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The Effect of siRNA Transfection on the ARID3A and ERIC3A Gene Expression in Various Cell Lines Invitro

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ABSTRACT

Background: *Thousands of distinct long non-coding RNAs are encoded in the human genome, and it is becoming clear that these transcripts play a crucial role in controlling gene expression and cell destiny. However, the transcriptional control of their expression is not well understood. The long noncoding RNA E2f1-regulated inhibitor of cell death (ERICD) is essential for inducing both cell death and proliferation and is a critical downstream target of the tumor suppressor. However, E2F-dependent transcription is triggered by ARID3A's binding to the E2F transcription factor.* ***Aim of the study:*** *Detection of the expression level of ARID3A and ERICD by transfection of siRNA and comparison with normal and negative control.* ***Material and methods:*** *Osteosarcoma cells (U2OS) were performed for ERICD and ARID3A expression. Experiments including overexpression and knockdown of ARID3A and a knockdown of ERICD were conducted. Assays for colony development and migration were also carried out in U2OS. SiRNA were used by performing FASTA program from PubMed and used for the inhibition of both ERICD and ARID3A in U2OS. Extraction of mRNA from U2OS then converting to cDNA by using random primer then qPCR was used for detection of bands.* ***Results:*** *This investigation demonstrated that is the indirect pathway through which ARID3A and ERICD interact. In addition, ERICD and ARID3A exhibit carcinogenic properties in osteosarcoma. The discovery of a unique interaction between the ERICD and ARID3A marks a significant advancement in the understanding of lncRNAs that target DNA-binding proteins.*

Conclusion: *The siRNA-mediated knockdown of ARID3A and ERICD significantly decreased colony formation and hindered cell migration in U2OS. Conversely, overexpression of ARID3A verified a noteworthy enhancement in wound closure and heightened capacity of U2OS cells to form colonies. ARID3A and ERICD have roles in transcription factors for the expression of cancer cells. During the transfection of siRNA, both genes inhibited cancer cells. ERICD when compared with non-transfected normal cells showed a significant decrease in the level.*

Keywords: siRNA Transfection , ARID3A and ERIC3A Gene .

Article Information

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INTRODUCTION

The term "cancer" refers to a broad category of illnesses, but one of their commonalities is the development of aberrant cells that proliferate beyond their normal limits. Since carcinogenesis is a multistage process, normal cells eventually become neoplastic and develop unique properties that make them tumorigenic during this time [(1)]. Uncontrolled cell proliferation is one of the characteristics of the cancer class of disorders and considered a global public health concern of great importance. As a result of mistakes in the genes that regulate essential biological functions, including cell division and proliferation, cancer is a hereditary illness. Proto-oncogenes, tumor suppressor genes, and DNA repair genes are the three main gene groups that are impacted by genetic alterations that lead to cancer [(2)]. Cancer types usually differ between both sexes, for example male most commonly get lung, prostate, colon,

rectum, abdominal, and liver cancer, while females most commonly develop breast, colon, rectum, lung, cervix, and stomach cancer [3,4]. For instance, in the United States, the lifetime risk of cancer is around 44% for males and 38% for women [5].

ARID4A and ARID4B are the two members of the fourth mammalian ARID subfamily. The ARID region of these proteins exhibits 74% commonality, and the complete length of each protein displays 40-50% similarity. It has been determined that ARID4A is an E2F transcription repressor that is attracted to pRb [6,7]. ARID4A is expressed extensively. Only the testis expresses ARID4B abundantly; expression in normal tissue is severely restricted. However, in human carcinomas, it was initially found to be a frequently expressed tumor marker [8].

Different regulatory paradigms for the duration of ncRNA function have been revealed by recent investigations by inhibiting the recruitment of RNA Pol II to that region and chromatin remodeling, respectively [9], programming from the promoter region of the non-coding RNA upstream has a negative [10] or positive [11] effect on the expression of the downstream gene [12]. The spliceosome is unable to recognize fusion sites when an antisense transcript hybridizes with the overlapping sense transcript. Thus, reasons for alternative splicing [13]. Thirteen Alternatively, Dicer generates endogenous siRNA by the hybridization of sense and antisense transcripts. A noncoding transcript can change the activity of a protein [14], function as a structural element that facilitates the creation of a bigger RNA-protein complex [15], or change the location of a protein within a cell by binding to particular protein partners [16].

The goal of this study was to determine whether the lncRNA ERICD and ARID3A could interact. It is known that both have putative binding sites for E2F, which are controlled by E2F and have been linked to several biological functions. However, the cell cycle controls the conflicting roles that ARID3A and ERICD play in apoptosis upon DNA damage. This leads me to believe that they have opposing roles in biological functions and look to identify potential relationships between them.

METHODS

Cell Culture

Cell culture is used to cultivate cells from many cell types, including fetal liver, bone marrow, lung, colon, skeletal muscle, stomach, and prostate. All cell lines were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 100 U/ml of Penicillin, and 100 mg/ml of Streptomycin in a humidified atmosphere containing 5% CO2 at 37 °C in the Cell Culture Lab at Medical Research Center, Hawler Medical University.

Primer Design

Appropriate synthetic primers were designed for intron regions of *ARID3A AND ERIC3A* genes by using the NCBI Primer Blast database. Primer sequences, length, annealing temperature, GC content and PCR product length of primers designed for intron sequences of *ARID3A AND ERIC3A. (***Table 1)**

RNA isolation from cell line:

Once the cells reach nearly 85% density, they are processed for RNA isolation from the cell culture under the right circumstances by using a high pure RNA isolation kit (Roche, Mannheim, Germany) [17]. Trypsin is used to eliminate the cells that have reached the proper density, and then Dulbecco's Modified Eagle Media (DMEM) with FCS is added to counteract the enzyme's effects for five minutes then cells are centrifuged at 3500 rpm. The particle is not touched during the removal of the supernatant.

200 µl of PBS was used to resuspend the leftover pellet to this mixture and added 400 µl of Lysis Buffer, and vortex for 15 seconds [18].

After being moved to filter tubes, the entire mixture is centrifuged for 30 seconds at 9200 rpm. The bottom portion gets thrown away, filling the filtered tubes with 100 µl (10 µl DNAse and 90 µl DNAse incubation buffer), then let them sit at room temperature for forty-five minutes. After adding 500 µl of washing buffer I, centrifuge for 30 seconds at 9200 rpm. The bottom portion gets thrown away. After adding 500 µl to washing buffer II, the mixture was centrifuged for 30 seconds at 9200 rpm. A fresh tube is inserted instead of the bottom tube. After adding 200 µl of Wash Buffer II, centrifuge at 11800 rpm for two minutes. A fresh tube is introduced and the lower tube is discarded. After adding 50 µl of Elution Buffer, the mixture was allowed to sit at room temperature for a minute and then centrifuged at 9200 rpm. The filtered tube is disposed of, and the amount of RNA is measured using the NanoDrop 1000. Until the working time, RNAs are kept at -80 ºC [19].

RNA Quantitation:

With the use of a Nanodrop spectrophotometer, the amount and caliber of the acquired RNA samples were ascertained by measuring the A260/A280 ratio (**Table 2**). RNA was diluted for PCR reactions based on its density [20].

cDNA components and their amounts:

Single-stranded cDNA was obtained from RNA-isolated samples and tissue RNAs by using Maxima H Minus First Strand cDNA Synthesis Kit # K1652 (Thermo Scientific). RNA at a final concentration of 2 µg / µl RNA and tissue RNA at a final concentration of 1 µg / µl RNA were added to perform cDNA synthesis from the cell culture samples [21].

Real-Time PCR (qPCR):

In this investigation, a Rotor-Gene Q (QIAGEN) Real-Time PCR device was employed. qPCR tests were conducted using the Maxima SYBR Green / ROX qPCR Master Mix (# K0251) under the guidance of the manufacturer's company. Using the NCBI/Primer Blast database, suitable synthetic primers were created for the exon regions of the ERICD and ARID3A genes. Image J program was used for the detection of the concentration of the pure band.

Delta CT analysis

The average of the Ct values for the GAPDH control gene and ARID3A and ERICD genes being tested in the experimental and control conditions, returning 2 values. The values of ARID3A and ERICD, and GAPTH Normal (Reference).

Statistical analysis

All result data was statistically measured by GraphPad Prisma version 8.

Table 2: Primers with their details used in the study.

Genes	sequence (5'->3')	Primer length	Temp (°C)	GC%	PCR product(bp)
ARID3A	GTTGCATCAGCTGTCCTCCT	17	57.75	64.71	221
	AAAAAGGGGTTGGGGTAGG	20	61.90	60.00	
ERICD	ACCAGACCTACTCTTCCGCT	20	59.88	55.00	246
	GGGAAGAGCCAAGTCAGAC	20	60.03	55.00	

Table 1: The RNA quantity of cell lines by using a Nanodrop spectrophotometer.

No	Name of cell	ng/µl	260/280
1	U2os	1502	2,07
2	MDA-MD	1451	2,05
3	CRL2327	761	2,06
4	CRL4010	336	2,02
5	A549	329	2,07
6	Beas2B	814	2,05
7	CRL8798	1060	2.03

RESULTS

The ARID3A expression level was analyzed in u2os different human tissues. Real-Time PCR methods performed gene expression analyses. ARID3A is most expressed in osteosarcoma among normal tissues and it has also been shown to be overexpressed in normal, bone marrow, lung, and prostate tissues. However, ARID3A was found to show low expression in the colon, skeletal muscle, stomach, and liver tissues (Figure 1).

Table 3 illustareted the Delata CT results showed that ARID3A and ERICD genes and GAPDH control gene and being tested in the experimental and control conditions.

Figure 2 demonstrates that the ARID3A gene makes silencing in the U2OS, and acts an effect as a superuser gene on the Osteosarcoma cells.

After silencing ARID3A, its effects on ERICD expression were determined. Gene expression analysis of ERICD was performed using both RT-PCR and qPCR methods and compared with non-transfected normal cells showed a significant decrease in level P=0.003 (Figure 3).

Expression level of ERICD after silencing ARID3A detects fold change value by qPCR. After analysis by the Image J program to determine band concentration and compare with negative control and normal and the resultsof Image J program showed that integreted density (the product area and mean value) was between 130491.575_99984.989. While, the results RawIntDen (the sum of the values of the pixels in the image) was 143924-110277 (Figure 4).

RT-PCR outputs showed changes in decreasing expression level of ERICD after silencing ARID3A. Results showed no significant levels seen between both ERICD and normal after transfection siRNA for decreasing ERICD P=0.038(Figure 5).

Figure 6 illustrated comparing both ERICD and ARID3A expreion levels during 48 hrs and 72 hrs. ARID3A expresion level in 48 hrs showed higher expreesion level by transfection siRNA. While, in 72hrs ERICD expresion level revealed decresed its exepresion (Figure 6).

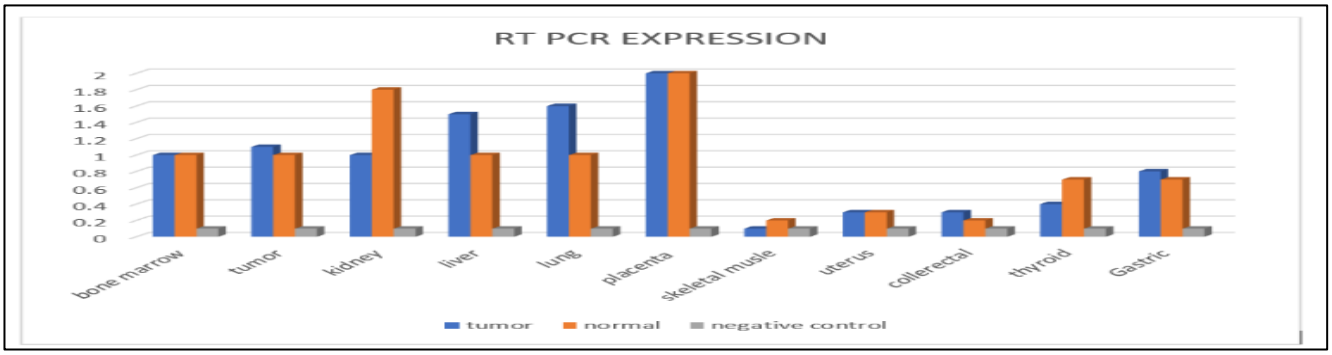

Figure 1: The ARID3A expression level was analyzed in U2OS's different human tissues. Quantity PCR and Real-Time PCR methods performed gene expression analyses.

Table 3: Delta Ct results of ARID3A and ERICD genes and GAPDH control gene in various cell lines.

Name of Genes	Mean	DCT	P value
ARID3A	22.06 Control 19.55 Disese	0.0043 Control 0.0070 Disese	0.043
EROICD	11.97 Control 12.23 Disese	0.0032 Control 0.0004 Disease	0.038

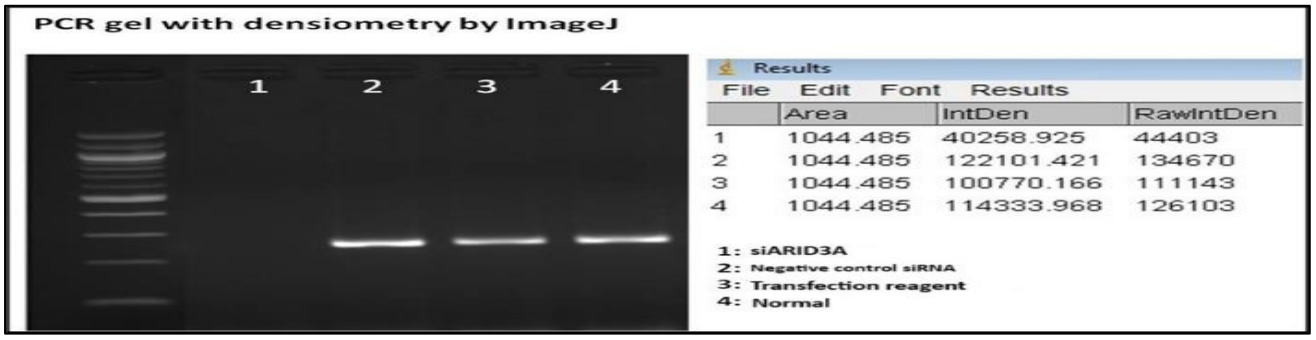

Figure 2: Demonstration of ARID3A silencing in the U2OS cell line by RT-PCR. (24 hours after transfection). Gene expression analysis was performed by gel electrophoresis and the ImageJ program. Lane-1 siRNA (ARID3A), lane-2 Negative control, Lane-3 Transfection agent, and Lane-4 Normal.

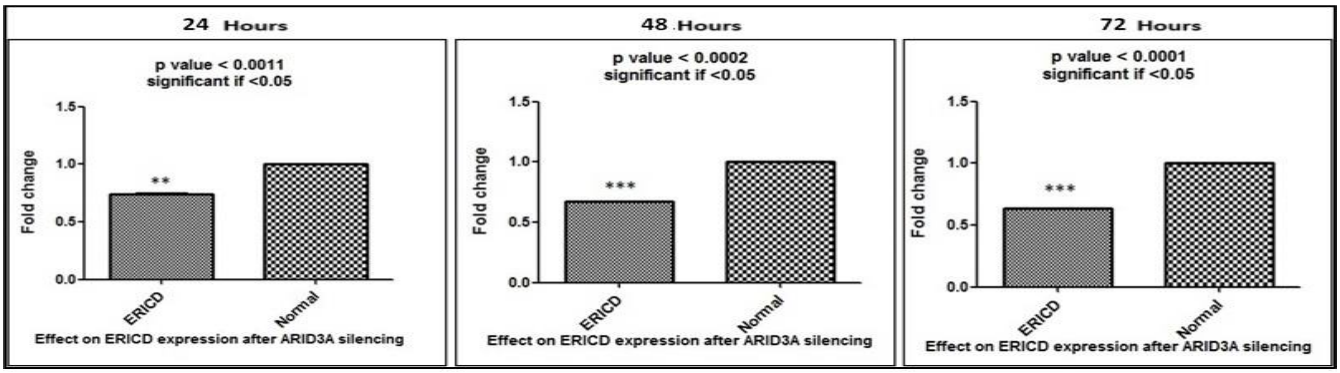

Figure 3: Decreased expression of ERICD after silencing ARID3A. Fold change values were significantly decreased in the level.

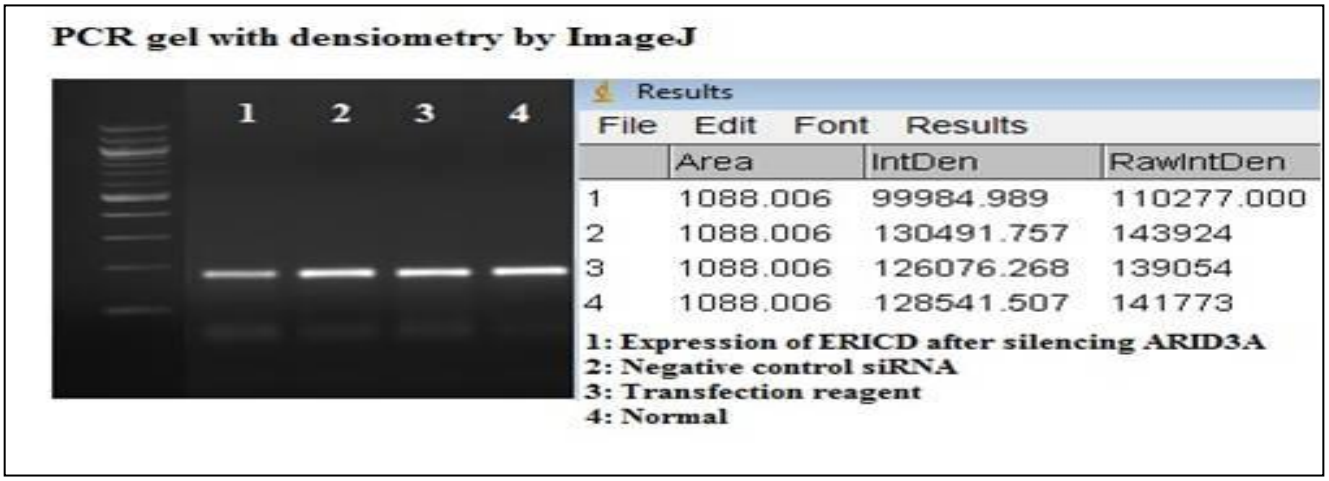

Figure 4: RT-PCR showed a decrease in the expression of ERICD after silencing ARID3A.

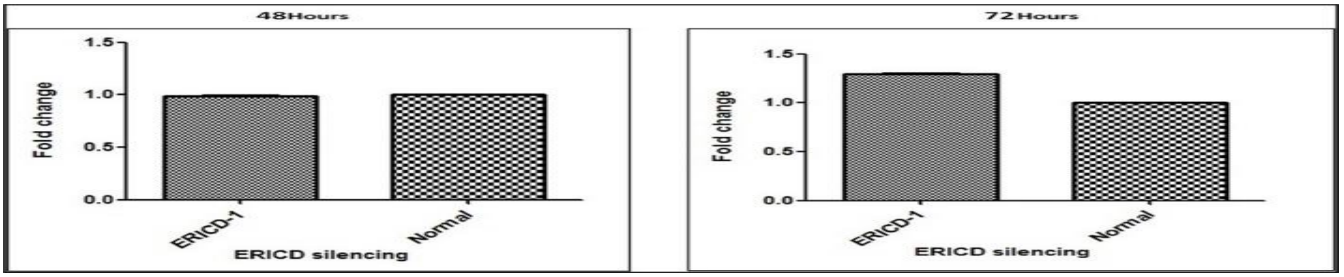

Figure 5: Fold change analysis of ERICD expression level using siERICD-1 (ERICD-1) as siRNA. No significant decrease was observed.

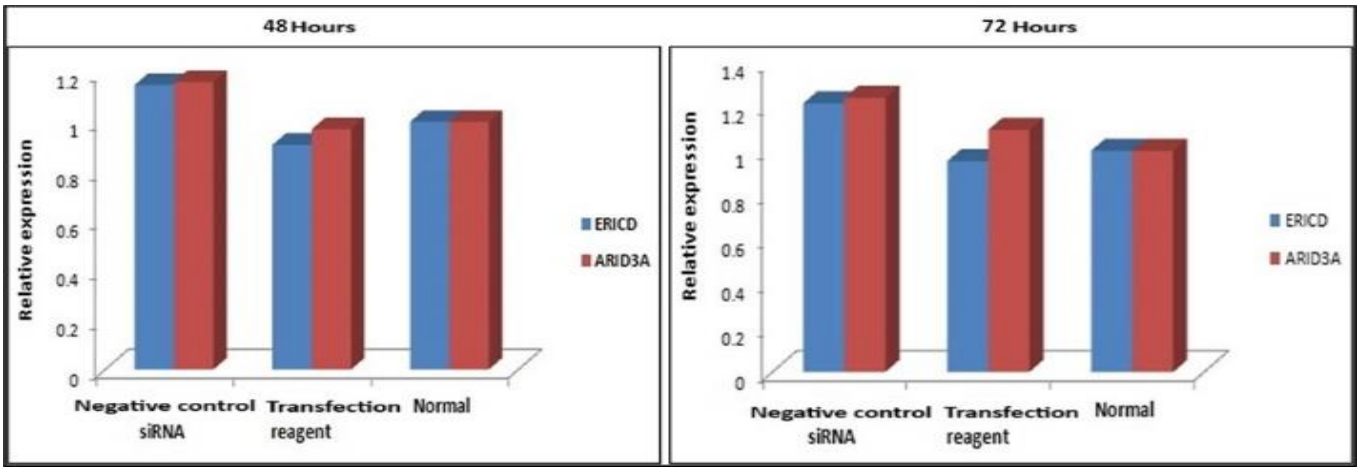

Figure 6: ARICD expression level by using siRNA between negative control and transfection. No significant decrease.

DISCUSSION

Genome regions that did not encode proteins were regarded as "garbage" by protein-centered orthodoxy. Many lncRNAs are produced from so-called "junk" areas of the genome, including pseudogenes, simple repetitions, and transposons that are biologically significant functional regulators [22,23]. With a length of more than 200 nucleotides, long non-coding RNAs (lncRNAs) are a broad and varied family of produced RNA molecules devoid of protein-coding. The significance of lncRNAs as a cancer research subject is growing. Thus far, a large number of lncRNA molecules involved in malignancies have been found. While some lncRNAs function as oncogenes, others function as tumor suppressors. For instance, by inhibiting

the production of p15 and consequently cell proliferation (senescence), the lncRNA ANRIL plays an oncogenic function in leukemia and prostate cancer [24,25]. A lncRNA called ERICD was found lately. It has two exons and is found on chromosome 8 (chr8:141646242-141648531). There are 1745 bps in the transcript. Transcription factor 1 (E2F) controls ERICD, which modifies the cell's reaction to DNA damage [25].

Numerous lncRNAs, including MALAT1, H19, and HOTAIR, have been found to function as oncogenes in a variety of cancer types, including breast, colon, lung, and liver cancer [26,27]. Tumor suppressor long non-coding RNA PTCSC3 (Papillary Thyroid Carcinoma Susceptibility Candidate 3) is linked to thyroid cancer [28].

Recently, ERICD was discovered to be a long noncoding RNA. It is located on chromosome 8 (chr8:141646242-141648531) and has two exons. The transcript has 1745 bps. The cell's response to DNA damage is altered by ERICD, which is regulated by transcription factor 1 [29].

A member of the AT-rich interaction domain (ARID) family of DNA-binding proteins, ARID3A is involved in the regulation of gene expression and chromatin remodeling. The ARID DNA binding domain is a characteristic that several proteins share. "AATTAA" is bound by a consensus sequence in ARID3A.44 E2F-dependent software [30] and the E2F software agent are enabled by ARID3A and prevent Ras-induced premature senescence in primary murine fibroblasts [31].

DNA damage and p53 both transcriptionally activate ARID3A, and it has been observed that ectopic production of ARID3A stimulates the development of Saos-2 cells lacking in p53 while inhibiting the growth of U2OS cells expressing normal p53 [32]. Additionally, it was discovered that a favorable prognosis for colorectal cancer was correlated with high ARID3A gene expression [33]. In the expression of the E2F target gene, ARID3A plays a crucial function. It has been demonstrated that the transcription of E2F target genes, including E2F1, p107, CDC2, and CDC6, is inhibited by siRNA-mediated suppression of ARID3A. It has also been discovered that ARID3A silencing inhibits the development of human tumor cell lines and weakens the S phase entrance of normal human dermal fibroblasts (NHDFs). Consequently, it is believed that they play tumor-suppressive roles [34]. The question is still up for debate whether ARID3A is an oncogene or a tumor suppressor. It is known that a large number of lncRNAs target DNA-binding proteins in many biological processes [35]. LncRNAs epigenetically control DNA transcription through their interaction with DNA-binding proteins.32 It is not yet known how ARID3A interacts with long non-coding RNAs [36].

The idea behind this study was to determine whether the ERICD and ARID3A could interact. It is known that both have putative binding sites for E2F, which are controlled by E2F and have been linked to several biological functions. However, the cell cycle controls the conflicting roles that ARID3A and ERICD play in apoptosis upon DNA damage. This leads us to believe that they have opposing roles in biological functions and look to identify potential relationships between the two genes with normal cells.

CONCLUSION

The transcription role of ARID3A and ERICD are very essential during expression of cancer cells. Both genes under study inhibited cancer cells when transfection of siRNA. Significant decrease in ERICD level when compared with non-transfected normal cells.

Statement of Permission and Conflict of Interests

The others declare that there are no any conflicts.

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