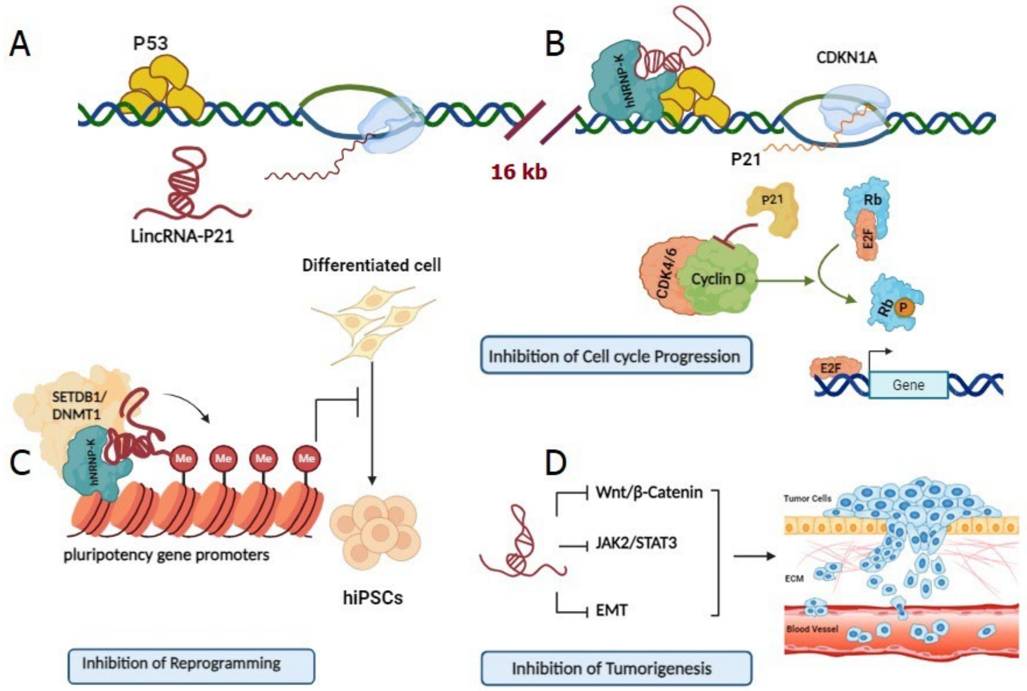

Figure 1. Regulatory mechanisms and functional impact of *lincRNA-p21* in cancer progression (Designed by the authors, 2025, adapted from the concepts reported in references 6, 8–12).

A) *LincRNA-p21* is transcriptionally regulated by tumor- suppressor protein p53.

B) Residing about 16 kb upstream of the *CDKN1A* gene, *lincRNA-p21* interacts with hnRNP-K to induce p21 expression. In turn, p21 controls the G1/S cell cycle checkpoint by inhibiting CDK2 activity, which leads to the repression of the E2F1 transcription factor and subsequent cell cycle arrest.

C) *LincRNA-p21* impedes cell reprogramming by maintaining H3K9me3 histone modifications and CpG-DNA methylation at the promoters of pluripotency-associated genes.

D) It also inhibits pro-oncogenic signaling pathways, including JAK2/STAT3 and Wnt/β-catenin, thereby suppressing EMT, tumor invasion, and metastasis.

2. Materials and Methods

2.1 Patients and Clinical Samples

For this study, a total of 40 pairs of matched gastric adenocarcinoma and adjacent non-tumor tissues were collected from the Iran National Tumor Bank, funded by the Cancer Institute of Tehran University for Cancer Research. For each sample, information on gender, age, tumor site, size, and TNM stage was recorded (Table1).

Tumor staging was determined according to the TNM classification system of the American Joint Committee on Cancer (AJCC), which considers the size and extent of the primary tumor (T), regional lymph node involvement (N), and the presence of distant metastases (M).

Ethical approval for this study was obtained from both Imam Khomeini Hospital, Tehran University of Medical Sciences and Zanjan University of Medical Sciences. Tumor status (diffuse or intestinal) and malignancy grade were confirmed by an expert pathologist through representative formalin-fixed paraffin-embedded (FFPE) sections for each sample.

2.2 Cell Lines and Cell Culture

In this study, we examined *lincRNA-p21* expression across various gastric, esophageal, and breast cancer cell lines, as well as stem-like cells. These included the NTERA2 (NT2) cell line sourced from the Pasteur Institute of Iran, alongside human GC cell lines AGS and MKN45, as well as MDA-MB-231 breast cancer cell line (a triple-negative subtype). Additionally, we utilized FLO-1 and OE-19 cell lines (representing distal esophageal adenocarcinoma) which were generously provided by Prof. Axel Hillmer (Institute of Pathology, University Hospital of Cologne), hiPSC lines; NP-40 and NP-41 kindly provided by Dr. Tomo Saric (Institute for Neurophysiology, University Hospital of Cologne), and human MSCs obtained from Prof. Samad Nadri (Department of Nanotechnology, Zanjan University of Medical Sciences). All cell lines were cultured under their respective standard culture conditions, maintained in either DMEM or RPMI supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37°C in a humidified atmosphere containing 5% CO_2. The hiPSC lines were cultured using E8 medium on the collagen- coated plates.

2.3 RNA Extraction, cDNA Synthesis, and Real-time PCR

Using TRIzol reagent (Invitrogen, USA), total RNA was extracted from tissue samples. DNase I treatment (Takara, Japan) was applied prior to cDNA synthesis using the PrimeScript RT Reagent Kit (Takara, Japan). Using SYBR Premix Ex Taq II (Takara, Japan) and primers (Bioneer, Korea; Table 2), quantitative real-time PCR was carried out on an Applied Biosystems StepOnePlus real-time PCR system (Thermo Fisher Scientific, USA). Each experiment was conducted in at least two independent replicates. PCR efficiency was calculated by means of the LinRegPCR software (ver. 12.x; AMC, Amsterdam; http://LinRegPCR.nl). *B2M* and *GAPDH* served as reference genes for data normalization.

2.4 Data Analysis

Gene expression analysis was conducted using GenEX (Ver. 5; MultiD Analyses AB, Sweden) and GraphPad Prism (Ver. 8; USA). To assess gene expression differences between tumor and non-tumor samples, *lincRNA-p21* expression in each sample was normalized to the sample showing the lowest expression level, and the resulting values were determined on a $\log_2$ scale. In comparative gene expression analyses across various malignancy grades, the fold change values within tumors were calculated relative to the corresponding non-tumor samples by the Pfaffl method, and the difference was analyzed using non-parametric tests (Mann-Whitney U or Kruskal-Wallis test), with the significance threshold set at $p < 0.05$. To assess the discriminatory ability of *lincRNA-p21* between tumor and non-tumor gastric samples, as well as across different malignancy grades the receiver operating characteristic (ROC) curve analysis was performed.

In our research, we investigated key genes associated with *lincRNA-p21*-p21-p53 regulatory axis that contribute to cell cycle regulation and proliferation including *STAT3, CDK2, CDKN1A*, and *E2F1*. The expression levels were evaluated in gastric adenocarcinoma across *TP53*- wild type and mutated *TP53*-mutated samples using the TCGA dataset through the University of Alabama at Birmingham Cancer Data Analysis Portal (UALCAN). As a valuable tool for cancer omics data analysis, UALCAN allows for identification of biomarkers and in silico validation of potential genes of interest through its pan-cancer gene expression analysis feature. (https://ualcan.path.uab.edu/) (15).

Table 1. Clinico-pathological characteristics of the patients with GC.

Category	Subtype	Number
Gender	Female	11
	Male	29
Years (age)	>55	30
	<55	9
Differentiation	Grade I	12
	Grade II	14
	Grade III	14
Lymph Node Metastasis	N0	14
	N1	16
	N2	7
	N3	3
Invasion Depth	T1	2
	T2	5
	T3	33
Distance Metastasis	M0	20
	M1	6
	Unknown	14

Table 2. The primer sequences utilized in this study.

Gene	Product length (bp)	Sequence
LincRNA-p21	79	F: 5′-GGGTGGCTCACTCTTCTGGC-3′
		R: 5′-TGGCCTTGCCCGGGCTTGTC-3′
GAPDH	215	F: 5′-GTGAACCATGAGAAGTATGACAAC-3′
		R: 5′-CATGAGTCCTTCCACGATACC-3′
B2M	161	F: 5′-CAGCAAGGACTGGTCTTTCTATCT-3′
		R: 5′-CGGCATCTTCAAACCTCCAT-3′

F: Forward and R: Reverse primer, *LincRNA-p21*: long intergenic non-coding RNA p21, *GAPDH*: Glyceraldehyde 3-phosphate dehydrogenase, *B2M*: beta-2 microglobulin.

3. Result

3.1 Expression Profile of *lincRNA-p21* in Gastric Samples

In the expression analysis of *lincRNA-p21*, we found that it was detected in 60% of tumor and 51% of non-tumor samples. Interestingly, we observed a significant downregulation of *lincRNA-p21* in tumor samples relative to non-tumor counterparts ($p = 0.01$, Figure 2A).

Moreover, we conducted ROC analysis to determine whether *lincRNA-p21* expression can effectively discriminate between tumor and non-tumor samples. The analysis revealed that *lincRNA-p21* exhibited good/moderate sensitivity in distinguishing between these sample types, as evidenced by an area under the curve (AUC) value of 0.72 and a *p-value* of 0.02 (Figure 2B).

Additionally, we investigated the tumor-to-normal (T/N) fold change of *lincRNA-p21* expression across different histological grades of gastric adenocarcinoma. Our results indicated a consistent decrease in the fold change of gene expression in all tumor grades compared to non-tumor samples (<1), suggesting an early transcriptional downregulation of *lincRNA-p21* in gastric adenocarcinoma. However, no significant differences were observed among the different grades of malignancy (Figure 3A and 3B).

Furthermore, we explored the potential correlation between the expression of *lincRNA-p21* and clinicopathological parameters such as lymph node metastasis (N), invasion depth (T), and distant metastasis (M) however,no significant correlation was found between *lincRNA-p21* expression and these parameters, indicating that *lincRNA-p21* may not be directly associated with the metastatic potential or invasive behavior of gastric adenocarcinoma cells.

3.2 Assessment of *lincRNA-p21* Expression Profile in Cancer and Stem Cell Lines

In this investigation, we employed a diverse panel of cancer and stem-like cell lines to investigate *lincRNA-p21* expression across distinct biological contexts. Specifically, we examined its expression in gastric, esophageal, and breast cancer cell lines, alongside the pluripotent and multipotent stem cell models. This comparative analysis was designed to evaluate whether *lincRNA-p21* is differentially expressed between cancer cells and stem cell populations, providing insight into its potential role in regulating stemness and tumorigenicity, in accordance with the cancer stem cell hypothesis. Our assessment revealed consistently low levels of *lincRNA-p21* expression across all examined cell lines, with an average Ct value of 33 ± 1.0. As expected, the expression of *lincRNA-p21* was markedly reduced in all cancer cell lines (AGS, MKN45, FLO-1, OE-19, MDA-MB-231, and NT2), as well as in stem cells (MSCs and hiPSCs; NP40 and NP41), when compared with normal gastric tissue samples (Figure 4).

3.3 Analysis of Expression Patterns of Genes Involved in Cell- Cycle Regulation

We further investigated the genes regulated by the *lincRNA-p21*-p21-p53 axis, including *CDK2, E2F1*, and *STAT3*, in gastric adenocarcinoma using data from the TCGA dataset through the UALCAN portal. The analysis demonstrated a notable increase in the expression of *CDK2*, *E2F*, and *STAT3* genes, consistent with their roles in promoting cell-cycle progression and tumor proliferation. Also, a decreased expression of *CDKN1A* was obtained in both *TP53*-mutated and *TP53*–wild type gastric adenocarcinoma compared with non-tumor samples (Figure 5).

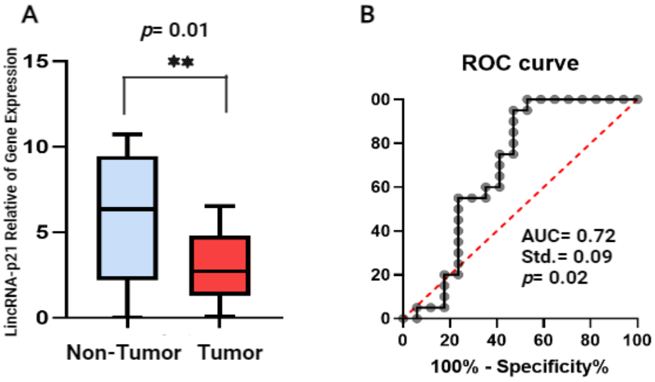

Figure 2. Analysis of *lincRNA-p21* expression levels in gastric tumor versus non-tumor samples (Designed by Authors, 2025).

A) Histograms illustrate the median values of relative gene expression in tumor (n=20) and non-tumor (n=18) samples with error bars representing the 95% confidence interval. The statistical significance between groups was assessed using an unpaired Student's t-test. As shown, the expression of *lincRNA-p21* was significantly reduced in tumor compared to non-tumor samples ($p \leq 0.01$). B) ROC analysis confirmed the discriminatory ability of *lincRNA-p21* expression in distinguishing tumor from non-tumor samples.

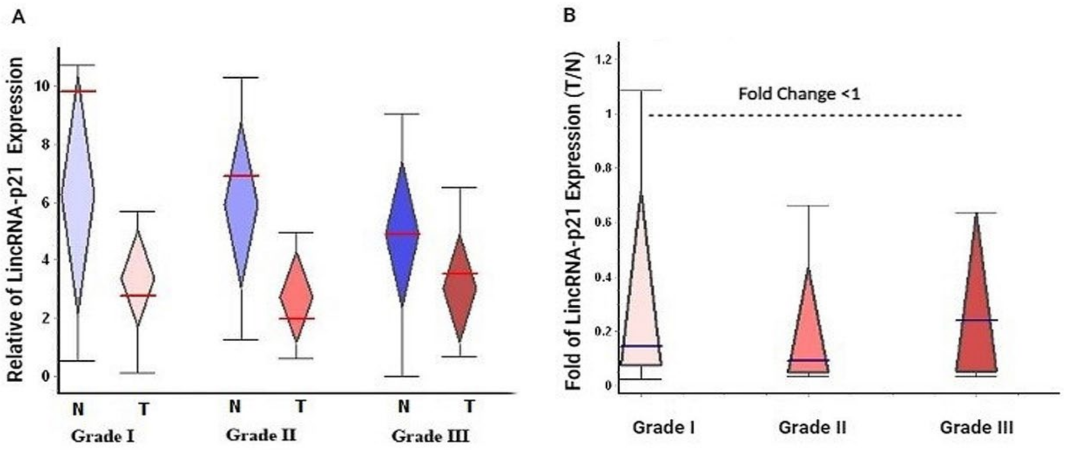

Figure 3. Analysis of *lincRNA-p21* expression level in gastric adenocarcinoma with various grades of malignancy (Designed by Authors, 2025).

A) Comparison of gene expression levels between tumor and adjacent non-tumor tissues across histological grades of gastric adenocarcinoma. B) The median fold change in gene expression between tumor and non-tumor samples demonstrates consistently reduced expression (fold change < 1) across all malignancy grades.

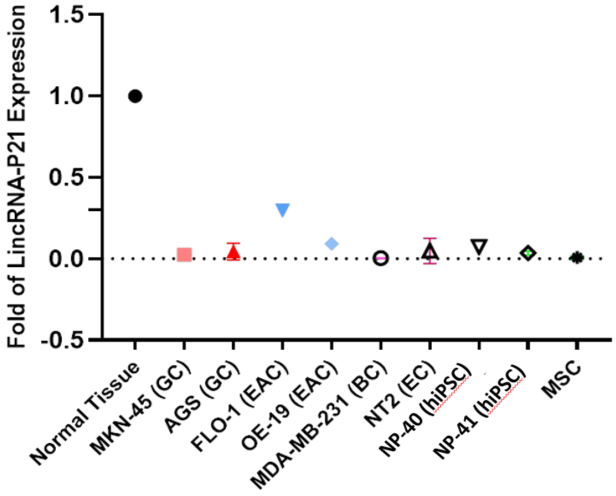

Figure 4. Differential expression of *lincRNA-p21* across multiple cell lines (Designed by Authors, 2025).

The histograms depict the median fold change in *lincRNA-P21* expression across different stem cell types (MSCs, hiPSCs and NTERA2) and various cancer cell lines (gastric, esophageal, and breast cancer cell lines). It is evident that the gene expression levels of *lincRNA-P21* in all cell lines was significantly lower compared with normal gastric tissue samples ($P<0.001$). GC: gastric cancer; EAC: esophageal adenocarcinoma; BC: breast cancer; EC: embryonic carcinoma.

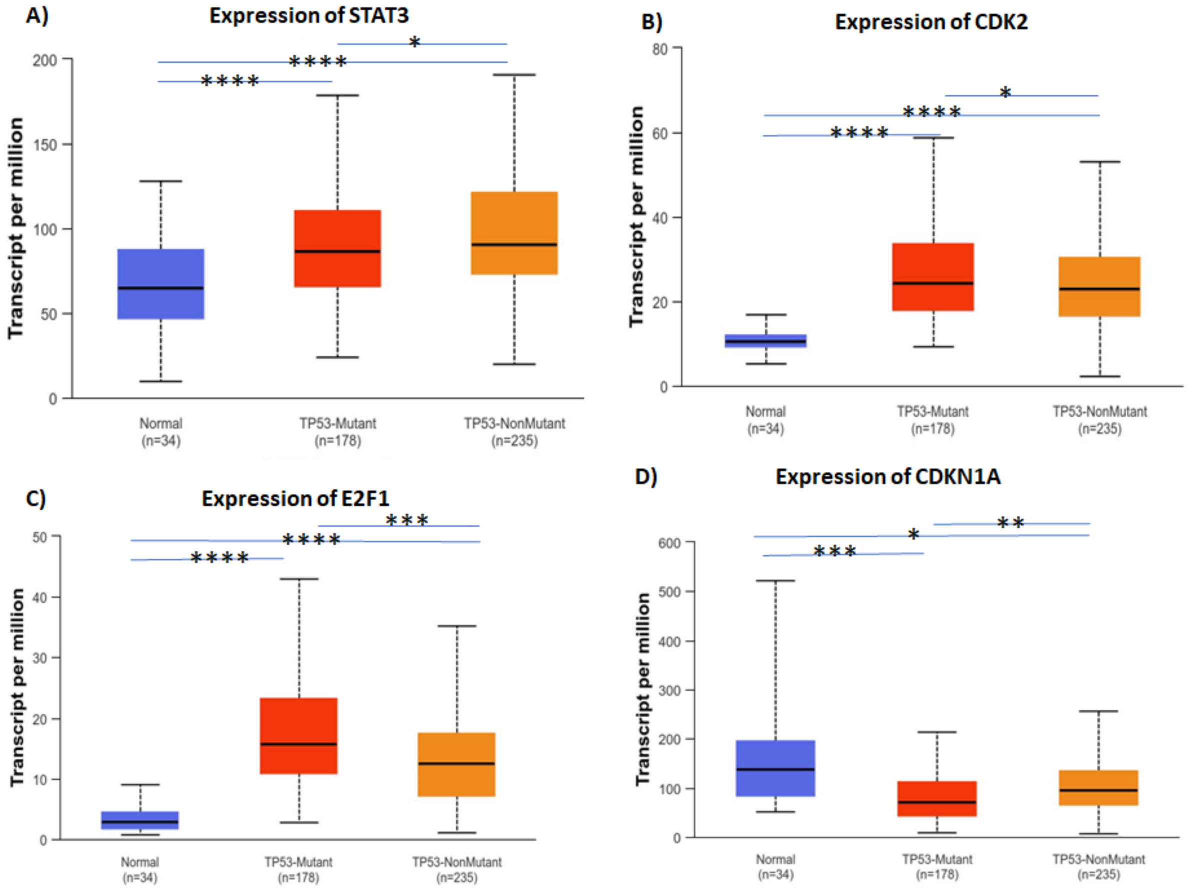

Figure 5. Analysis of *CDK2*, *E2F1*, and *STAT3* expression involved in cell cycle regulation in gastric adenocarcinoma (**Adapted from data source: UALCAN portal, https://ualcan.path.uab.edu/**).

TCGA data analysis (UALCAN portal) showed a significant increase in the expression of *STAT3* (A), *CDK2* (B), and *E2F1* gene(C), along with a significant decrease in *CDKN1A* expression (D) in both *TP53–mutated* and *TP53–wild type* gastric adenocarcinoma compared with non-tumor samples.

4. Discussions

Our investigation revealed a significant downregulation in the *lincRNA-p21* expression in gastric tumor tissues compared to adjacent non-tumor samples (p = 0.01). ROC curve analysis effectively discriminated tumor from non-tumor samples, supporting our findings. This result aligns with recent reports showing decreased *lincRNA-p21* expression across various cancers, including skin tumors **(16)**, hepatocellular carcinoma **(17)**, colorectal cancer **(18)**, prostate cancer **(19)**, and chronic lymphocytic leukemia **(20)**.

Given that *lincRNA-p21* is located upstream of the *CDKN1A* gene, it is thought to modulate p21 expression. Therefore, its downregulation may contribute to reduced p21 levels **(12, 13)**. Consistent with this hypothesis, our previous research using both qRT-PCR and immunohistochemistry demonstrated a marked reduction in *CDKN1A* gene expression in gastric tumor samples **(14)**, further supporting our current findings.

Moreover, *lincRNA-p21* expression exhibited a notable decrease across different tumor grades, suggesting a potential association between its reduction and tumor initiation and its possible role as a biomarker for early detection of malignancy. Conversely, some studies report tumor-promoting functions of *lincRNA-p21*, including the facilitation of the Warburg effect and stabilization of HIF-1α **(21)**, indicating its context-dependent functionality.

Given its regulatory roles in cell cycle control and programmed cell death, the concurrent downregulation of *lincRNA-p21* and p21 may contribute to GC tumorigenesis. Chen et al **(22)** demonstrated that *lincRNA-p21* is downregulated in GC tissues and cell lines. Ectopic expression of *lincRNA-p21* inhibited cell proliferation and migration by suppressing β-catenin and c-Myc expression thereby, supporting its tumor-suppressive function **(22)**. These findings further support the tumor-suppressive role of *lincRNA-p21* and highlight its potential therapeutic relevance alongside its value as a diagnostic biomarker in GC.

Importantly, our findings also revealed reduced *lincRNA-p21* expression in both stem-like and cancer cell lines, suggesting a distinct expression pattern within this population. This observation is consistent with the proposed role of *lincRNA-p21* in repressing the expression of pluripotency associated genes through promoter methylation, a critical process in the p53-p21 pathway. Such insights could advance our understanding of the molecular regulation of cancer stem cells which play a key role in tumor recurrence and therapy resistance **(10, 23, 24)**.

However, despite previous studies reporting correlations between *lincRNA-p21* expression and TNM staging, we did not observe a significant association within our cohort **(16, 25, 26)**. This discrepancy might be attributable to limited sample size, tumor heterogeneity, or methodological differences and therefore warrants further exploration.

Our gene expression analysis of *CDK2*, *E2F1*, and *STAT3* — main effectors within the *lincRNA-p21*–p21–p53 regulatory axis — revealed altered expression patterns in gastric adenocarcinoma. Specifically, we found elevated expression of *STAT3*, *CDK2*, and *E2F1* alongside reduced *lincRNA-p21* and p21, indicating potential dysregulation in cell cycle control and increased tumorigenicity. Moreover, expression analyses in both *TP53*-mutant and *TP53*-wild type samples suggests that additional regulatory mechanisms beyond *TP*p53 mutation may drive these changes, underlining the complexity of GC biology. While our findings provide important preliminary insights, future studies would benefit from incorporating functional assays, particularly in stem-like cell lines, to better define the mechanistic role of *lincRNA-p21*.

5. Conclusion

In summary, our study reveals a significant decrease in *lincRNA-p21* expression in gastric tumors, suggesting its potential contribution to the development and progression of gastric adenocarcinoma. This pattern, observed across different malignancy grades, underscores its potential utility as a biomarker for early diagnosis and prognosis. Furthermore, the dysregulation of the *lincRNA-p21*–p21–p53 axis and associated genes (*STAT3*, *E2F1*, *CDK2*) illuminates the underlying molecular mechanisms in gastric tumorigenesis.

6. Declarations

6.1 Acknowledgments

The samples utilized in this investigation were collected from the Iran National Tumor Bank, with funding support from the Cancer Institute of Tehran University for Cancer Research. We express our appreciation to Dr. Forouzandeh Fereidooni, the former head of the Iran Tumor Bank, as well as Dr. Fatemeh Kamali and Dr. Emamian for their contributions in providing clinical samples and supplying clinicopathological information from patients registered in the Iran Tumor Bank (Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran). Special acknowledgment is extended to Dr. Masoud Sotoudeh (Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran) for verifying the malignancy grades. Additionally, we extend our sincere thanks to Prof. Axel Hillmer, Dr. Tomo Saric (University of Cologne, Cologne, Germany) and Prof. Samad Nadri (Zanjan University of Medical Sciences) for generously providing EAC cell lines, hiPSCs and MSCs respectively.

6.2 Ethical Considerations

All procedures were conducted in accordance with relevant laws and institutional guidelines, following approval from the appropriate institutional committees. Specifically, the research received ethical approval from both the Ethics Committee of Zanjan University of Medical Sciences (ZUMS) and the Ethics Committee of Imam Khomeini Hospital, Tehran University of Medical Sciences (Approval ID: ZUMS.REC.1394.303). Informed consent was obtained from all participants involved in the study, and their privacy and confidentiality were strictly maintained.

6.3 Authors' Contributions

All authors contributed to the study conception and design. Mitra Khalili conceived and designed the study, analyzed and interpreted the data, and wrote the manuscript. Somayeh Jahandoust and Pourandokht Farhangiyan, as MSc students in Medical Genetics, performed all experiments under the supervision of Mitra Khalili. All authors read and approved the final manuscript.

6.4 Conflict of Interest

The authors have no conflict of interest.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors did not use any AI tools for writing this manuscript.

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