Review Article

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DIFFERENTIAL EXPRESSION OF MICRORNAs IN LUNG CANCER: A REVIEW ARTICLE

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ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNA molecules of approximately 16-24 nucleotide length. The miRNA biogenesis is a 2 step cleavage process mediated by Dorsha and Dicer. The nuclear cleavage by Dorsha / DiGeorge syndrome critical region 8 (DGCR8) generates 60-70 nucleotide long precursor microRNA (pre-miRNA). Furthermore, the pre-miRNA is exported to the cytoplasm by exportin 5 to be cleaved by Dicer. This resultant miRNA is further processed to generate a mature miRNA and get assembled into a RNA-induced silencing complex (RISC). Hence leading to transcriptional repression of the target mRNAs. It has been reported that one miRNA may target many genes accounting from a few to as many as thousands. Lung cancer (LC) ranks third worldwide and is marked by poor prognosis. The early staged LC patients usually exhibit no symptoms and the condition worsens till the time of first diagnosis. Therefore, studies are required to outline good early detecting and surveillance biomarkers for LC. Several evidences support the role of miRNAs in the pathogenesis of LC. They show differential expression pattern i.e. may be either upregulated or downregulated. The oncogenic miRNAs remain upregulated while the tummor suppressive miRNAs remain downregulated. In LC miRNAs are the important factors for tumour initiation, differentiation, apoptosis, proliferation as well as tumor progression. Thus, this review article focuses on the diagnostic significance of miRNAs in LC.

KEYWORDS: Lung Cancer, microRNA, Oncogene, Tumor Suppressor, Diagnosis

INTRODUCTION

LC is one of the most common leading cause of cancer related deaths globally. It ranks 3rd amongst all the cancers preceded by breast and prostate cancer. According to The Global Cancer Observatory (GLOBOCAN)-2018 data, the estimated age-standardized incidence rates (for both sexes) for LC was 11.6 %. While the mortality rate was found to be 18.4%, thus accounting for the highest number of deaths in 2018 (1). It has also been predicted that males have higher rate of mortality than females i.e. 22.0% and 13.8% respectively. The rate of diagnosis is also higher for males (14.5%) than females (8.4%) (2). Since LC is associated with high mortality rates it is important to evaluate the significance of early diagnostic biomarker. Early staged LC patients usually experience no symptoms and the disease remains undiagnosed for a longer period of time (3, 4).

On the contrary, higher LC stages are difficult to treat and are associated with low survival rate. According to GLOBOCAN 2014 data, the survival rate of LC patient was lowest 14.70% (5-year net survival) in the United Kingdom and the highest survival rate was observed in Canada 22.60% (5).

Several human studies have shown promising results for the evaluation of miRNAs as diagnostic biomarkers in LC (6, 7, 8). The miRNA was first discovered in 1993 by Ambros and colleagues in *Caenorhabditis elegans*. It is a small non-coding RNA molecule of about 22 nucleotides. They are known to regulate the gene expression post-transcriptionally (9). miRNAs can be oncomir or tumour suppressors depending upon the nature of their activity (10). OncomiRs are cancer causing and are found to be upregulated in LC patients such as miRNA-17, miRNA-21, miRNA-155 and miRNA-27a(6, 7, 11,12) while tumor suppressors control the abnormal growth of cells by inhibiting various oncogenic factors. Few tumour suppressors such as miRNA-126, miRNA-let-7a, miRNA-29b-3p and miRNA-145 are reported to be down regulated in LC patients (13, 14, 15, 16).

MICRORNABIOGENESIS

The miRNAs are produced endogenously in our body through a regulated process. The double stranded miRNA is composed of a single stranded RNA complementarity paired with its own nucleotide. This results in a hairpin loop like structure known as primary miRNA (pri-miRNA). The miRNA biogenesis is a two-step cleavage process performed firstly in nucleus then in cytoplasm (figure 1). The nuclear enzymes dorsha and RNA binding protein DGCR8 combine together to cut the pri-miRNA into small segments called pre-miRNA. Once the pre-miRNA is produced, it is transported to the cytoplasm via transporter protein exportin 5. The second cleavage process is mediated by an enzyme known as dicer (RNAse III type endonuclease) (17). It binds to the pre-miRNA and cuts it from two locations on the either ends. The resultant product is without a hairpin loop. This structure is known as miRNA: miRNA*duplex which is loaded on RISC having 'Slicer/TRNC6 and Argonaut' protein. Argonaut protein have two domains, PIWI and PAZ (18). This double stranded RNA loaded on RISC will no longer be active unless one strand is released, which is a key task of RISC Complex (19, 20). One strand remain bound to RISC through PAZ domain and is known as the guide strand, while the other strand eventually leaves the RISC with the help of PIWI domain is known as the passenger strand. The guide strand binds complementarity to the target mRNA sequence. This process is called nucleation which represses translational activity by Argonaut protein having RNase H activity and cleaves the target mRNA to repress its translational activity. Guide strand with Argonaut protein are again ready to bind with another target mRNA (21)

CHARACTERISTICS OF miRNAs AS DIAGNOSTIC BIOMARKERS IN LUNG CANCER

miRNAs proves to be a potential diagnostic biomarker for early stage LC. The non-coding RNAs i.e. miRNAs has been long established as diagnostic and prognostic biomarkers in various type of cancers (18). In table 1, we have reported 42 miRNAs identified through extensive search of reported data in LC cases. The patients' characteristics are summarized in table 2. Generally, the expression value of significant miRNAs can either be low or high due to its association with the clinical characteristics of the patients while the expression value of non-significant miRNAs are not dependent on the patient characteristics.

In this review we have focused on the potential aspects of the various types of miRNAs studied as diagnostic biomarkers in LC patients.

Oncogenic miRNAs Targets/Functions in Lung Cancer

Shan et al., 2018 investigated targets of the miRNA-21-5p by DIANA-miRPath v3.0, a pathway analysis Web server. And further analysed the cascades regulated by them through KEGG database (26). The miRNA-21-5p was found to significantly regulate lysine degradation, fatty acid metabolism, adheren junctions, along with FoxO, Hippo, p53, prolactin, thyroid hormone, HIF-1, ErbB, and PI3K-AKT signalling pathways (26). The KEGG analysis also identified role of miRNA-21-5p in various other cancers such as renal cell carcinoma, prostate cancer,

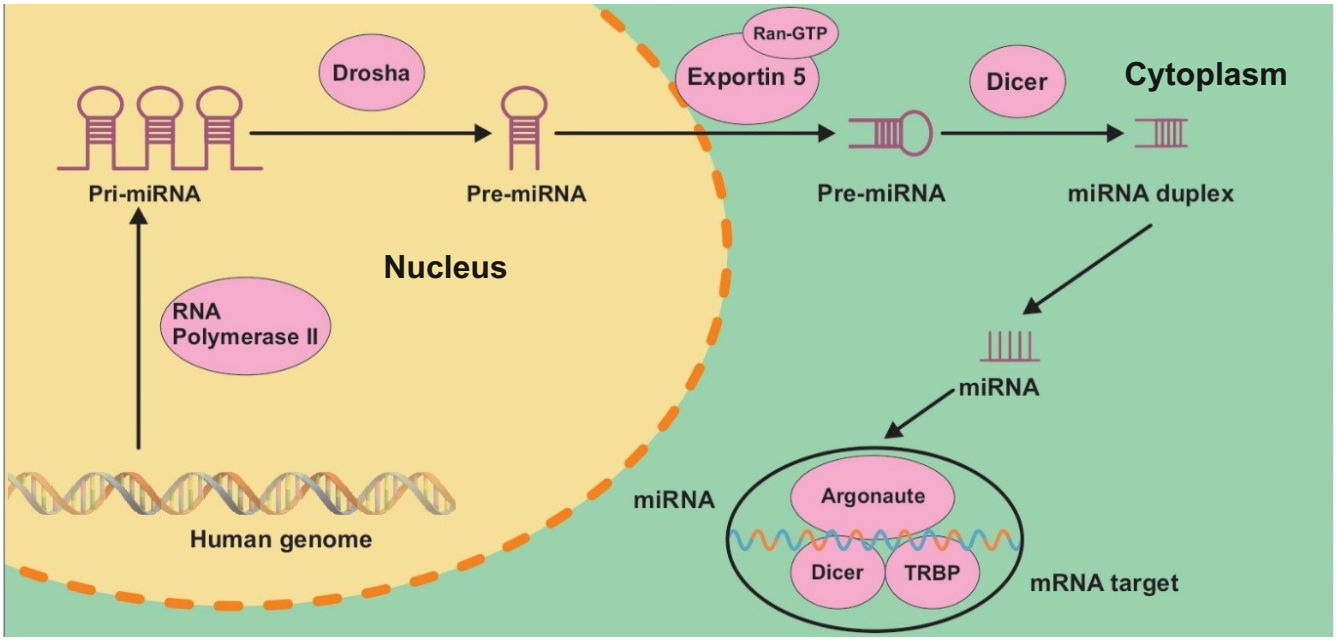

Fig. 1: Figure 1 miRNA Biogenesis Pictorial Representation

pancreatic cancer, endometrial cancer etc. (26). In another study researchers identified 709 target genes of miRNA-210 with the use of 12 online prediction software tools (30). Ten gene ontology terms and KEGG pathways were found by using DAVID 6.7. The gene ontology terms fell into the categories of molecular function, cellular component, and biological process. The highly significant pathways reported in KEGG were the cGMP-PKG signalling, renin secretion, and cell adhesion molecules (30). The authors also employed STRINGS to further narrow down the target genes of miRNA-210. They found 6 key miRNA-210 target genes i.e. cholinergic receptor muscarinic 2, adenylate cyclase 9, CXCL12, IL-6, G protein subunit γ 11, and adrenoceptor beta-2 (30).

Tumor Suppressive miRNAs Targets/Functions in Lung Cancer

The miRNA-let-7a mimic mediates the downregulation of dicer enzyme in lung cancer cell line (14). It also arrests lung cancer cells in G0/G1 phase and to a lesser extent in S phase, thus limiting cell proliferation (14). The authors also determined miRNA-let-7a prognostic significance and proved it to be an independent predictor of LC (14). Li and co-workers investigated the molecular pathways targeted by miRNA-195-5p (35). They retrieved nine significant signalling cascades through Ingenuity Pathway Analysis and suggested IL-8 pathway to be the most significant (35).

S. No	miRNA	Type of sample	Expression	AUC (95% CI)	Diagnostic value	Ref. No.
1	miRNA-33a-5p	Blood	Down regulated	0.870 (0.778 – 0.961)	sensitivity = 86.67% specificity = 73.33%	22
2	miRNA-28-3p	Serum	Upregulated	1.51 (1.24 – 1.85)		23
3	miRNA-128-3p	Blood	Down regulated	0.927 (0.861 – 0.993)	sensitivity = 93.33% specificity = 80%	22
4	miRNA-17	Plasma	Down regulated	0.615 (0.574 – 0.655)		23
		Plasma	Upregulated	0.833 (0.577 – 0.966)	sensitivity =77.78% specificity =87.50%	11
	miRNA-17-5p	Serum	Upregulated	0.738 (0.649 – 0.814)	sensitivity = 66.7% specificity = 76.6%	24
5	miRNA-222	Plasma	Upregulated	0.542 (0.289 – 0.780)	sensitivity = 50% specificity =88.89%	11
6	miRNA-190b	Plasma	Down regulated	0.814 (0.779 – 0.845)		23
7	miRNA-155	Plasma	Upregulated	0.8648 (0.8011–0.9329)		25
		Sputum	Upregulated	0.697 (0.616 – 0.779)	sensitivity = 62.67% specificity =78%	13
		-	Upregulated	0.87 (0.84–0.90)	sensitivity = 82% specificity =62.96%	12
8	miRNA-150	Plasma	Upregulated	0.752	sensitivity = 81.8% specificity =81.8%	8
9	miRNA-let-7a	Serum	Down regulated	0.847	sensitivity = 68.5% specificity =91.1%	14

Table 1: The Relationship between the Expression Levels, Area Under the ROC Curve (AUC) and Diagnostic Value of miRNA in Lung Cancer Patients

S. No	miRNA	Type of sample	Expression	AUC (95% CI)	Diagnostic value	Ref. No.
10	miRNA-375	Sputum	Upregulated	0.666 (0.594 – 0.756)	sensitivity = 66.23% specificity =62.22%	13
		Plasma	-	0.6088 (0.4721 – 0.7455)	sensitivity = 66.7% specificity = 57.58%	27
		Sputum	Upregulated	0.713	sensitivity = 60.3% specificity =71.7%	16
11	miRNA-21-5p	Plasma	Upregulated	0.739 (0.670 –0.808)		26
	miRNA-21	Plasma	Upregulated	0.8913 (0.8394 – 0.9431)	sensitivity = 80% specificity =80%	6
		Plasma	Upregulated	0.653	sensitivity = 79.17% specificity =55.15%	36
		Sputum	Upregulated	0.819 (0.753 – 0.874)	sensitivity = 78.16% specificity =71.08%	13
		Sputum	Upregulated	0.752	sensitivity =58.8 % specificity =73.8%	16
		Plasma	Upregulated	0.5862 (0.4348 – 0.7186)	sensitivity = 56.25% specificity =63.64%	27
12	miRNA-210	Plasma	Upregulated	0.6913 (0.5611 – 0.8215)	sensitivity = 56.25% specificity =72.73%	27
		Serum	Upregulated	0.73 (0.63–0.85)	sensitivity = 76.8% specificity =72.3%	28
		Serum	Upregulated	0.616 (0.534 –0.694)	sensitivity = 33.9% specificity =100%	29
		Body fluids	Upregulated	0.77 (0.73 – 0.80)	sensitivity = 65% specificity = 76%	30
		Sputum	Upregulated	0.853 (0.792 –0.901)	sensitivity = 75.27% specificity =85.88%	13
13	miRNA-486-5p	Plasma	Down regulated	0.6288 (0.5779 – 0.8312)	sensitivity = 71.8% specificity =66.67%	27
		Sputum	Down regulated	0.748 (0.674 – 0.821)	sensitivity = 74.03% specificity = 66.67%	13
	miRNA-486	Sputum	Down regulated	0.727	sensitivity = 62.6% specificity = 69.4%	16
		Plasma	Upregulated	0.926	sensitivity = 90.9 % specificity = 81.8 %	8
14	miRNA-708	Sputum	Down regulated	0.656 (0.561 –0.750)	sensitivity = 64.71% specificity =62.50%	13
15	miRNA-200b	Sputum	Upregulated	0.679 (0.589 –0.768)	sensitivity = 65.22% specificity =61.19%	13
		Sputum	Upregulated	0.789	sensitivity = 55.1% specificity =72.2 %	16

Table 1: The Relationship between the Expression Levels, Area Under the ROC Curve (AUC) and Diagnostic Value of miRNA in Lung Cancer Patients

S. No	miRNA	Type of sample	Expression	AUC (95% CI)	Diagnostic value	Ref. No.
16	miRNA-182	Sputum	Upregulated	0.684 (0.611 – 0.778)	sensitivity = 64.94% specificity =59.76%	13
		Plasma	Upregulated	0.77 (0.68 – 0.87)	sensitivity = 70% , specificity =79%	7
		Sputum	Upregulated	0.825	sensitivity = 64.3% , specificity =79.5%	16
		Serum	Upregulated	0.734 (0.657 –0.803)	sensitivity = 63.4% , specificity =80%	29
		Tissue	Upregulated	0.825	sensitivity = 64.3 %, specificity = 79.5 %	16
		Plasma	Upregulated	0.7081 (0.6246 –0.7916)		25
17	miRNA-372	Sputum	Upregulated	0.707 (0.628 – 0.786)	sensitivity = 63.64% , specificity =60.98%	13
18	miRNA-143	Sputum	Upregulated	0.723 (0.644 –0.803)	sensitivity = 63.38% specificity = 61.73%	13
		Tissue	Down regulated	0.97	sensitivity = 99% specificity = 83%	35
19	miRNA-126	Sputum	Down regulated	0.777 (0.704 – 0.851)	sensitivity = 77.63% specificity = 75.00%	13
		Serum	Down regulated	0.793 (0.719 –0.854)	sensitivity = 60.7% specificity = 92.5%	29
		Plasma	Down regulated	0.5767 (0.4348 – 0.7186)	sensitivity = 62.5% specificity = 63.64%	27
		Sputum	Down regulated	0.824	sensitivity = 67.2% specificity = 73.8%	16
20	miRNA-31	Plasma	Upregulated	0.71 (0.61 – 082)	sensitivity = 73% , specificity = 61%	7
		Peripheral blood	Upregulated	0.785 (0.486–0.763)	sensitivity = 76.9% specificity = 74.5%	31
		Sputum	Upregulated	0.789 (0.719–0.849)	sensitivity = 60.23% specificity = 82.67%	13
21	miRNA-145	Sputum	Down regulated	0.807	sensitivity = 59.5 % , specificity = 82.9%	16
22	miRNA-27a	Plasma	Upregulated	0.95 (0.9 –0.99)	sensitivity =94% , specificity =81%	7
23	miRNA-195	Plasma	Down regulated	0.82 (0.74 – 0.90)	sensitivity =74% , specificity =80%	7
		–	Down regulated	0.92	sensitivity = 79% , specificity =100%	35

Cont. Table 1: The Relationship between the Expression Levels, Area Under the ROC Curve (AUC) and Diagnostic Value of miRNA in Lung Cancer Patients

S. No	miRNA	Type of sample	Expression	AUC (95% CI)	Diagnostic value	Ref. No.
24	miRNA-23a	Plasma	Upregulated	0.742	sensitivity = 50.00% specificity =92.31%	36
25	miRNA-205	Sputum	Upregulated	0.635 (0.552 –0.719)	sensitivity = 59.74% , specificity =53.93%	13
26	miRNA-30a	Plasma	Upregulated	0.727 (0.645 –0.810)	sensitivity =61% , specificity =84.3%	33
27	miRNA-197	Plasma	Upregulated	0.8792 (0.8254–0.9330)		25
28	miRNA-661	Serum	Upregulated	0.726	sensitivity = 60.7% , specificity =84.6%	34
29	miRNA-181a-5p	Plasma	Upregulated	0.731 (0.661-0.800)		26
30	miRNA-106a-5p	Plasma	Upregulated	0.737 (0.667-0.807)		26
31	miRNA-93-5p	Plasma	Upregulated	0.687 (0.614–0.761)		26
32	miRNA-183	Serum	Upregulated	0.626 (0.554-0.703)	sensitivity = 41.1% , specificity =82.5%	29
33	miRNA-576-3p	Peripheral blood mononucleated cells	Upregulated	0.7576 (0.6667–0.8486)		15
34	miRNA-19b-3p	Peripheral blood mononucleated cells	Upregulated	0.7546 (0.6651-0.8441)		15
35	miRNA-29b-3p	Peripheral blood mononucleated cells	Down regulated	0.7536 (0.6589–0.8482)		15
36	miRNA-29a-3p		Down regulated	0.6050 (0.4969–0.7131)		15
37	miRNA-628-3p	Plasma	Upregulated	0.730	sensitivity =42.7% , specificity =91.2%	32
38	miRNA-425-3p	Plasma	Upregulated	0.734	sensitivity =67.1% , specificity =68.1%	32
39	miRNA-532	Plasma	Down regulated	0.662	sensitivity =53.7% , specificity =80.2%	32
40	miRNA-339-3p	Plasma	Upregulated	0.720	sensitivity =64.6% , specificity =71.4%	32
41	miRNA-26b	Plasma	Down regulated	0.657 (0.616 – 0.696)		23
42	miRNA-19b	Plasma	Down regulated	0.559 (0.517 – 0.600)		23

Cont. Table 1: The Relationship between the Expression Levels, Area Under the ROC Curve (AUC) and Diagnostic Value of miRNA in Lung Cancer Patients

S.No	Name of miRNA	Age	Gender	Tumor size	Tumor stage	Smoking	Ref. No.
1	miRNA-33a-5p	✓	✓	✓	✓	✓	22
2	miRNA-128-3p	✓	✓	✓	✓	✓	22
3	miRNA-17	✓			✓	✓	11
4	miRNA-17-5p	✓	✓	✓	✓		24
5	miRNA-155	✓	✓		✓	✓	25
6	miRNA-197	✓	✓		✓	✓	25
7	miRNA-182	✓	✓	✓	✓	✓	7, 25, 29
8	miRNA-183			✓	✓	✓	29
9	miRNA-21	✓	✓	✓	✓	✓	6, 16, 27, 36
10	miRNA-let-7a	✓	✓	✓	✓	✓	14
11	miRNA-210	✓	✓	✓	✓	✓	27, 29, 30
12	miRNA-31	✓		✓	✓	✓	7, 31
13	miRNA-222	✓			✓	✓	11
14	miRNA-19b-3p	✓	✓		✓	✓	15
15	miRNA-29b-3p	✓	✓		✓	✓	15
16	miRNA-628-3p	✓	✓		✓	✓	32
17	miRNA-425- 3p	✓	✓		✓	✓	32
18	miRNA-532	✓	✓		✓	✓	32
19	miRNA-339-3p	✓	✓		✓	✓	32
20	miRNA-195		✓	✓	✓	✓	7
21	miRNA-195-5p		✓			✓	35
22	miRNA-23a	✓		✓	✓	✓	36
23	miRNA-375	✓	✓	✓	✓	✓	16, 27
24	miRNA-486	✓	✓	✓	✓	✓	16, 27
25	miRNA-200b	✓	✓		✓	✓	16
26	miRNA-27a	✓	✓	✓	✓	✓	7
27	miRNA-126	✓	✓	✓	✓	✓	27, 29
28	miRNA-30a	✓	✓		✓	✓	33
29	miRNA-661	✓	✓	✓	✓		34

Table 2: Clinical Association of the miRNAs Reported in Lung Cancer Patients

Significant ***Non-Significant***

CONCLUSION

This review article signifies the evaluation of various miRNAs as diagnostic biomarkers in LC patients. As the miRNAs target several genes they may serve as potential therapeutic targets. It may further be beneficial in controlling several other oncogenic signalling cascades.

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