Review Article

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MicroRNA as a New Blood-Borne Novel Biomarker for the Earlier Diagnosis of Lung Cancer

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ABSTRACT

Throughout the world, lung cancer is the first leading cause of cancer-related death, estimating roundabout 1.6 million cancer deaths occur annually. Lung cancer with its highest incident and deaths/mortality all over the world due to its limited diagnosis and treatment strategies. The earlier diagnosis of lung cancer plays an important in its treatment. There are different techniques used for the diagnosis of lung cancer including sputum cytology, different nanoparticles, and biomarkers such as CYFRA 21-1, NSE, SCC, CEA, ProGRP, Tumor M2-PK, miRNA. The main objective of this study is the role of miRNA as a novel biomarker for the earlier diagnosis of lung cancer. MicroRNAs are a very effective diagnosis marker for the earlier detection of lung cancer with high specificity and sensitivity about 96.6% and 86.2% respectively.

KEYWORDS: Cancer; Lung cancer; Biomarker; MicroRNA; Biogenesis; Cell signalling pathways

INTRODUCTION

Cancer has many types, in which one of the most common types of cancer is lung cancer, it is the most common type which is diagnosed worldwide. Within five years of diagnosis, 90% of lung cancer patients die. The mortality rate can be reduced by the early detection of this disease [1]. Different types of strategies are used for the analysis of biomarkers in the blood such as changes in the expression of the gene, protein, and micro RNA [2]. The discovery of micro-RNA found in serum has introduced new methods for the diagnosis of the tumor. The micro-RNA can be analyzed through different techniques such as quantitative RT-PCR based on Taqman probe to check the expression level of micro-RNA in the serum [3]. MicroRNAs are noncoding small sequences of RNA that control the expression of mRNA at post transcription level which has a role in cell proliferation, apoptosis, metabolism, and differentiation as well as has a role in oncogenic and anti-oncogenic signals. The abnormal level of microRNA found in malignant cells related to tumorigenesis, diagnosis, prediction, treatment, prognosis, and progress so microRNA has become a promising therapeutic target for several diseases such as cancer [4].

The microRNAs play an essential role in lung cancer diagnosis particularly present in the bloodstream including non-small cell lung cancer [5]. Some types of microRNAs are highly sensitive and more specific for the early diagnosis of lung cancer. The results of individual studies show that there may be inaccuracy in the diagnosis results of lung cancer [6]. MicroRNAs can be used for many solid tumors diagnosis including lung cancer and it can work as a non¬¬-invasive diagnostic marker by using the serum, whole peripheral blood, or plasma as a starting material and many techniques have been developed to analyze microRNA expression [7].

Various body fluids exhibit a different level of expression of microRNAs and it can be de-regulated through physiological and pathological conditions. MicroRNAs have a high diagnostic efficiency which is confirmed by various studies. Various trials are made for the profiling of microRNAs which are associated with different diseases; hence microRNAs can be used in the near future as a prognostic and diagnostic tool for many diseases especially in lung cancer because microRNAs are present in sufficient amount in sputum and blood of lung cancer patients. microRNAs can be easily obtained and analyzed which makes it a promising diagnostic tool [8]. Different types of microRNAs have different potential as a diagnostic tool such as miRNA-98 which

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suppresses the interleukin-10 expression producing B cells as well as interleukin-13 also reduces the production of interleukin-10 Which plays role in tumor tolerance. The study showed that mi RNA-98 are present in large quantity in peripheral B cells of a lung cancer patient as compare to a healthy person also the serum of lung cancer patient has a high level of interleukin-13 [9].

This review paper aims to explain the role of microRNA as a biomarker in early detection of lung cancer, to develop precautions at earlier stages of lung cancer, and to persuade researchers to perform further research in this field.

CANCER

Our body is composed of many cells, in which each cell takes an appropriate place in the body. Instead of white blood cells (WBCs), that prevent the body from microbial infection and tissue damage, the normal cells of the body stay in tissues. However, the cancer cells are spread aggressively into other parts of the body or tissues, the process is known as metastasis.

It is easy for a surgeon to remove a primary tumor from the body but once it is spread from one part of the body to other parts, they make different colonies in a different part of the body that is impossible for a surgeon to cure it [10]. Cancer is the irregular growth of cell division. Cancer is essentially a genetic disorder that inherited genetic mutations among the individuals and they may appear as the primary onset of this cancer [11].

Cancer causes deaths in many countries such as Canada, the United Kingdom (UK), New Zealand, Australia, and Denmark. In 2015 more than 1.65 million American people suffer from cancer and roundabout 5 lac and 90 thousand people died. In recently roundabout, 15 million people in America is cancer survivor [12].

LUNG CANCER

Throughout the world, lung cancer is the first leading cause of cancer-related death, estimating roundabout 1.6 million cancer deaths occur annually [13]. Lung cancer is the uncontrolled and irregular cell division in lung cancer that leads to the cause of death in both males and females. The rate and trends of lung cancer are different by age, sex, geography, socioeconomic, etc. because of the differences of the smocking pattern [14-15].

Lung cancer with its highest incident and deaths/mortality all over the world due to its limited diagnosis and treatment strategies [16]. The most important cause of lung cancer in both men and women is tobacco smoking either by active or passive [17]. But it has been reported that more than half of the factors contributing to lung cancer are never smokers other than active smoking and lung cancer in never smoker differ from smokers in their molecular profile and to their targeted therapy [18].

Other factors that have contributed to lung cancer included genetic susceptibility, occupational exposures, poor diet, environmental/air pollutions, and many others. It has been reported that food having rich vegetables and fruits may prevent the effect of lung cancer. A diet rich in meat may increase the risks of lung cancer. Many studies showed that lung cancer risk is associated with a high intake of β-carotene or total carotenoids [19].

Instead of great efforts and research of carcinogenesis, the molecular mechanisms of lung cancer are still unclear but currently, the dysregulation of long noncoding RNA has been identified in various cancer because it plays a key role in the regulation of cellular processes. GAS5 rs145204276 has been identified by Tao et al, increased the expression of GAS5 leads to the risk of hepatocellular carcinoma. Evidence showed that GAS5 rs145204276 was significantly related to the risk of lung cancer while GAS5 play a role as a tumor-suppressive [20].

Recently it has been identified that the chromosome 5p15.33, having TERT and CLPTM1L genes was the susceptible region for lung cancer. Two uncorrelated disease markers (rs402710 and rs2736100) have been identified located on TERT and CLPT1L, evidence that both have a role in lung cancer [21-22].

Lung cancer can be diagnosed via different methods depending on the type of lung cancer (small cell lung cancer or non-small cell lung cancer), the location and size of the tumor, and the patient overall clinical status. Sputum cytology one of the key techniques/methods used for the diagnosis of lung cancer has a rate of specificity 99% and the sensitivity rate is 66% [23]. In addition, nanotechnology has been developed various types of nanoparticles (NPs) such as inorganic, organic, metallic, and polymeric nanoparticles (NPs) for the diagnosis of lung cancer. Hybrid NPs are incorporated with targeting agents, multiple drugs, and photosensitive reagents for the production of a more sensitive and specific system for diagnosis and treatment of lung cancer [24].

Further, the expression of biomarkers provides very useful data for the diagnosis of lung cancer. The most studied and interesting biomarkers for lung cancer diagnosis are CYFRA 21-1, NSE, SCC, CEA, ProGRP, and Tumor M2-PK [25]. MicroRNA (miRNA) is another type of novel biomarker used for the diagnosis of lung cancer because the expression profile of miRNA differs from tumor tissue and normal tissue. Human cancer probably shows an altered profile of microRNA expression with tumor-suppressive or oncogenic activity [26].

BIOMARKER

A biomarker is a measuring tool that shows both either morbid or normal condition of a body. The term biomarker is also known as molecular marker. They are biologically important molecules having both intercellular and intracellular functions. Molecular markers can be measured both physically (e.g. during any microbial infection raising the temperature of the body is the well-known biomarker) or biochemically (e.g. the amount of protein in urine) [27]. World Health Organization (WHO) and United Nation (UN) with the coordination of International Labour Organization (ILO) has defined biomarker as "any substance, molecule or process that identify any medical state or the incidence of any disease." [28].

Many chronic diseases in the body bring changes in different molecular pathways of the body but in the inter-relationship between the diseases and biomarkers is extremely challenging [29]. Biomarkers include several types of techniques that are used to understand disease progression, causes, detection and diagnosis, prediction, and strategies for their treatment (Figure 1); [30].

Biomarkers are important roles in the study of Alzheimer's disease for different reasons. It increases the precision and accuracy of the clinical diagnosis of Alzheimer's disease. [31].

Biomarkers have an important role in the early prediction and diagnosis of acute kidney injury (AKI). These are necessary for the differentiation of one type of kidney disease from other types (e.g. urinary tract infection), detection of the severity of AKI, etiologies of AKI identification like a toxin, sepsis, and many more [32].

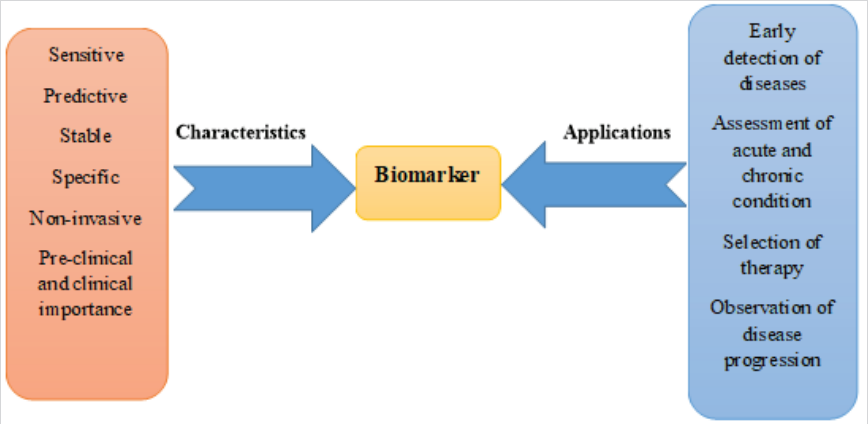

Figure 1: The applications and characteristics of biomarker.

Role of Biomarkers in Lung Cancer

There have many applications of the biomarker in oncology like their risk's assessment, diagnosis, prognosis, and screening, response prediction to treatment, and monitoring to the progression of the disease. Because biomarkers have important roles in all stages of the disease [33]. There are a few invasive techniques have been used for the early detection of lung cancer. One of them sputum cytology, that has been used for the detection of proximal bronchial lesions, but this very technique has time-consuming and less sensitive. More recently in blood and sputum biomarkers have been used for the investigation and early detection of bronchial lesions [34].

In addition, there have many numbers of DNA biomarkers that have been discovered as lung cancer biomarkers such as hyper methylations of promoters and mutations in K-ras, p53. Furthermore, the oncogenic gene such as MYCN, EGFR, MYCI, AKT2, and ERBB2 in DNA that has been taken from lung cancer patients and used as a biomarker for the evaluation with respect to a healthy individual having normal lung tissue [16-35]. The identification and analysis of protein have been done in a biological system by Mass spectrometry. There are many proteins protein used as biomarkers for early detection of lung cancer such as haptoglobin, serum amyloid A (SAA), apolipoprotein A-1 (APOA1), annexin (ANXA), and many other [36]. Furthermore, different circulating and tissue-specific miRNA having high specificity and sensitivity could be used as a novel biomarker for the diagnosis of lung cancer [37].

MICRORNA

Introduction to MicroRNA

MicroRNAs are small endogenous RNAs, which are approximately 22 nucleotides long that play a regulatory role in plants, animals, and some viruses. It cleaves messenger RNAs (mRNA) which in turn repress or inhibit translation and the targeted protein is not produced in Figure 2 & 3. In multicellular organisms, miRNAs are one of the most important classes that regulate gene expression. miRNAs can affect the products of many genes that code for proteins by inhibiting it from translation [38].

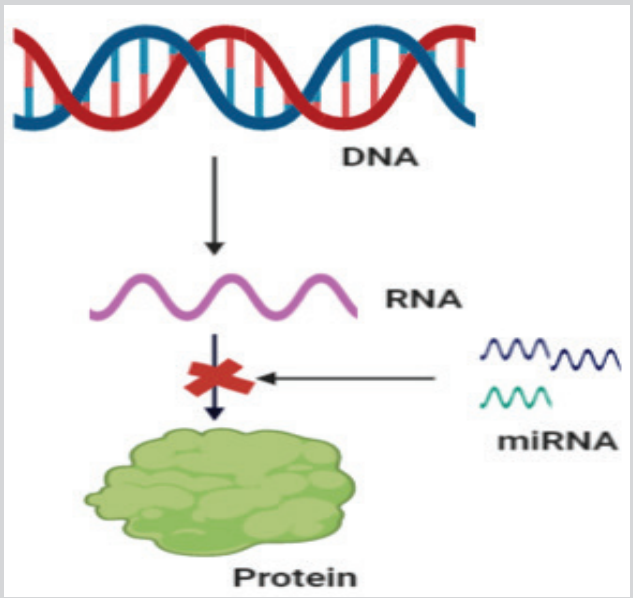

Figure 2: General Function of microRNA: first DNA plays its role as a database of instructions and codes for a specific mRNA then mRNA, containing specific instructions is translated into proteins and forms a functional product. As shown in figure microRNA plays its role as a regulator and inhibits the mRNA to form a specific functional protein or product.

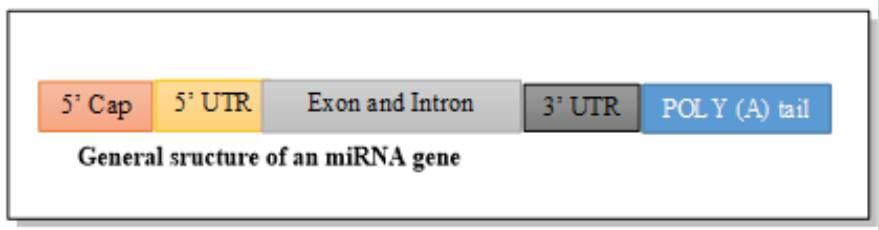

Figure 3: The general structure of a miRNA gene as shown in the figure, the miRNA gene contains the Transcription site, Poly (A) signal, Start Codon, and Stop Codon. These all play their roles to synthesize a miRNA molecule.

These small miRNAs are used as guides for post-transcriptional and epigenetic regulation [39]. miRNAs can perform the same function as of small silencing RNAs or small interfering RNAs (siRNAs), which directs the post-transcriptional gene silencing of their mRNA targets as guides for RNA-induced silencing complex (RISC). siRNAs and miRNAs both are composed of double-stranded structures. miRNAs can perform post-transcriptional gene silencing in a sequence-specific manner, these miRNAs need to form RISCs to perform their function, Argonaute is a family of proteins, which acts as a catalytic engine to stop the mRNA to be translated into protein. Argonaute is an essential enzyme of different RNA silencing pathways and it plays an important role in the process of miRNAs. In the regulation of genes, these small RNAs have an important role [40-41].

About 40% of miRNA genes may be present in introns or exons of other genes [42]. MiRNAs generally play their function as post-transcriptional repressors, and these miRNAs collectively determine different forms of physiology and development. miRNA performs a similar function as RNA interference (RNAi) promoted by small-interfering RNAs (siRNAs) [43].

Biogenesis of MicroRNA

MicroRNAs are a large family of small RNAs that are synthesized by a two-step process from long primary miRNAs (pri-miRNAs). The microprocessor complex consists of RNAs III enzyme Drosha and the double-stranded RNA binding domain (dsRBD) protein DGCR8, Microprocessor complex converts these pri-miRNAs to approximately 60–70 nucleotide precursor miRNA (pre-miRNA) intermediates. These pre-miRNAs are hair-pin shaped, which are transported to the cytoplasm, where they are chopped by Dicer to produce an approximately 22 nucleotides miRNA. A single strand of miRNA duplex is inserted into a rib nucleoprotein effector complex, also called the RNA-Induced Silencing Complex (RISC). RISC identifies the targeted mRNA with the help of guide RNA, which is already bound to the target mRNA and results in the breakage of target mRNA or translational repression in Figure 4; [44].

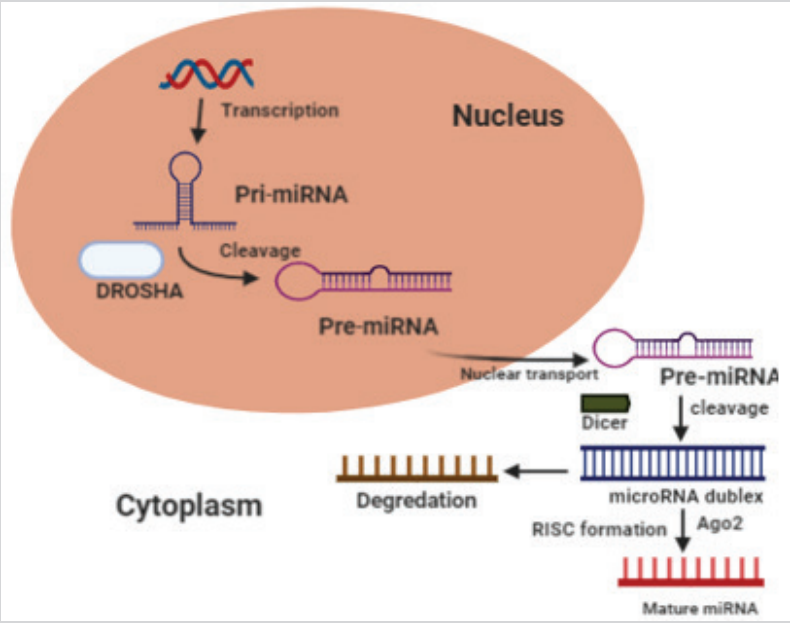

Figure 4: MicroRNA biogenesis: As shown in the figure first a microRNA gene is converted through the process of transcription to pri-miRNA and then with the help of DGCR8 and DROSHA this pri-miRNA is converted into pre-miRNA; this whole process is done in the nucleus. This pre-miRNA is then transported into Cytoplasm, which is then converted by Dicer to mature miRNA. Argonaut 4 helps in the unwinding of miRNA. The single-stranded miRNA then combines with the RISC to degrade the targeted mRNA

MicroRNAs are key regulators in cellular functions, that's why they need to be tightly controlled [45]. Thousands of miRNAs are reported to be found in plants, unicellular eukaryotes and animal miRNAs play a critical role in regulating proteomes and transcriptome of eukaryotic organisms. MiRNAs manage the regulation of specific genes, basically by making complementarity with the 3-prime untranslated regions (UTRs) of targeted mRNAs, to repress the target mRNA, making it unable to produce protein. The target mRNA is inhibited from its function either by translational inhibition, transcript destabilization, or both. Although through recent studies it is reported that inhibition of translation alone is responsible for the inhibition of mRNAs in mammalian miRNAs [46].

For a miRNA to perform its function and to acquire an effective gene silencing, it must be complexed with the RISC loading complex (RLC) proteins Dicer, TRBP, and Argonaut 2 (AGO2). Pre-miRNAs are generated from the nucleus through exportin-5 when pre-miRNAs are released from the nucleus to cytoplasm, so RLC, Dicer, and TRBP help pre-miRNAs to generate miRNAs and then it is combined with AGO2. AGO2 directs this miRNA to the site of the target, inhibiting the target mRNA to function and form a protein [47].

Gene expression is negatively regulated by miRNAs. Drosha has an essential role in the biogenesis of miRNA. Recently it was discovered that proteins other than Drosha can also play an important role in the biogenesis of miRNA, these are called Drosha-associated components. To find out that whether these Drosha-associated components plays role in miRNA biogenesis, Drosha is biochemically purified from the human cell through affinity chromatography and identified approx. 20 Drosha-associated proteins through mass spectrometric sequencing, which confirmed the role of Drosha-associated components in the biogenesis of miRNA [48]. RNA Polymerase II transcribes miRNAs as pri-miRNAs, which vary from 100-1000 nucleotides in length. In animals mature miRNAs are synthesized by two steps, ribonuclease III catalyzes each step (RNAs III) [49].

Circulating MiRNA as Novel Bloodborne Biomarker for Diagnosis of Advance Lung Cancer

The miRNA circulating in liquid biopsies for example serum and plasma were used as a potential biomarker for the earlier diagnosis of lung cancer through different analysis techniques such as RT-PCR (Table 1); [50].

Table 1: The table shows the miRNAs circulating in the blood which were used as a biomarker for the diagnosis of lung cancer by comparing the expression of different miRNAs in healthy individuals and lung cancer patients at different stages of lung cancer.

Name of MiRNA	Type of Sample	Efficiency	Number of Patients and Stages of Lung Cancer	Ref*
miRNA-let-7/miRNA-29/ miRNA-155/miRNA-221/miRNA-146b	Serum	AUC 1 value is about 0.60	220 controls and 20 cases at stage 1 and 2 of lung cancer	[51]
miRNA-486/miRNA-126/ miRNA-210/miRNA-21	Plasma	96.6% specificity and sensitivity is about 86.2%	29 controls and 58 cases from which 28 are at stage 3 and 4,30 at stage 1 and 2 of lung cancer	[52]
miRNA-182/miRNA-155/ miRNA-197	Plasma	86.8% specificity and about 81.3% sensitivity	161 controls and 83 cases of stage 1 and 2 as well as 41 cases of stage 3 and 4 of lung cancer	[26]
miRNA-7/miRNA-483/ miRNA-25/miRNA193a-3p/ miRNA-214	Serum	Area under curve (AUC) value is about 0.979	161 controls and 83 cases of stage 1 and 2 as well as 130 cases of stage 3 and 4	[26]
13 miRNAs	Plasma	Specificity about 81% and sensitivity 87%	870 controls and 37 cases of stage 1,12 cases of stage 2and 4 and 19 cases of the stage of sage 4	[53]
24 miRNAs	Serum	Specificity is 74.8% and sensitivity is about 77.8%	1115 controls and 42 cases of stage 1 and 2,32 cases of stage 2 and 4	[54]
24 miRNAs	Plasma	AUC value is about 0.92	100 controls and 42 cases of stage 1 and 3 of lung c	[55]

The decrease in the expression level of six miRNAs such as miRNA-146b, let-7b, miRNA-221, miRNA-155, miRNA-27b, miRNA_17-5p, miRNA-106a as well as the increase in the expression level of miRNA-29 was observed in the serum of patients particularly in non-small cell lung cancer (NSCLC) through real-time PCR(RT). The above study also showed that the serum and plasma contain the different level of miRNAs in the blood sample of the same patient which revealed that different composition of miRNAs are present in various components of the blood so many miRNAs such as miRNA-210, miRNA-146b miRNA miRNA-21 miRNA-155, and let-7a were used for the analysis of miRNAs expression level in different components of the blood to differentiate between the level of miRNAs present in healthy and lung cancer patients with the specificity of 96.6% and sensitivity of 86.2% while increasing the efficiency of histological diagnosis for adenocarcinoma as compared to squamous cell carcinoma.

Three of these miRNAs also play an important role to distinguish benign tumors from malignant tumors. Also, a series of miRNAs such as miRNA-155, miRNA-197, and miRNA-182 used to differentiate the lung cancer patient at stage1 from a healthy individual with the specificity of 81.77% and sensitivity of 81.33% which shows the importance of these miRNAs in the earlier diagnosis of lung cancer.

Besides these, a set of miRNAs such as miRNA-214, miRNA-7, miRNA-25, miRNA-193a-3p, and miRNA-483 level were increased in the lung cancer patients especially NSCLC patient as compared to a healthy individual in citizens of China and USA which indicate that the miRNAs may be used as a most potential biomarker for diagnosis of lung cancer among different ethnicities of the world. All of the above studies describe the role of miRNAs in the diagnosis of advanced lung cancer [50-55].

Circulating MiRNA as a Novel Bloodborne Biomarker for the Earlier Diagnosis of Lung Cancer

The noninvasive methods used to diagnose lung cancer at earlier stages are now a day became very popular through which various body fluids are analyzed such as analysis of miRNA in the blood [56-57]. The abnormal level of miRNA have been observed in different types of cancers including lung cancer so recently many studies were performed to develop a connection between lung cancer and dysregulation of miRNAs as result some miRNAs are over-regulated or down-regulated in the blood so measuring the quantities of miRNAs which have a role in lung cancer can be used to diagnose the lung cancer at earlier stages [58].

Different types of technique can be used for the analysis of miRNAs expression level in the blood such as real-time PCR (RT- PCR) which is a very powerful tool for the analysis of gene expression level the quantitative endpoint for real-time PCR is the thresh hold value (CT value) which can be defined as the cycle at which the fluorescent signal become above from the background activity (CT value) of real-time PCR is inversely proportional to the number of amplicons present in the mixture (shown in graph) i.e. lesser the number of amplicons more will be the (CT value) of real-time PCR [59]. Microarrays techniques were also used to quantify the level of the miRNA in the blood for earlier diagnosis of lung cancer.

Types of MiRNA and their Respective Role in the Earlier Diagnosis of Lung Cancer

Different miRNAs regulate the expression of various genes which has a role as oncogenes or as tumor suppressor genes [60]. The role of different types of miRNAs in earlier diagnosis of lung cancer is described below.

MiRNA-14A and MiRNA-16

miRNA-15a and miRNA-16 are located at chromosome 13q14 this region is deleted in 68% of chronic lymphocytic leukemia [61]. The miRNA-14a and 16 regulate the expression of many genes and some of these genes have a role as an oncogene or in the control of tumorigeneses such as the miRNA-15a and miRNA-16 down-regulate the expression of SLUG(transcriptional factor)which has a role in the apoptosis process [62] by positive regulation of PLD2(phosphor lipase D isoform) genes which is overexpressed during many types of cancers phosphor lipase D is a membrane protein which hydrolase phosphatidylcholine (PC) into phosphatidic acid (PA) and choline phosphatidic acid work as lipid secondary messenger which has a role in chemotaxis and cell proliferation of cell as well as in cell-cell communication through protein-protein interactions as phosphatases and kinases [63].

The miRNA-14a and miRNA-16 are express in less quantity among the cancer patients as compared to the normal as a result the SLUG protein is overexpressed which inhibits the apoptosis process of the cell [61].

MiRNA Let-7

The family of miRNA let-7 regulates the KRAS protein upon binding with the 3- UTR region of the KRAS mRNA and downregulates its expression [64]. The KRAS gene encodes for a KRAS protein which works as a GTPase transducer and hence regulates the cell division [65]. When EGF along with ligand is bind to a specific receptor called EGFR which is present on the cell membrane activate the tyrosine kinase, the KRAS protein is activated when binding to the GTP which transfer the signal to the nucleus of the cell through MAPKs or AKT cell signaling pathway, as a result, some genes are activated or turn off which lead to the cell proliferation, Angiogenesis, survival, and migration of the cell [66].

The miRNA let-7 play important role in non-small lung cancer (NSCLC) because miRNA let-7 regulates the expression of oncogenes such as the KRAS gene if the miRNA let-7 does not express due to some reasons such as single nucleotide polymorphism (SNP) as a result the KRAS gene will overexpress which will lead to the abnormal cell divisions so the lung cancer patients usually have less quantity of miRNA let-7 in the blood [67]

MiRNA-22, MiRNA-24 and MiRNA-34a

The miRNA-22, miRNA-24, and miRNA-34a target the mRNAs of genes involved in the folate mediated One Carbone metabolism which consists of a set of biochemical reactions involve the folate coenzymes these enzymes have a role in the cell proliferation, DNA methylation, and the synthesis of nucleic acids and amino acids [68]. Tetrahydrofolate (THF) polyglutamate is the group of enzymes that regulate the pathway of folate-mediated One Carbone metabolism which is the set of independent biochemical pathways that take place in the Nucleus, Mitochondria, and Cytoplasm of the cell [69]. Folate –activated one carbon is essential for the synthesis of thymidylate, purines, and remethylation of homocysteine to form methionine [70]. Methionine is an important amino acid that can be adenylated to S-adenosyl methionine also called SAM or Ado Met. SAM is important for many SAM-dependent methylation reactions such as Histone proteins, cytosine bases of DNA, phospholipids, neurotransmitters, and other small molecules as well as for the synthesis of polyamines [71]. Thus, folate mediated on carbon

metabolism is vital for the synthesis of high-fidelity DNA, the methylation of DNA and chromatin structure hence has a role in the regulation of gene expression as well as in cell proliferation and genome stability [70]. So, the patients of lung cancer have a high level of miRNA-34a, miRNA-22, and miRNA-24 in the body fluids such as in serum or plasma [68].

MiRNA-452-5p

The miRNA-452-5P is overexpressed in liver cancer, esophageal cancer, and urinary tract epithelial tumors while down-regulated in prostate and breast cancer now the studied also shown the role of miRNA-452-5p in lung cancer [72]. The study showed that the miRNA-452-5P is overexpressed in LUSC (Lung squamous cell carcinoma) as compared to the non-cancerous tissues of the Lungs the studied also indicated that the patients with a high level of miRNA-452-5p and LUSC are associated with the earlier stage of the tumor but survive for a short time as compared to the patients which have a lower level of the miRNA-452-5p and can live at last stage of the disease [73]. The sequence for miRNA-452-5p is located at Xq28 which can regulate the expression of many genes and thus has a role in carcinogenesis through many mechanisms such as it target the mRNA of CDKN1B which acts as a tumor suppresser gene in hepatocellular carcinoma [74]. When the protein complex cyclin E ad CDK2 combine with the protein complex RB and E2F by hydrolyzing ATP the E2F detached from RB and bind to the promoter regions of the genes responsible for the S phase of the cell cycle [75]. Thus, it has been hypothesized that the miRNA-452-5p may be upregulated in the lung cancer patients so measuring the level of miRNA-452-5p through RT-PCR diagnose the lung cancer at earlier stages [72].

MiRNA-183

cell invasion and motility are the main characteristics of the metastasis process so the understanding of molecules and pathways involve in metastasis are essential for the treatment and diagnosis of different types of cancer [76]. The miRNA-183 involved in the regulation of a gene called VIL2 at a post-transcriptional level which is responsible for the synthesis of Ezrin protein the VIL2 gene has the complementary sequences for miRNA-183 at the 3-UTR region [76]. The Ezrine proteins are involved in the tumor metastasis and invasion thus downregulation of Ezrine protein may reduce the ability of tumor cells invasion and metastasis [77]. The ERM protein bind with another protein called PtdlnsP2 and recruited to the specific site on the cell membrane through his FREM domain it exposes the conserved threonine residue of F-actin domain now then a specific kinase enzyme phosphorylated the tyrosine residue and the ERM proteins are now ready to work as a linker between the cell membrane and cytoskeleton. Once the ERM is activated it can bind to many cell membrane receptors and initiate many cell signaling pathways [78]. The lung cancer patients have about 2-3 fold decrease in the expression level of miRNA-183 which lead to the overexpression of Ezrine protein thus increase the capability of tumor cells metastasis and invasions [76]

MiRNA-21

MiRNA-21 is up-regulated in many types of cancers which regulate the expression of genes involved in important biological processes of the cell such as development, differentiation, and apoptosis as well as in carcinogenesis and other diseases [79]. The sequence for miRNA-21 is located on17q23.2 and like other types of malignancies, the miRNA-21 is also overexpressed in NSCLC [80]. The miRNA-21 has a role in the growth of the tumor cells, affects the metastatic characteristics of tumor cells as well as cell proliferation, cell survival, and suppressing of IFN [81]. The miRNA 21 down-regulate the Ras/MEK/ERK pathway [82] as shown below in the following Figure 5. When a specific ligand such as growth factors, tumor-promoting factors, differentiation factors, and hormones are bind with corresponding RTK receptors on the cell membrane the tyrosine kinase domain of the RTK receptor is phosphorylated and work as a carrier to activate the conversion of Ras-GDP to Ras-ATP. The phosphorylation of Ras protein then recruits the Raf into the cell membrane which is responsible for the activation of the MEK1 gene. The MEK family has 5 genes MEK1, MEK2, MEK3, MEK4, and MEK5 the activation of these proteins will activate the ERK proteins which will transfer certain signals to the nucleus of the cell as result the cell will turn on or turn off certain genes thus the Ras/MEK/ERK pathways play important role in cell proliferation, differentiation, development, and survival when the MEK and ERK pathways are suppressed [83].

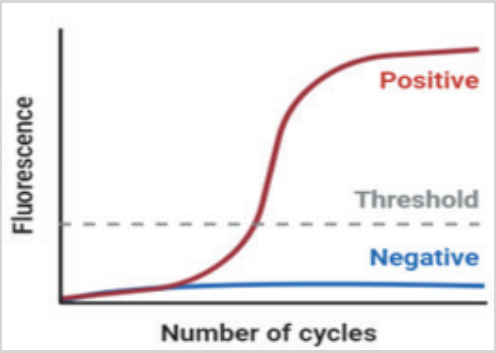

Figure 5: CT-Threshold cycle is the number of cycles at which fluorescence level become above from the background activity.

MiRNA -21 is up-regulated in lung cancer patient involved in the regulation of cell proliferation, development, differentiation, apoptosis as well as in metastasis and angiogenesis of tumor cells by targeting many genes involved in the above biological process such as tropomysine1 (TPM1), methyl-adenosine phosphatase gene (MATP), programmed cell death gene 4(PDCD4), SOX4, genes involved in p53-mediated cell signaling pathway and transforming growth factor cell signaling pathway, Bcl2 as well as phosphatase and tensin homolog(PTEN) [84].

MiRNA-198-5p

Lung adenocarcinoma (LUAD) is the sub-type of non-small cell lung cancer and many miRNAs including miRNA-98-5p have an important role in its development. The expression level of miRNA-98-5p is dependent on the Tumor-Node-Metastasis, blood vessels invasion, and age of the Lung adenocarcinoma patient [85]. The potential target for miRNA-98-5p are CCNA2, CCNB, AURKB, TOP2A, AURKA, BIRC5, CENPN, RACGAP1, PRC1, and CDKN3 the product(protein) of these genes are present in high quantity in the patients of Lung adenocarcinoma (LUAD) [86]. The genes mentioned above are involved in the P53 cell signaling pathway.

The p53 signaling is activated by DNA damage or mutation which prevents the accumulation of mutation and prevents damage to DNA. Different types of upstream cell signaling pathways may be activated by different factors damaging DNA such as ATR and ATM (ataxia telangiectasia-mutated) are activated in response to UV or ionizing radiation. P53 gene plays an important in the process of tumor suppression and the p53 protein encoded by the p53 gene

has a role in the cell cycle, induces apoptosis as well as in the DNA damage repairing process [87].

The miRNA-98-5p prevent the proliferation of lung cancer because it induces the process of apoptosis through regulating the expression of fibroblast growth factor receptor [88]. miRNA-98-5p is down regulated in LUAD patients and it has a role as a prognostic and diagnostic tool because of miRNA-98-5p target the genes involved in different cell signaling pathways [85].

CONCLUSION

Lung cancer is the second most leading cause of death after different heart diseases which may cause by different factors such as genetic factors, active or passive tobacco smoking, and certain environmental factors. The earlier diagnosis of lung cancer plays an important in its treatment and about 90% of mortality is caused because it does not diagnose at earlier stages. Lung cancer can be diagnosed through different techniques such as microarrays and RT-PCR by analyzing certain biomarkers also called molecular-markers in the body fluids of the patients. Biomarkers can be used for the diagnosis, prognosis, progression, and response to the treatment of lung cancer. Different types of biomarkers are analyzed in body fluids (sputum and blood) such as proteins and DNA based biomarkers. Now recently miRNA is one of the most effective biomarkers for earlier diagnosis of lung cancer miRNA is a small non-coding endogenous RNA which is about 18-25 nucleotides in size. The miRNA is considered as junk gene product which plays important role in the development of human being as well as involved in carcinogenesis and can be used as a therapeutic agent for the treatment of different diseases, particularly cancer.

In the biogenesis of miRNA, many proteins are involved such as RNAs III type of enzyme Drosha, double-stranded RNA binding domain (dsRBD) protein DGCR8, and Argonaut 4 any abnormality in this protein will lead to the abnormal expression of miRNA. miRNAs regulate the expression of genes at the post-transcriptional level and when these miRNAs are up or down-regulated in the body causes different diseases such as cancer due to the abnormal expression of the miRNAs certain genes involved in tumorigenesis are overexpressed while the genes involved in tumor suppression and apoptosis are down-regulate.

Different types of miRNAs have a specific role in the development of cancer such as miRNA-15a and miRNA-16 down-regulate the expression of SLUG (transcriptional factor) which has a role in apoptosis, miRNA-let-7 down-regulate the expression of KRAS protein, miRNA-22 and miRNA-24 target the genes involved in folate mediated One Carbon metabolism, miRNA 452-5p up-regulated in lung cancer and target the genes involved in tumor suppression such as CDKN1 gene,miRNA-183 target the gene of Ezrine protein which is involved in metastasis of the tumor cells, miRNA-21 target the genes involved in Ras/MEK/ERK pathways and these pathways play important role in development, differentiation, metastasis and apoptosis of the tumor cells and miRNA-198-5p target the genes involved in the P53 cell signaling pathway which play important role in the tumor suppression, cell cycle and induce the process of apoptosis.

During the development of Lung cancer, the level of the miRNA is down and up-regulate and its quantity can be measured in body fluids such as serum and plasma by using RT-PCR and microarrays techniques with high specificity and sensitivity about 96.6% and 86.2% respectively.

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