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REVIEW ARTICLE

Therapeutic Consequences of microRNAs in Non-Small Cell Lung Cancer.

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Abstract:

Background: Non-small cell lung cancer (NSCLC) is now progressing past standard chemotherapy thanks to new treatments that target specific molecules, and an important approach is blocking certain cytokines that are crucial for the growth of blood vessels in tumors. Currently, angiogenesis quantification to assess and predict the efficacy of antiangiogenic drugs is mainly based on the evaluation of microvascular density. However, this procedure is highly invasive, and its association with the clinical outcome is uncertain in many tumor types, including NSCLC.

Aim of study: To evaluate the target genes' promoter CpG islands methylation using bisulphate conversion, selection of cancerous (A549) and normal (WI38) cell lines and target molecules (ncRNA) for transfection, agomirs and antagomirs miRNAs (miR34a and miR135a), sense ADV-lncRNA, and antisense lncRNA (HOTAIR).

Materials and Methods: Methylation DNA sequence Methylation-Specific PCR (MS-PCR) by Bisulfite Conversion of DNA, the conventional MS-PCR stage was started. Primers designed according to the promoter regions of target genes were used for DNA without bisulfite conversion, methylation of promoter region sequences (CGIs) of target genes associated with ncRNA transfection. effect in the A549 cell line transfected with molecules of miR135, miR34a antagomirs, and HOTAIR antisense.

Results: Methylation revealed a significant outcome of promoter blocking of target genes in A549 after transfection with some ncRNA molecules, and there was a significant relation between ncRNA transfection and CGI methylation, especially at specific promoter regions of ncRNA transcription genes, which in turn impacted the blocking of oncogene and TSG promoter regions.

Conclusion: There was a significant relationship between ncRNA transfection and CGI methylation, especially in specific promoter regions of ncRNA transcription genes, which in turn impacted the blocking of oncogenes and TSG promoter regions.

Keywords: non-small cell lung carcinoma, adenovirus, methylation-specific PCR, tumor suppressor gene, non-coding RNA, Hox transcript antisense RNA

Introduction

Epigenetic transcriptional silencing is strongly influenced by DNA methylation in genomes (1, 2, 3, 4). DNA methyltransferases are responsible for catalyzing DNA methylation and are considered crucial players in this process (5, 6, 7, 8). These methyltransferases can be categorized into two chief sets: "de novo methyltransferases (DNMT3a-b)" and preservation methyltransferases (DNMT1) (9, 10, 11, 12, 13). DNA methylation, the adding of a group of methyl to the 5' carbon of cytosine that remains in CpG dinucleotides, is a significant epigenetic alteration that regulates expression of genes (Schübeler, 2015a)(22). CpG dinucleotides are irregularly dispersed throughout mammalian genomes, with a higher concentration in CpG islands, which are commonly located within gene promoter regions (14, 15, 16, 17). In order to develop a therapeutic strategy as a biological inhibitor of cancer cell uncontrolled proliferation, using transfection of synthetic RNA molecules into a lung adenocarcinoma cell line and blocking CGIs of target mRNA promoter sequences (18, 19, 20). This study aimed to find the inhibitors of essential splicing elements as useful tools in treating lung carcinoma. The unique novelty of the project is to impair splicing to the extent of adversely influencing the growth and proliferation of non-small cell lung carcinoma without harm or least effect to the normal cells (23, 24, 25, 26). Monitor CpG island methylation using bisulfite conversion (27, 28, 29). selection of cancerous (A549) and normal (WI38) cell lines and target molecules (ncRNA) for transfection, agomirs and antagomirs miRNAs (mir34a and mir135a), sense

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ADV-lncRNA and antisense lncRNA (HOTAIR), selection of suitable methods for transfecting these molecules utilizing liposomal particles and ncRNA-loaded virus, and selection of some specific genes that are responsible for normal cell transformation and malignant tumor development and tumor suppressor genes (30, 31).

Materials and Methods:

Methylation DNA sequence: Targeted bisulfite sequencing

The bisulfite conversion step was started. The EZ DNA Methylation-Gold™ Kit (Catalogue No. D5005) was supplied by ZYMO RESEARCH (UK).

Methylation-Specific PCR (MS-PCR)

After bisulfite conversion of DNA, the conventional MS-PCR stage was started. At this stage, primers designed according to the promoter regions of target genes were used for DNA without bisulfite conversion. PCR 2X Master (Catalogue No. W1401) was provided by WizPure™ (S. Korea). Amplification mixture components used in MS-PCR() were included: Table 1:

Table(1):Amplification mixture used for MS-PCR

MasterMix Components	Volume
PCR 2X MasterMix	10 µl
Forward Primer (10 uM)	0.5 µl
Reverse Primer (10 uM)	0.5 µl
Template DNA	2 µl
Water	7 µl
Total	20 µl

2. Conventional oligonucleotides primers

Specific primers used for detection of target sequences were listed in table(2).

Table (2): Oligonucleotides primers for un-methylated sequences.

Primer	Sequence(3`-5`)
U-TP53-F	GTATAAAGTGGTTGGTATGTGGTA
U-TP53-R	ATCATAAAACAAAAAAAACAAACCC
U-CASPASE-8-F	GGGTGGAGCAAAAGGAGGTAT
U-CASPASE-8-R	GAGAGGTGGAACCAGCCTAGA
U-SMAD1-F	GCAGCTTCAAGAGTTAGCCAAG
U-SMAD1-R	GCATGCCATAAGGAGATACTGC
U-VEGF-F	CAGCGGTTAGGTGGACCG
U-VEGF-R	GCCCGATTCAAGTGGGGAAT
U- TNFa-F	GAGATAGAAGGTGTAGGGTTTATTATTG
U- TNFa-R	ACCTTTATATATCCCTAAAACAAAA
U-TGFB1-F	AGAAATTGTGTTTGGTTGGTT
U-TGFB1-R	AATATTCCTCTAATCCACACAATTCA
U-IFN-G –F	GATTATTGATTGGGTTTGGTA
U-IFN-G –R	ACTTCTAAAAACACTATACACCCCC

3. Methylation specific primers used for detection of target sequences were listed in the table(3).

Table (3): Methylated specific primers for methylated sequences.

Primer	Sequence(3`-5`)	Brand,origin
M-TP53-F	GTATAAAGTGGTCGGTACGC	Oligomer,Turkey
M-TP53-R	CGTCGTAAAACGAAAAAAACG	
M-CASPASE-8-F	GGGTGGAGCAAAAGGAGGTA	
M-CASPASE-8-R	AGAAGCAGCCAGCTAAGGTAA	
M-SMAD1-F	GGTAAGAGTTAAGTGCGGGGG	
M-SMAD1-R	CCCTGAGTCAACAGATGCGT	
M-VEGF-F	GGTCAGCGGACTCACCG	
M-VEGF-R	TAGAGCAATCTCCCCAAGCC	
M- TNFa-F	GAGATAGAAGGTGTAGGGTTTATTATC	
M- TNFa-R	AACAACTACCTTTATATATCCCTAAAACG	
M-TGFB1-F	TTTAAGAAATTGTGTTTGGTCG	
M-TGFB1-R	ATATTCCTCTAATCCACACAATTCG	
M-IFN-G –F	ATTATTGATTGGGTTCGGTA	
M-IFN-G –R	CACTTCTAAAAACGCTATACGCC	

Results:

Methylation influence on TNFα gene expression

The results shown in the tables (4) and (5) are methylated blocking gene promoters in TNFα after transfection of agomirs, sense, antagomirs, and antisense firstly on A549.

Table(4): Methylated of CPG islands on TNFα gene in A549 cell line.

Agomir3 Sense		Antigomir3 Antisense	
(TNFa)	Methylation%	(TNFa)	Methylation %
UM-Control	67.15665781	UM-Control	64.42817275
M-Control	35.31242315	M-Control	37.56492832
UM-mir34a	32.33147715	UM-mir34a	43.13988206
M-mir34a	69.57832373	M-mir34a	27.85610792
UM-miR135a	35.25475736	UM-miR135a	72.42456776
M-miR135a	21.65324612	M-miR135a	31.58643129
UM-HOTAIR	15.76837861	UM-HOTAIR	82.71952427
M-HOTAIR	85.63762158	M-HOTAIR	23.18107876

Table(5): Methylated of CPG islands onTNFa gene in WI38 cell line

Agomir Sense		Antigomir Antisense	
(TNFa)	Methylation%	(TNFa)	Methylation %
UM-Control	25.22645762	UM-Control	32.54817253
M-Control	76.33742723	M-Control	70.73592720
UM-mir34a	30.26147385	UM-mir34a	37.43883901
M-mir34a	63.94251359	M-mir34a	29.68710590
UM-miR135a	36.23765803	UM-miR135a	78.74739706
M-miR135a	28.50324375	M-miR135a	37.58743340
UM-HOTAIR	18.65237860	UM-HOTAIR	88.46553129
M-HOTAIR	82.94764390	M-HOTAIR	21.04707703

2. methylation influence on TP53 gene expression:-

Table6: Methylated of CPG islands on TP53 gene in A549 cell line

Agomir Sense		Antigomir Antisense	
(TP53)	Methylation %	(TP53)	Methylation%
UM-Control	32.56484718	UM-Control	25.5862595
M-Control	69.53215291	M-Control	73.5437532
UM-mir34a	65.69742663	UM-mir34a	33.63268719
M-mir34a	21.51547347	M-mir34a	44.26741395
UM-miR135a	25.11402123	UM-miR135a	75.34225716
M-miR135a	75.74593358	M-miR135a	21.78485187
UM-HOTAIR	16.56847184	UM-HOTAIR	65.89258596
M-HOTAIR	71.43151946	M-HOTAIR	33.12742343

Table7: Methylated of CPG islands on TP53 gene in WI38 cell line

Agomir Sense		Antigomir Antisense	
(TP53)	Methylation %	(TP53)	Methylation%
UM-Control	75.764844307	UM-Control	65.8752553
M-Control	25.85615564	M-Control	30.6547843
UM-mir34a	62.06812874	UM-mir34a	31.86568542
M-mir34a	24.51547347	M-mir34a	44.26741395
UM-miR135a	27.34484121	UM-miR135a	75.34225716
M-miR135a	75.74593358	M-miR135a	25.90385163
UM-HOTAIR	14.53847607	UM-HOTAIR	60.03750294
M-HOTAIR	65.84651495	M-HOTAIR	31.10794846

3. methylation influence on SMAD gene expression:-

Table8: Methylated of CPG islands on SMAD gene in A549 cell line

Agomir Sense		Antigomir Antisense	
(SMAD)	Methylation%	(SMAD)	Methylation%
UM-Control	63.17341382	UM-Control	61.40283254
M-Control	32.63568507	M-Control	37.56709837
UM-mir34a	30.42568723	UM-34a	72.06187514
M-mir34a	67.86971269	M-34a	25.75610657
UM-miR135a	24.23723286	UM-miR135a	73.41936436
M-miR135a	75.76276753	M-miR135a	24.58063427
UM-HOTAIR	88.46831334	UM-HOTAIR	32.83463524
M-HOTAIR	11.53168671	M-HOTAIR	62.16536541

Table 9: Methylated of CPG islands on SMAD gene in WI38 cell line

Agomir Sense		Antigomir Antisense	
(SMAD)	Methylation%	(SMAD)	Methylation%
UM-Control	25.6534133	UM-Control	31.32433295
M-Control	72.57478517	M-Control	65.84949864
UM-mir34a	31.85568723	UM-34a	72.06193510
M-mir34a	65.39971269	M-34a	23.70610395
UM-miR135a	23.09723229	UM-miR135a	70.41936436
M-miR135a	71.23276729	M-miR135a	28.67063431
UM-HOTAIR	84.05831347	UM-HOTAIR	31.83463583
M-HOTAIR	15.28168684	M-HOTAIR	60.53536849

4. methylation influence on CASPASE8 gene expression:-

Table(10): Methylated of CPG islands on CASPASE8 gene in A549 cell line:-

Agomir Sense		Antigomir Antisense	
(CASPASE8)	Methylation %	(CASPASE8)	Methylation %
UM-Control	75.679342137	UM-Control	65.31263689
M-Control	26.34565854	M-Control	34.54936537

UM-mir34a	71.61432578	UM-34a	25.53746380
M-mir34a	25.32057835	M-mir34a	70.47655437
UM-miR135a	31.85425254	UM-miR135a	60.48537470
M-miR135a	67.23674943	M-miR135a	40.786360543
UM-HOTAIR	26.48932627	UM-HOTAIR	68.86923370
M-HOTAIR	71.42367338	M-HOTAIR	31.01556317

Table(11): Methylated of CPG islands on CASPASE8 gene in WI38 cell line.

Agomirꞵ Sense		Antigomirꞵ Antisense	
(CASPASE8)	Methylation %	(CASPASE8)	Methylation %
UM-Control	8.085232710	UM-Control	25.53210973
M-Control	95.61476721	M-Control	78.23488742
UM-mir43a	91.276208365	UM-mir34a	20.42989528
M-mir43a	8.735971945	M-mir34a	81.95610239
UM-miR135a	15.84578786	UM-miR135a	87.98467386
M-miR135a	86.85409215	M-miR135a	13.09174597
UM-HOTAIR	25.96482310	UM-HOTAIR	92.97528754
M-HOTAIR	75.98346516	M-HOTAIR	10.98764401

5.methylation influence on TGF-ß gene expression:-

Table(12): Methylated of CPG islands on TGF-ß gene in A549 cell line.

Agomirꞵ Sense		Antigomirꞵ Antisense	
(TGF-ß)	Methylation %	(TGF-ß)	Methylation %
UM-Control	31.76430915	UM-Control	25.89402217
M-Control	70.99640436	M-Control	76.21640982
UM-mir34a	75.76302105	UM-mir34a	30.97432206
M-mir34a	25.54493218	M-mir34a	69.79577321
UM-miR135a	20.99504326	UM-miR135a	75.10438763
M-miR135a	76.21040874	M-miR135a	21.98904122
UM-HOTAIR	16.99706054	UM-HOTAIR	68.10443852
M-HOTAIR	80.88653520	M-HOTAIR	31.12044327

Table13 : Methylated of CPG islands on TGF-ß gene in WI38 cell line.

Agomirꞵ Sense		Antigomirꞵ Antisense	
(TGF-ß)	Methylation %	(TGF-ß)	Methylation %
UM-Control	25.23880654	UM-Control	30.44302127
M-Control	71.54633215	M-Control	65.54566320
UM-mir34a	27.66505332	UM-mir34a	76.98977650
M-mir34a	71.56544367	M-mir34a	23.65744368
UM-miR135a	75.10878554	UM-miR135a	33.77659034
M-miR135a	21.56544389	M-miR135a	65.65799834
UM – HOTAIR	67.65478763	UM-HOTAIR	35.76844536
M-HOTAIR	31.55478434	M-HOTAIR	66.76852249

6. methylation influence on VEGF gene expression:-

Table14: Methylated of CPG islands on VEGF gene in A549 cell line.

Agomirꞵ Sense		Antigomirꞵ Antisense	
(VEGF)	Methylation %	(VEGF)	Methylation %
UM-Control	31.76430915	UM-Control	25.89402217
M-Control	70.99640436	M-Control	76.21640982
UM-mir34a	74.85630213	UM-mir34a	26.93432235
M-mir34a	23.54493218	M-mir34a	71.85577320
UM-miR135a	21.79504338	UM-miR135a	74.94438769
M-miR135a	75.31040863	M-miR135a	20.98904123
UM-HOTAIR	17.48706053	UM-HOTAIR	69.98443850
M-HOTAIR	81.42653524	M-HOTAIR	30.32044326

Table(15): Methylated of CPG islands on VEGF gene in WI38 cell line.

Agomirꞵ Sense		Antigomirꞵ Antisense	
(VEGF)	Methylation %	(VEGF)	Methylation %
UM-Control	25.23880654	UM-Control	30.44302127
M-Control	71.54633215	M-Control	65.54566320
UM-mir34a	28.46505331	UM-mir34a	75.48977653
M-mir34a	73.94544373	M-mir34a	21.39744364
UM-miR135a	74.43878538	UM-miR135a	31.83659084
M-miR135a	20.49544350	M-miR135a	63.94799864
UM – HOTAIR	68.94478798	UM-HOTAIR	32.53844505
M-HOTAIR	30.95478494	M-HOTAIR	64.59852231

7. methylation influence on VEGF gene expression:-

Table(16): Methylated of CPG islands on IFNG gene in A549 cell line.

	Agomir3 Sense		Antigomir3 Antisense
(IFNG)	Methylation %	(IFNG)	Methylation %
UM-Control	71.80834391	UM-Control	76.867342021
M-Control	25.21090654	M-Control	22.02155498
UM-mir34a	21.21062362	UM-mir34a	73.06391848
M-mir34a	75.99633265	M-mir34a	25.87210465
UM-miR135a	72.74932568	UM-miR135a	25.97620097
M-miR135a	24.01205496	M-miR135a	76.87631043
UM-HOTAIR	86.39874628	UM-HOTAIR	18.10385638
M-HOTAIR	12.74300863	M-HOTAIR	83.74092165

Table(17): Methylated of CPG islands on IFNG gene in WI38 cell line.

	Agomir3 Sense		Antigomir3 Antisense
(IFNG)	Methylation %	(IFNG)	Methylation %
UM-Control	25.32965018	UM-Control	31.84397601
M-Control	73.20519378	M-Control	65.92022839
UM-mir34a	31.32530486	UM-mir34a	75.84016343
M-mir34a	67.64469529	M-mir34a	22.42983634
UM-mir135a	75.86309801	UM-mir135a	23.65368243
M-mir135a	24.78736192	M-mir135a	78.24631886
UM-HOTAIR	66.36370859	UM-HOTAIR	18.70159584
M-HOTAIR	31.03629157	M-HOTAIR	80.17840410

Concerning the A549 cell line, it indicated High percent of methylation and unmethylation of agomirs, sense, antigomirs, and antisense sequences due to the results reflected a significant consequence matching effect of gene expression after transfection with the mir43a, mir135, and HOTAIR. This means that the therapeutic miR-34a index of transfection and methylation elevated A549 cell line regression and is considered a promising program for lung carcinoma treatment.

Discussion:

Current findings that DNMT1 associates with lncRNAs suggest that these lncRNAs may influence DNMT1 genomic occupancy or activities, thereby indirectly regulating the methylome. Thus, deregulation of one or more of DNMT1-associated lncRNAs in human disease would lead to changes in DNA methylation patterns and potentially significant changes in gene expression without any detectable changes in DNMT1 expression levels. Indeed, we found in our study that the induction of the lncRNA is sufficient to change DNA methylation patterns in lung cancer cells. Also, transfection of lncRNA could affect DNMT1 activity at specific CpG sites, potentially by regulating protein components of the DNMT1 macromolecular protein complex. The results showed methylation played a crucial role in repressing gene expression, perhaps by blocking the promoters at which activating transcription factors should bind. Presently, the exact role of methylation in gene expression is unknown, but it appears that proper DNA methylation is correlated with the transfection of the A549 and WI38 cell lines that have the same effect on SMAD, TNFα, TGF-β, VEGF, TP53, CASPASE8, and IFNG gene expression downregulation. In some cases, methylation has been observed to play a role in mediating gene expression after transfection with agomirs, sense, antigomirs, and antisense (miR-34a, miR-135a, and HOTAIR). Evidence of this has been found in this study that showed that methylation near gene promoters varies considerably depending on cell type, with more methylation of promoters correlating with low or no transcription. Also, while overall methylation levels and completeness of methylation of particular promoters are similar in individual humans, there are significant differences in overall and specific methylation levels between different normal cells and cancer cells. Views About the current results, synergistic relation between transfection and CGIs methylation related to agomir molecules of miR-34a, miR-135a, and sense-HOTAIR CGIs-methylation and antagomir, antisense of these molecules transfection-CGIs-methylation (35, 36). Cell lines that were transfected with significant agomir and antagomir molecules showed an increase in the “switching off” of CGIs in the promoter region of oncogenes and the switching on of the promoter region of TSGs. Hyper-methylation of CGIs in regulatory regions may be included in cancer development by repressing gene expression and increasing mutation occurrence via cytosine-to-thymine substitution after deamination of methylated cytosine and silencing of DNA repair enzyme by promoter Hypermethylation exhibits mutation. percent, hypermethylation occurs in many genes that have a crucial role in essential cellular processes like cell cycle regulation and repair of double-stranded breaks, genes involved in cell adhesion, metastasis and angiogenesis inhibition, and genes that regulate cancer cell survival or pro-apoptotic functions (33, 34).

Conclusion

Utilization of epigenetic levels using ncRNA is a promising therapeutic mechanism for lung adenocarcinoma regression. Antagomir and antisense ncRNA molecules were more effective than mimic and ADV-ncRNA molecules.

Ethics Consideration

This study is in accordance with the ethics committee of Al-Diwaniaya Teaching Hospital, Iraq. Participants in the study of the relatives’ pre-taking samples verbally agreed.

Conflict of interest: No known conflict of interest correlated with this publication.

Regarding this publication, there are no known conflicts of interest.

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Availability of data and materials: The data used and analyzed throughout this study are available from the corresponding authors on reasonable request.

Consent for publication: Not applicable.

Competing interest: The authors declared that they have no competing interest.

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