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Original scientific article

HOTAIR/MIR1 AXIS ACTS AS A POTENTIAL CHEMOTHERAPY TARGET IN GASTRIC CANCER

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Gastric cancer is one of the most common cancers in the world. Delayed diagnosis is the most common cause of death in patients. Long noncoding RNAs (lncRNAs) are a group of non-coding RNAs that are effective in the incidence of cancers. Studies in different cancers determined *HOTAIR* as an important lncRNA in tumorigenesis. In gastric cancer, the function of *HOTAIR* in the initiation and progression of cancer seems to be crucial. In this study, we confirmed the significant differential expression of *HOTAIR* between gastric tumors and normal tissues in different datasets. In the following, the regulatory function of *HOTAIR* and its interaction with miRNAs in development of gastric cancer was analyzed. Our analysis determined that the upregulation of *HOTAIR* is essential to different pathways associated with the progression of gastric cancer. Further analysis determined numerous miRNAs as potential targets for *HOTAIR*. Among them, we demonstrated *miR-1* as a significant miRNA with negative correlation with *HOTAIR* in gastric tumors. Validation analysis determined that *HOTAIR* is a target of cisplatin as a common chemotherapy drug. Eventually, the effect of cisplatin on the expression of *HOTAIR* and its potential target, *miR-1*, was checked by an *in vitro* study. Cisplatin treatment on the gastric cancer cell line showed that there is a significant negative correlation between the downregulation of *HOTAIR* and the upregulation of *miR-1* in

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treated cells. In conclusion, comprehensive *in silico* analysis and experimental study provided evidence for the importance of the *HOTAIR/miR-1* axis as potential diagnostic and treatment strategies for gastric cancer.

Keywords: cisplatin, gastric cancer, *HOTAIR*, *miR-1*, non-coding RNA

INTRODUCTION

Gastric cancer is the fifth most common type of cancer and one of the most important causes of cancer-related deaths in the world. Approximately 80% of patients are diagnosed with advanced stages, and chemotherapy is considered to be the main treatment for patients (CORREA, 2013; WAGNER *et al*., 2017; NECULA *et al*., 2019). Cisplatin is one of the most well-known chemotherapy drugs and plays an essential role in different regimens for advanced gastric tumors. The prominent antitumor effect of cisplatin is binding to Purine bases on the DNA and inducing apoptosis in cancer cells (DASARI and TCHOUNWOU, 2014). Cisplatin alters cell cycle, DNA synthesis, proliferation, as well as some other cellular and molecular processes. Recent studies show that different genes are effective in regulation of cisplatin response processes. However, the regulatory mechanism by which cisplatin induces apoptosis and inhibits cancer cell proliferation remains unclear (WANG *et al*., 2016; VELMA *et al.*, 2016).

Nowadays, non-coding RNAs(ncRNAs) are considered as potential cancer biomarkers as well as potential markers for the detection of drug response in cancers (WANG *et al*., 2019). ncRNA is a functional RNA molecule that is transcribed from DNA but not translated into protein. ncRNAs are usually classified by size and divided into two groups of less than and more than 200 nucleotides(WANG *et al*., 2017). Studies show that interactions between ncRNAs can play a role in regulating the expression of genes involved in cancer; and so may play a role in the treatment of cancers (PENG and CROCE, 2016; WANG *et al*., 2018; HE *et al*., 2019). One of the most well-known interactions is the sponge role of long non-coding RNAs (lncRNAs) in regulating the expression of target genes of microRNAs (miRNAs). LncRNAs compete with miRNA target genes and alter the miRNA regulatory effect (HUANG *et al*., 2019). HOX Transcript Antisense Intergenic RNA (*HOTAIR*) is an lncRNA by 2.2 kb length. *HOTAIR* is associated with the regulation of genes in different pathways. *HOTAIR* usually act through interaction with polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1 (LSD1) complexes causing regulation transcription of target genes (HAJJARI and SALAVATY, 2015).

Additionally, recent studies determined that *HOTAIR* can regulate transcription of genes with competing endogenous RNA(ceRNA) function. For example, *HOTAIR* plays an important role in the progress of gallbladder cancer by regulating the expression of *MYC* by sponge effect on miR- 130a (MA *et al*., 2014). The regulatory oncogenic function of *HOTAIR* and the effect of cisplatin on *HOTAIR* expression are not well studied in gastric cancer.

Following previous studies revealing the potential role of *HOTAIR* in gastric cancer development and progression, the current study was aimed to validate its role through large number of tissues. In this study, comprehensive *in silico* analyses were used to identify the differential expression of *HOTAIR* and its role in different biological processes in gastric cancer. Furthermore, due to the importance of the ceRNA network in the regulation of different pathways, the ceRNA network of *HOTAIR* in gastric cancer was analyzed. The correlation

between *HOTAIR* and target miRNAs in gastric tumors was also evaluated. Also, as cisplatin is a first-line chemotherapeutic drug for gastric cancer, the effect of this drug on *HOTAR* expression as well as its correlation with *miR-1*, as a potential target of *HOTAIR*, was investigated by *in silico* and validated by *in vitro* study.

MATERIALS AND METHODS

Microarray analysis for Gene expression

Gene Expression Omnibus (GEO) [http://www.ncbi.nlm.nih.gov/geo/] (EDGAR *et al*., 2002) database is an international repository archives of microarray data. In this study, we used the GEO2R web tool to investigate the differences in expression of candidate lncRNAs between gastric tumors and normal samples. The 5 public microarray datasets were analyzed. The datasets were GSE13911, GSE26942 (untreated samples), GSE37023, GSE54129, and GSE66229 which included 558 tumors and 200 normal control samples. Adj.p-value < 0.05 was considered as significant.

RNA-seq analysis for Gene expression

GREIN [http://www.ilincs.org/apps/grein /? gse =] (MAHI *et al*., 2019) is an interactive web platform to analyze the GEO RNA-seq datasets. In this study, we used this web platform to analysis GSE122401 including 80 tumors and 80 normal samples. Adj.p-value < 0.05 was considered as significant.

Identification of functions and pathways affected by lncRNA HOTAIR

LncTarD [http://biocc.hrbmu.edu.cn/LncTarD/index.jsp] is a comprehensive database of experimentally supported for analyzing the function of lncRNAs in different diseases. We used this database to find the functions in which *HOTAIR* is involved in gastric cancer.

Prediction of lncRNA-miRNA interaction

ENCORI [http://starbase.sysu.edu.cn] is the updated version of StarBase database that presents the perfect comprehensive network from CLIP-Seq data sets by predicted sequences overlapping with CLIP-Seq peaks. We used this database to build the ceRNA network based on the HOTAIR-miRNA interactions.

Identification of lncRNA-miRNA co-expression

ChIPBase v2.0 [http://rna.sysu.edu.cn/chipbase/] is an open database that uses ChIP-seq data to provide a network of transcription factors that affect non-coding RNAs. On the other hand, using more than 20,000 samples (9,900 miRNA-seq and 10,300 RNA-seq data from 32 different cancers), it is a useful tool for co-expression analysis. This database was used to find the degree of co-expression between lncRNA-miRNAs. P-value < 0.05 was considered as significant.

Identification of cisplatin-associated lncRNAs

D-lnc[http://www.jianglab.cn/D-lnc/] is a comprehensive query and analysis platform to detect the experimentally validated and the computationally predicted modification of drugs on

lncRNA expression. In this study, we used this database to investigate the effect of cisplatin on the expression of lncRNAs in cancer.

Cell culture

The human gastric cancer cell line AGS was obtained from the Pasteur Institute of Iran (Tehran, Iran). AGS cells were cultured in RPMI 1640 medium with 10% of fetal bovine serum (FBS) and 1% Penicillin-Streptomycin (PenStrep). The cells were incubated at 37 ° C and 5% CO2. All cell culture solutions were preheated to 37°C before use. Cell growth was monitored using an inverted microscope. Cells in the logarithmic growth phase were cultured for further analysis.

MTT assay

Among the various methods used to measure cell viability, the MTT assay is considered to be the most popular method. In this study, we used the MTT assay to understand the effect of cisplatin treatment on cell viability and to detect IC50 concentration in 48 hours. Initially, 5×10^3 cells were cultured in each well of a 96-well plate. The next day, after cell proliferation and adequate cell confluency, treatment was performed in 1.5, 3, 6, 12, and 24 µM concentrations of cisplatin, and control was provided on the protocol of drug manufacturer (Ribosepharm, Germany). After 48 hours of treatment, the medium was discarded and 30 µl of MTT solution (at a concentration of 0.5 mg/ml in PBS) was added to each well. After 4 hours of plate incubation, 120 µl of DMSO was added to each well. Finally, the plate was shaken for 20 minutes and read at 570 nm by ELISA reader.

RNA extraction

To provide adequate cells for the extraction of RNA, we cultured 120×10^3 cells in a 6-well plate. After 24 hours, AGS cells were treated in 4 and 8 µM of cisplatin and control in distinct wells. Cells were harvested 48 hours after treatment. For RNA isolation, we used RNX-plus reagent (Cinnagen, Iran) to extract the total RNA according to the protocol provided by the manufacturer. Extracted RNA was stored at -80 °C.

cDNA synthesis for HOTAIR and HPRT1 as endogenous control

The extracted RNA was treated with DNaseI (Sigma) and complementary DNA (cDNA) was synthesized in 10 µl reaction using random hexamer and oligo (dT) primers by the reverse transcription Kit (Takara, Japan) and the synthesis was performed according to the manufacturer's protocol.

cDNA synthesis for miR-1 and SNORD as endogenous control

The stem-loop Primer method was used to synthesize the *miR-1* and *SNORD*. In this approach, specific stem-loop RT primers were used in the cDNA synthesis process. The stem-loop RT primers were as follows: miR-1-RT: 5′-GTCGTATCCAGTGCAGGGTCCGAGGTGCACTGGATACGACATACAT-3′, SNORD-RT:5′-GTCGTATCCATCAGGGTCCGAGGTATTCGCACTGGATACGACAACCTC-3′.

Reaction was performed under the following conditions: 30 minutes at 16°C, 30 minutes at 42°C and Finally, it was incubated for 5 minutes at 85 ° C to inactivate the enzyme.

Real-time PCR

Quantitative real-time PCR was performed with a step-one Real-time PCR system (Applied Biosystems, Foster City, CA, USA). Reaction mixture (10 µL) containing 1 µL of cDNA and 5 µL of 2X SYBR-Green PCR Mix (Takara, Shiga, Japan) was used in addition to 0.5 µL of each sense and antisense primers. Amplifications were performed as follows: primary denaturation for 5 minutes at 95° C followed by 40 cycles of denaturation at 95° C for 5 s and annealing/extension at 60° C for 30 s. Primers were designed by Gene Runner software (version 6.0; http://www.generunner.net/) and Primer-Blast (https://www.ncbi.nlm.nih.gov/tools/primer-blast/). The primers were mentioned in Table1.

Table1. Details of primers used in this study

Target gene	Primer name	sequence
HOTAIR	F	5′- AGGCCCTGCCTTCTGCCT-3′
	R	5′- TGCTCTCTTACCCCCACGGA-3′
HPRT1	F	5′-GGACTTTGCTTTCCTTGGTCAG-3′
	R	5′- GTCAAGGGCATATCCTACAACA-3′
miR-1	F	5′-GGTTGCGGTGGAATGTAAAGAAG-3′
	R	5′-CAGTGCAGGGTCCGAGGT-3′
SNORD	F	5′-ATCACTGTAAAACCGTTCCA-3′
	R	5′-GTGCAGGGTCCGAGGT-3′

F: forward; R: reverse

Statistical analysis and Construction of the regulatory network

Expression analysis was performed using the Two-way ANOVA test and correlation analyses were estimated by Pearson's correlation coefficient. All statistical tests and heatmaps were analyzed by Graphpad Prism 8 software. In our analysis, the p-values less than 0.05 were considered as significant. Subsequently, the network of *HOTAIR*-related functions was constructed using Cytoscape software (version 3.6.1). Three biological replicates were performed to ensure the accuracy of the results.

RESULTS

HOTAIR is upregulated in gastric tumors

Analysis of datasets determined that the expression of *HOTAIR* is increased in several tumor datasets in comparison to normal tissues (Table2). Through this in silico study, we found that up-regulation of *HOTAIR* in gastric tumors maybe indicates its potential role in gastric cancer progression.

Table 2. Expression of HOTAIR in gastric cancer datasets (adj. p-value < 0.05)

Dataset	LogFC	Adj.p-val
GSE 13911 GPL570	1.899	5.02e-04
GSE 26942 GPL6947	0.373	2.45e-03
GSE 37023 GPL97	0.404	1.13e-02
GSE 54129 GPL570	0.541	9.45e-03
GSE 66229 GPL570	0.346	9.58e-17
GSE122401	4.203	5.729E-18

Adj.p-val: adjusted p-value; LogFC: log2 foldchange

Biological function of HOTAIR in gastric cancer

The upregulation of *HOTAIR* in gastric cancer may be effective in cancer-related processes. This led us using the LncTarD database providing great data to the biological functions of lncRNAs in different diseases. This database upon validated data showed that different processes such as cell invasion, cell migration, and chemoresistance are under the influence of *HOTAIR* in gastric cancer (Figure1).

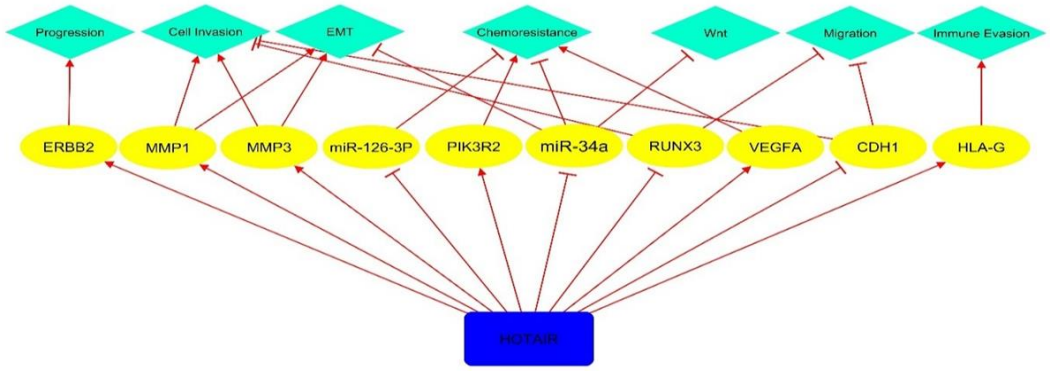

Figure 1. *HOTAIR* plays a crucial role in regulating different pathways that are essential to tumorigenesis and chemoresistance in gastric cancer

miR-1 as a potential target for HOTAIR in gastric cancer

Interaction between lncRNAs and miRNAs is effective in gene expression regulation, but the network of *HOTAIR*-miRNAs interactions and its role in gastric cancer tumorigenesis is not clear. Based on the ENCORI database, *HOTAIR* could interact with 30 miRNAs, and so it may have effect on the expression of their target genes. The co-expression between *HOTAIR* and predicted miRNAs was measured through the CHIPBASE database. Among the miRNAs, Co-expression analysis of *HOTAIR* and miRNAs showed that there is a significant negative correlation between *HOTAIR* and *miR*-1 in gastric tumor samples (Figure2).

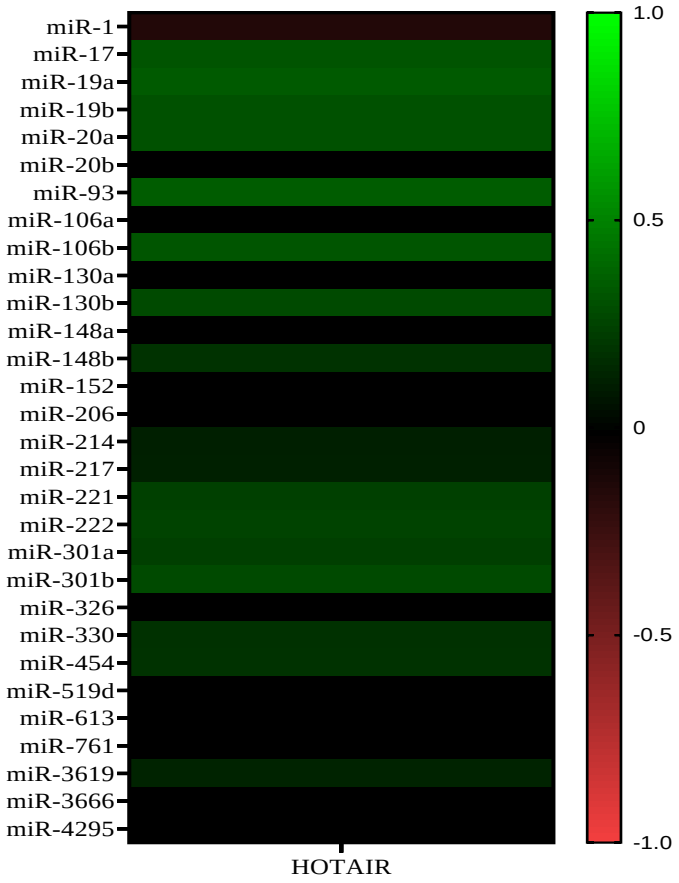

Figure 2. Co-expression between *HOTAIR* and target miRNAs in gastric tumors. Between 465 tumor samples, there is a significant negative correlation between *HOTAIR* and *miR*-1. This result showed that the upregulation of *HOTAIR* is a regulatory mechanism for *miR*-1 dependent pathways in gastric cancer. (*p-value* < *0.05*)

HOTAIR as a target for cisplatin function

The effect of chemotherapy on the expression of *HOTAIR* in gastric cancer is unclear. Between different chemotherapy drugs used for gastric cancer cases, cisplatin is very common in chemotherapy regimens. Analysis with the D-lnc database on the effect of chemotherapy on the expression of lncRNAs revealed that *HOTAIR* was downregulated by cisplatin. This data showed that *HOTAIR* may play an important role in tumor inhibition by cisplatin treatment. Therefore, according to the importance of cisplatin in gastric cancer chemotherapy, the effect of cisplatin on the expression of *HOTAIR* and *miR*-1- as potential target in gastric cancer- was selected for more studies.

HOTAIR and miR-1 are differentially expressed following exposure to cisplatin

Sensitivity of the AGS cell line to cisplatin in 48 hours was determined by MTT assay and IC50 was evaluated at the concentration of 5.832 μM. Then, to investigate the effect of cisplatin on *HOTAIR* and *miR-1*, AGS cells were treated in two concentrations 4 and 8 μM of cisplatin, and the expression of *HOTAIR* and *miR-1* were compared with the corresponding control. Our results showed a decrease in *HOTAIR* expression and an increase in *miR-1* expression in different concentrations of cisplatin compared to the control (Figure3). Correlation between *HOTAIR* and *miR-1* was calculated using Pearson's correlation. We found a significant negative correlation between the expression of *HOTAIR* and *miR-1* in AGS treated cells. The correlation coefficient was -0.84 (p-value <0.0001).

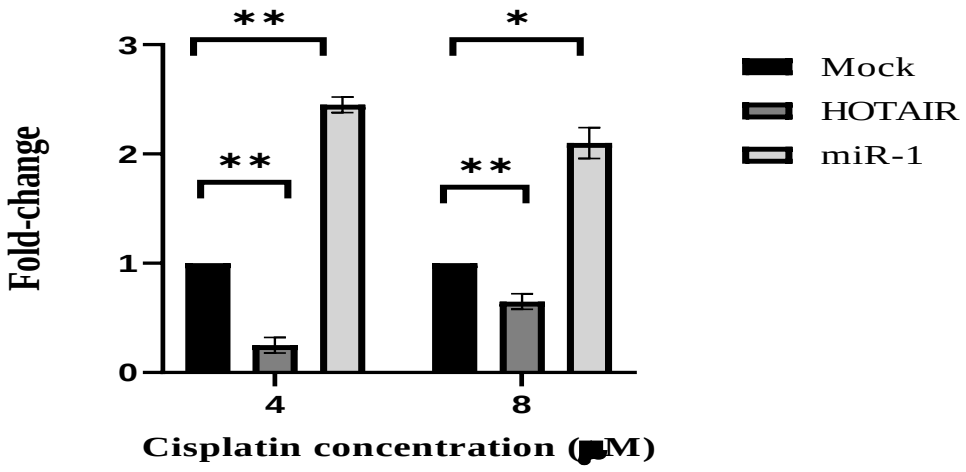

Figure 3. *HOTAIR* and *miR-1* expression analysis. Quantitative real-time PCR results by using equation $2^{-\Delta\Delta Ct}$ through the Two-way ANOVA test analyzed. The result showed the *HOTAIR* expression was significantly downregulated, and *miR-1* expression was significantly upregulated in treated cells. Data are expressed as mean ± SD (*$P \leq 0.05$, and **$P \leq 0.01$)

DISCUSSION

Among different cancers, gastric cancer is one of the most causes of death.(SITARZ *et al*., 2018) Different studies verified many lncRNAs function as oncogene or tumor suppressor in gastric cancer(TIAN *et al.*, 2017). Several studies show that increased expression of *HOTAIR* is associated with the incidence and progression of gastric cancer (HAJJARI *et al*., 2013; XU *et al*., 2019). Our analysis by bioinformatics databases and tools revealed that *HOTAIR* is an oncogene in gastric cancer. Through a comprehensive analysis of datasets including large number of tissues, we demonstrated that the up-regulation of *HOTAIR* maybe has a potential role for the prognosis of cancer.

Previous studies have reported that lncRNAs can play important roles in the regulation of many pathways in gastric cancer (YU and RONG, 2018). Our bioinformatics analysis also showed that *HOTAIR* has a foundational effect in gastric cancer. *HOTAIR* can play a role in regulating various processes by creating a network of interactions. This extended network includes non-coding RNAs and key genes involved in regulating important pathological processes. Indeed, changes in *HOTAIR* expression can activate or suppress a chain of different processes. Identified *HOTAIR* interactions with gene expression regulators are correct methods for recognition of the function of *HOTAIR*. Different studies determined that *HOTAIR* acts as an miRNA sponge to regulate different pathways in cancer (MA *et al*., 2014). Our analysis through ENCORI and CHIPBASE databases revealed that *HOTAIR* can act as a sponge for many miRNAs. Among them, there is a significant negative correlation between *HOTAIR* and *miR-1* in gastric tumors. This negative correlation is a potential marker of tumorigenesis.

Cisplatin is a first-line chemotherapy drug for gastric cancer patients. Cisplatin, like other platinum drugs inducing apoptosis, is effective in suppressing of cancer. Previous studies showed different processes such as EMT play a critical role in the efficiency of cisplatin in gastric cancer chemotherapy (TAKASHIMA *et al*., 2009; HUANG *et al*., 2016). Our analysis demonstrated cisplatin has the potential to influence *HOTAIR* expression. In the following, our experimental result showed a decrease in *HOTAIR* expression due to cisplatin treatment on gastric cancer cells. *HOTAIR* is effective on various pathways, and it is an opportunity for cisplatin to regulate different pathways with the suppression of *HOTAIR* expression. On the other hand, our results revealed that the expression of *miR-1* was upregulated in AGS-treated cells and showed a significant negative correlation with *HOTAIR*. Thus, the *HOTAIR/miR-1* axis beside, the potential function to induce tumorigenesis, may play an important role in targeted therapy of gastric cancer.

CONCLUSION

This study is a beginning for future studies to explore the role of *HOTAIR* in progression and chemotherapy response in gastric cancer patients. The effect of *HOTAIR* on different pathways regulated by cisplatin is necessary to explore the role of *HOTAIR* on the efficiency of chemotherapy. On the other hand, our result determined that *HOTAIR/miR-1* axis has a potential role in tumorigenesis and a target for chemotherapy in gastric cancer. Focuses on this interaction may be an aid to discover new methods of gastric cancer treatment.

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HOTAIR/MIR1 OSA DELUJE KAO POTENCIJALNI CILJ HEMOTERAPIJE KOD RAKA ŽELUCA

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Izvod

Rak želuca je jedan od najčešćih karcinoma na svetu. Odložena dijagnoza je najčešći uzrok smrti pacijenata. Duge nekodirajuće RNK (lncRNA) su grupa nekodirajućih RNK koje su efikasne u detekciji karcinoma. Studije različitih karcinoma su utvrdile *HOTAIR* kao važnu lncRNA u tumorigenezi. Kod raka želuca, funkcija *HOTAIR*-a u započinjanju i progresiji raka izgleda da je ključna. U ovoj studiji smo potvrdili značajnu diferencijalnu ekspresiju *HOTAIR*-a između tumora želuca i normalnih tkiva u različitim skupovima podataka. U nastavku je analizirana regulatorna funkcija *HOTAIR*-a i njegova interakcija sa miRNA u razvoju karcinoma želuca. Naša analiza je utvrdila da je povećanje regulacije HOTAIR-a od suštinskog značaja za različite puteve povezane sa progresijom raka želuca. Daljom analizom utvrđene su brojne miRNA kao potencijalne mete za HOTAIR. Među njima, pokazali smo miR-1 kao značajnu miRNA sa negativnom korelacijom sa HOTAIR-om u tumorima želuca. Validirana analiza je utvrdila da je HOTAIR meta cisplatina kao uobičajenog leka za hemoterapiju. Na kraju, efekat cisplatina na ekspresiju HOTAIR-a i njegove potencijalne mete, miR-1, proveren je in vitro studijom. Tretman cisplatinom na ćelijskoj liniji raka želuca pokazao je da postoji značajna negativna korelacija između smanjenja HOTAIR-a i povećanja regulacije miR-1 u tretiranim ćelijama. U zaključku, sveobuhvatna in siliko analiza i eksperimentalna studija pružili su dokaze o važnosti HOTAIR/miR-1 ose za dijagnostičke i strategije lečenja raka želuca.

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