Review Paper

Circulating microRNAs in oncogenic viral infections: potential diagnostic biomarkers

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Received: 20 June 2019 / Accepted: 12 February 2020 / Published online: 18 February 2020

Abstract
Cancer is a leading cause of high death rate worldwide. One strategy to control the disease is the early diagnosis by novel biomarkers that express during early stage of the disease. The recent diagnostic strategies in cancer don't have enough specificity to promote the detection of cancer at its beginning. Many biomarkers like protein biomarkers and metabolites are being used for diagnosis of various cancer types but miRNAs are excellent among them, because they have distinctive biochemical characteristics. Moreover, to raise the precision and capability of miRNA to diagnose cancer, the analyzing of both miRNAs and as well as selective mRNA will help in creating a more complete categorizer. Virus constitutes the cause of 20% of entire human cancer cases and both RNA and DNA viruses are linked with tumors in both animal and man. Even though many viruses can cause different tumors in animals, only some of them are linked with human cancers and are presently regarded as oncogenic viruses. These viruses include *Human Papillomavirus* (HPV), *Hepatitis B* (HBV) and *Hepatitis C Virus* (HCV), *Epstein Barr Virus* (EBV), *Human Herpes Virus 8* (HHV8), *Human T cell Leukemia Virus* (HTLV) and *Merkel Cell Polyomavirus* (MCPyV). Expression data of miRNA in several cancers reveal that miRNA profile is different in cancer cells as compared to normal cells. So, miRNA could be useful biomarker for the detection of cancer. The present study strengthens a foundation and gives a logic to investigate the ability of miRNAs as circulating biomarkers in various cancers.

Keywords miRNA · Biomarkers · Oncogenic viruses · Circulating · Detection

1 Introduction

Cancer is specified as a disease that has high mortality and low endurance rate because of no successful diagnostic approach accessible in clinics. Many protein biomarkers, including carbohydrate antigen (CA), gamma-Semino protein or kallikrein-3, also known as prostate specific antigen (PSA), carcinoembryonic antigen (CEA) have achieved a large number of acknowledgements. However, they are found to be less effective particularly when they are used for screening at early phase or they don't have the ability to differentiate between indolent and aggressive cancers at all [1]. This has developed the identification for novel and more responsive biomarkers which would help to monitor disease.

MicroRNAs (miRNAs) have shown to be a useful and key player in the regulation of gene predominantly 'post-transcriptional regulation' since their discovery. Similarly, miRNAs have ability to differentiate physiological and pathological conditions of diseased and normal individuals, therefore acting as biomarkers. Circulating miRNAs that exist in the secretory fluids (saliva, plasma, urine and serum) have been used as biomarkers in disease detections. The 1st circulatory miRNA identified is "placental miRNA". It was observed in maternal plasma throughout gestation [2]. Similar to this finding, an increased miRNAs

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concentration was observed in the serum of lymphoma patients as compared to healthy individuals. From then onward, circulating miRNAs can act as invasive biomarkers for detection of different diseases. A hallmark such as accessibility and prodigious stability increase their potential as biomarkers for disease.

2 MicroRNA discovery

MicroRNAs (miRNAs) are found in eukaryotes including human. They were first discovered in *Caenorhabditis elegans*. The first miRNA (lin-4) was identified by Victor Ambros and colleagues. The lin-4 gene doesn't have ability to encode protein but can create small RNA [3]. Second miRNA (let-7) was discovered by Gary Ruvkun's group to point the further stages of *C. elegans* development similar to lin-4. After the discovery of 1st miRNA, many miRNAs have been found and are in examine. At present, number of miRNAs have been discovered that act as an oncoMirs or in tumor prohibition [4]. Up till now 1900 miRNAs have been identified having regulatory roles in physiological processes e.g. cellular growth, multiplication, differentiation, holometabolism etc. Excitingly, there was a research on miRNA which concluded that 100 s of mRNA are repressed by a single miRNA [5].

For over a last few decades, various studies indicated the pertinence of miRNAs biology in cancer, showing that they can behave both as oncogenes and tumor repressors; negatively regulating the protein-coding oncogenes [6, 7]. Many researchers have dictated that miRNAs can influence cancer phenotypes and many reports have exhibited miRNAs expression profiles which provide detail about tumor origin, prognosis and diagnosis of cancer [8].

2.1 Canonical biogenesis of MicroRNA

miRNA biogenesis consists of two step processes; nuclear and subsequent cytoplasmic cleavage. The first step is in nucleus where RNA pol 2 transcripts Intergenic miRNA to form pri-miRNA (~60–70nt stem loop intermediary, called the miRNA precursor, or the pre-miRNA). Only that pri-miRNA with the proper stem length and the ability of creating 5′ and 3′ single-stranded RNA overhangs will be effectively continued and converted into useful miRNA. The maturation process starts by the DROSHA RNase III endonuclease and the double-stranded RNA-binding protein DiGeorge syndrome critical region gene 8 (DGCR8) complex collectively known as 'the microprocessor [9], which produces a cut on pri-miRNA, makes it shorter and forms pre-miRNA and thus the stem loop of pre-miRNA has a 5′ phosphate and ~2 nt 3′ overhang.

For further processing, nucleocytoplasmic transporter factor Exportin-5 and Ran-GTP brings pri-miRNA into the cytoplasm [10]. This stops nuclear damaging and promotes translocation in the cytoplasm. In cytoplasm there is an enzyme called dicer which performs an activity of RNase 3 endonuclease. Firstly, it recognizes the bases of pre-miRNA, binds with pre-MicroRNA, cleaves it and makes dsRNA without hairpin. The dicer loop cleavage is leaving the 5′ phosphate and ~2 nt 3′ overhang that binds with Argonaut (AGO) protein. The combination of RNA, Argonaut with RNA-induced silencing complex (RISC) target mRNA via direct base pairing. Finally the RNA duplex is untwisted and the single stranded mature miRNA is integrated into the protein complex RISC to function as a guide, controlling the suppression of target mRNA. The protein expression of targeted mRNA is being altered by the resultant miRNA/mRNA hybrid. MiRNA may be degraded or translation may be inhibited [9].

miRNAs are transcribed by RNA polymerase II or III as pri-miRNA, and then processed in the nucleus by Drosha-DGCR8 into pre-miRNA. The pre-miRNA is exported to the cytoplasm by exportin-5 and further cleaved by a complex composed of Dicer and TRBP. The functional strand of mature miRNA is incorporated into the RNA-induced silencing complex (RISC), which contains Argonaute protein (Fig. 1).

3 Biological role of miRNAs

As mentioned above, miRNAs are essential part of feedback loops having strength to control biological activity. Therefore, miRNAs might work to enhance the clarity of gene expression by controlling the proteins production [11]. Moreover, single miRNA may contribute to control

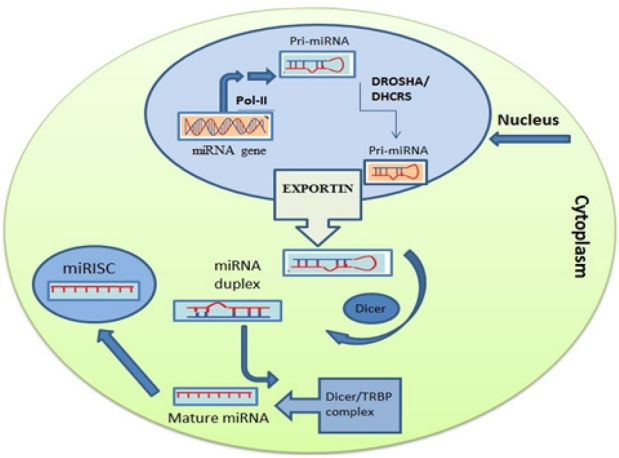

Fig. 1 Biogenesis of microRNAs

specific differentiation processes as demonstrated by early research in worms for example, the control of lin-41 by let-7. Concernedly, miRNA also play a major role in stem cell differentiation and in persuading pluripotency where individuals miRNA clumps, miR-302, was currently revealed to be effective to create iPSC from both human and mouse embryonic cells [12]. Their contribution in differentiation and development of cellular affinity proceeds that reduction of miRNAs function might develop the increased cellular flexibility, de-differentiation and increased tendency for oncogenic modifications. Moreover, because of many transcripts modulated by individual miRNA, their inclusive function in oncogenesis might be dependent on the context. Appropriately, a specific miRNA might be upregulated in various types of cancer and thus believably oncogenic, while downregulated in other types of cancer, hence show tumor suppressor function. For example miR-29 is responsible for tumor-suppressor in lung tumors while in breast cancer, miR-29 is responsible for oncogenic functions [13, 14] (Fig. 2).

miRNAs use two mechanisms to exert gene regulation. Some animal miRNAs can bind to mRNA targets with exact complementarity and induce the RNAi pathway. miRNAs also bind to targets with imperfect complementarity and block translation. miRNAs detection methods, advantages and their disadvantages are described in Table 1.

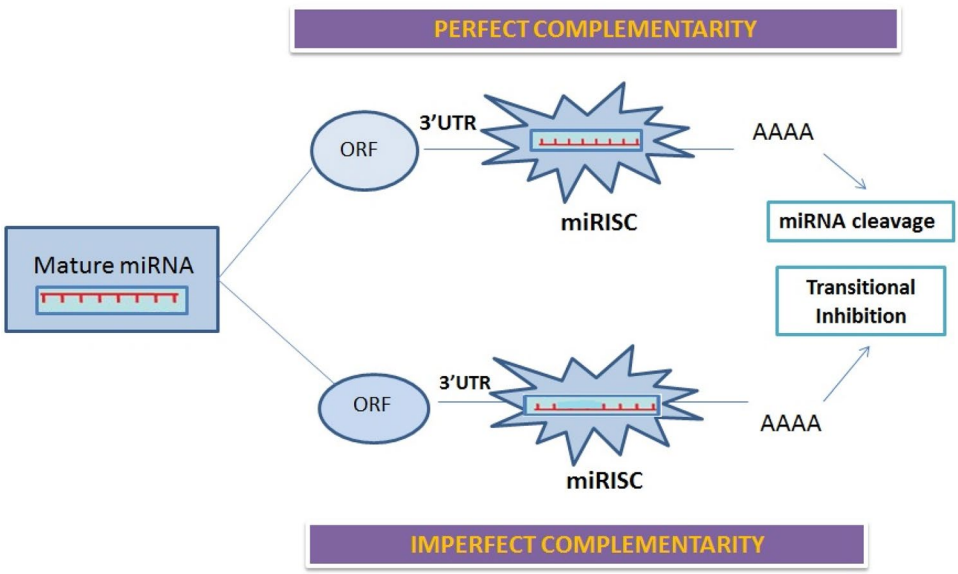

Fig. 2 MicroRNAs (miRNAs) as tumor suppressors and oncogenes

Table 1 miRNAs detection methods, advantages and their disadvantages

miRNAs detection methods	Advantages	Disadvantages	References
Isothermal exponential amplification-based methods	No PCR require Good sensitivity Real-time assay in some cases	Complex probe design Many enzymes are used	[86]
Amplification-based method	No PCR needed Better regulation of signal amplification In situ identification attain in some cases	Complex probe design Unspecific amplification	[87]
Direct Quantitative Analysis of Multiple miRNAs (DQAMmiR)	Easy probe design Various target detection	Specific equipment needed	[17]
qPCR	Fixed protocol high sensitivity high specificity	Needs quality miRNA annotation	[88]
RNA sequencing	Complete genome analysis No need of miRNA annotation	Need most input material Less sensitive	[89]
Multiplex RT-PCR	High sensitivity High specificity Easy data analysis	Not suitable for small scale experiments of 1-2 samples Needs quality miRNA annotation	[90]
miRNAs arrays	Fixed protocols Purpose built analysis tools	Less quantitative Needs quality miRNA annotation	[91]

4 Molecular biomarkers for cancer detection and treatment

Identification of cancer biomarkers (protein biomolecules) present in the body fluids have great significance in early detection and as well as therapy efficacy. Many devices have been made for detecting the molecular markers. Molecular biomarkers have the ability to improve the current state of early cancer detection, some of them are given in Table 2.

4.1 Circulating miRNA as a potential biomarker

Biomarkers have the capability to enable us to diagnose or examine disease. In the past decades many miRNAs have been examined in various forms of human cancer. The abnormal expression of miRNAs promote to cancer development via different kinds of mechanisms like deletions, mutations etc. [15]. MiRNAs expression profiling act as a useful diagnostic and prognostic tool and many studies have been done which indicates that miRNAs are considered as oncogene or a tumor suppressor. Currently, it has been observed that miRNAs are dispersed in the peripheral blood [16]. They perhaps are found inside extracellular vesicles in the plasma, bound to proteins such as Argonaut 2, and are not degraded hence used as intracellular communicators. Therefore, they may act as biomarkers for detecting different kinds of diseases. Particularly, biomarkers should be discovered so that it can be used to detect diseases at early stages.

Slide-based staining assay is used to detect the changes in miRNAs present in the tissues. Latter studies in the field of pancreatic cancer have shown that some changes have been seen in miRNA level in both normal and malignant tissues. So this technique is used to monitor treatment options [17]. There is a noninvasive way to expose miRNA from blood sample and from urine as a circulating tumor cells. MiRNAs are considered as highly stable in formalin-fixed, paraffin-embedded (FFPE) tissue from hepatocellular carcinoma [18], papillary thyroid carcinoma [19], renal tumor [5] and lung cancer [20]. So miRNA expression studied from repository tissue specimen and liquid body substances such as blood will be essential for identifying diseased state.

Serum of patients who were suffering from large B-cell lymphoma was examined and 1st circulating miRNA was used as a biomarker to identify this disease. For earlier screening of circulating miRNAs different technologies are involved like microarray profiling, NGS, and real-time PCR array [21]. Diseases like neurological disorders and cancers can be treated successfully if they are detected in their early phases. Both cancer and neurological affliction requires recognition of dependable and early biomarkers. Modulation of miRNAs and their target mRNAs give best choice for making of novel biomarkers in these disorders.

4.2 Oncogenic viral infections

Viral infections constitute around 20% of entire human cancer cases. Even though many viruses can cause different tumors in animals, only seven of them are linked with human cancers and are presently regard as oncogenic viruses. These viruses include *Human Papillomavirus* (HPV), *Hepatitis B* (HBV) and *Hepatitis C Virus* (HCV) [22], *Epstein Barr Virus* (EBV) [23], *Human Herpesvirus*-8 (HHV8) [24], *Human T-cell Leukemia Virus* (HTLV) [25] and *Merkel Cell Polyomavirus* (MCPyV) [26]. There are various mechanisms by which these viruses transformed normal cells into tumor cells [27]. These viruses will alter the gene

Table 2 Recent molecular biomarkers used for diagnosis and treatment of cancer

Cancers	Molecular biomarkers	Techniques	Treatment	References
Non-small cell lung cancer	EGFR overexpression	Immunohistochemistry, RT-q(PCR)	EGFR-tyrosine kinase inhibitor (TKI)	[92]
Breast cancer	HER2 overexpression, overexpression of estrogen receptor	CISH, IHC	Trastuzumab, Tamoxifen	[93]
Gastrointestinal stromal tumors (GISTs)	CD117 overexpression	Immunohistochemistry	Imatinib	[94]
Glioblastoma	(*MGMT*) overexpression	Immunohistochemistry	Temozolomide	[95]
Metastatic melanoma	CTLA-4	Immunohistochemistry	Ipilimumab	[96]
Thyroid cancer	BRAF and RAS point mutations	ThyroSeq version 2 next generation sequencing	histone deacetylase inhibitors and retinoids	[97]
Chronic myeloid leukemia	Philadelphia chromosome-positive BCR-ABL fusion gene	FISH	Imatinib	[98]

expression or they may produce changes in the genetic level. Oncogenic viruses are able to insert their genome in cellular chromosomes that leads to genetic abnormality. Virus oncoproteins can stimulate the cellular signaling processes that may divert the expression of cellular genes. Infection causes the alteration at gene level and reproduction of oncogenic viruses may cause the spreading of cancer stem cells in human [28] (Table 3).

Oncogenic viruses also causes latent infections as they stay in the body for a long time, e.g. EBV may survive in the body for lifetime [29]. These viruses also cause chronic infections that continue for a long time e.g. *Hepatitis* B or C. Epidemiological studies revealed that there is a strong association between HBV with liver cancer [30]. MCPyV can cause Merkel cell tumor [26] and HTLV-1 causes adult T-cell lymphoma. HHV8 (also known as Kaposi's sarcoma-linked *Herpesvirus*, KSHV) has been dependable for Kaposi's sarcoma generally found in patients with acquired immunodeficiency syndrome (AIDS) [24] (Tables 4 and 5)

4.3 miRNA for the detection of *Hepatitis C Virus*

Approximately 170–200 million people are infected with *Hepatitis C Virus* [22]. One of the critical provocations in the research of HCV is to detect the liver disease at its early stage which will better improve the result of antiviral treatment. The virus genomes consist of 5′ and 3′ untranslated regions that are used for viral translation and replication. Prestigiously, miRNAs are identified as important in pathogenesis of HCV infection that are linked with liver disease and the disruptions of miRNAs are involved in change of HCV replication [31].

Table 3 miRNA expression associated with different type of oncogenic viral infections

Oncogenic viruses	Cancer types	Sources	miRNAs	Expression	References
Hepatitis C Virus	Hepatocellular carcinoma	Serum	miR-29a, 146, 149, 221, 222	Increased	[34, 35]
			miR-196a	Decreased	
		Urine	miR-625, 532, 618	Increased	
			miR-516-5p/650	Decreased	
	Liver cirrhosis	Serum	miR-20a, 93	Increased	
			miR-92	Decreased	
Epstein Barr Virus	Nasopharyngeal carcinoma	Serum	BART7 and 13	Decreased	[99]
Hepatitis B Virus	Hepatocellular carcinoma	Serum	miR-885-5p, 122, 21	Increased	[46]
Human T-lymphotropic Virus	T-cell leukemia	Plasma	miR-93, 155	Increased	[56]
			miR-126	Decreased	
Human Papilloma Virus	Cervical cancer	Serum	miR-21, 146a, 224, 182	Increased	[63, 68, 100]
			miR-218	Decreased	
	Colon cancer	Serum	miR-21	Increased	
			let7a-1, 143, 145, 16, 125b, 31, 133b, 96, 145	Decreased	
	Prostate cancer	Serum	miR-141	Increased	
Merkel cell Polyoma Virus	Merkel cell carcinoma	Serum	MCV-miR-5p, 23	Decreased	[70]
Human Herpes Virus-8	Kaposi sarcoma/B-cell lymphoma	Serum	miR-143, 145, 126-3p and 13	Increased	[33, 82]
			miR-221, 222, let7 family	Decreased	

Table 4 miRNAs as an oncogene

Tumors	miRNAs	Target	References
Pancreatic cancer	miR-103, miR-107, miR-21, miR-155 miR-141, miR-220c	Tumor protein 53-induced nuclear protein 1 (TP53INP1) Zinc finger E-box binding homeobox 1 (ZEB1)	[101]
Colorectal cancer	MiR-21	induces invasion, intravasation, or metastasis in Colo206f-cells	[102]
Lungs cancer	miR-17-92 including miR106a, miR17-5p, miR19a, miR-25, and miR-93	Inhibition of apoptosis	[103]

Table 5 miRNAs as a tumor suppressor

Tumors	miRNAs as tumor suppressor	Functions	References
Pancreatic cancer	MiR-34a	Induced by P53 tumor suppressor protein Aberrant CpG methylation	[104]
Colorectal cancer	MiRNA-143 and 145	Targeting tumorigenic elements at the translational or posttranscriptional level	[105]
Lungs cancer	let-7 family, including let-7b, let-7c, let-7d, let-7f, and let-7g	Inhibit the RAS oncogene Inhibits the expression of HMGA2, a high-mobility group protein	[91]

A cohesion between miR-196 and 5A coding region of HCV JFH1 genome has been seen in previous studies. In addition to this, IFNβ therapy leads to substantial expression of miR-196 initiation in Huh-7 cell line. This showed that miR-196 have a significant role in changing the HCV expression. The past studies have recognized that miR-196a hinders the expression of HCV by targeting the genome of HCV. Later on it leads to the up regulation of heme oxygenase liberating anti-inflammatory molecules. Thus for the development of HCV infection miR-196 is an important factor. Later on it was theorize that the upregulation of miR-196 may be helpful in detection, prevention and treatment of the HCV infection [32].

Moreover, further studies have showed miR-196 as a biomarker for early diagnosis of HCV. Microarray analysis of miRNAs demonstrated that the HepG-HCV and HepG2-control have six differently expressed miRNAs. With over expression of HCV core protein, there was an upregulation of miR-29a, miR-146, miR-149, miR-221 and miR-222 and down regulation of miR-196a [33].

Shrivastava et al. [34] demonstrated the differential expression of miRNA as a biomarker related to liver disease. It was found that many circulating miRNA were upregulated in serum of HCV infected patient as compared to healthy individuals [34]. The serum of the patients with HCV showed high expressions of miR-20a and miR-93 and decreased expression of miR-92 with high level of fibrosis. Some sample studies showed that as disease developed from acute to chronic infection, the expression of miR-20 stayed higher while expression of miR-92 decreased post infection. MiR-625, miR-532 and miR-618 were found to be upregulated as 56%, 62.5% and 72% of Hepatocellular carcinoma (HCC) in post HCV infection. Similarly, expression of miR-516-5p and miR-650 were downregulated as 50% and 72%. Due to differential expressions of miRNAs it is now possible to target the genes which are associated to HCC progression [35].

4.4 miRNA for detection of *Epstein–Barr Virus*

Latent infections have been associated with large spectrum of non-cancerous and cancerous diseases caused by EBV [36]. This virus causes Burkitt's lymphoma, Nasopharyngeal Carcinoma (NPC) and Hodgkin's lymphoma. Clinically, NPC is vastly incursive and metastatic [37]. Large numbers of EBV encoded miRNAs have been found in NPC tumors.

EBV throughout its replication cycle represents two miRNAs; 'BHRF1 and BamHI-A Rightward Transcripts (BART) [38], which are largely expressed in NPC cells. In recent studies, circulating BART-miRNAs along with BamH1-W DNA were examined before and after treatment in patients. They selected three BART-miRNA which were miR-BART2-5p, miR-BART17-5p, and miR-BART18-5p out of 44 mature BART-miRNAs that were previously well-known as circulating freely in NPC patients. Circulating BamHI-W DNA was a functional biomarker for the identification of NPC before treatment. The recognition of circulating miR-BART17-5p was supposed to be a potential biomarker to evaluate a poor treatment outcome. Certain BART-miRNAs were discharged in the blood are now recognizing profusely in NPC patients [39].

A group of researchers analyzed the altered expression of BART miRNAs that are linked with EBV infecting B cells, noncancerous cells and cancerous NPC cells in order to identify BART miRNAs. Analysis of EBV infected cells identified extracellular secreted BART miRNAs; miR-BART3, miR-BART7 and miR-BART13. Utilizing these miRNAs as a marker, they examined plasma of NPC patients, non NPC cancer controls and healthy ones. Results demonstrated that the plasma from NPC patients contain miR-BART7 and miR-BART13 which were absent in non NPC controls. Moreover, by following radiotherapy plasma levels of miR-BART7 and miR-BART13 were reduced in patients. So circulating BART-miRNA may serve as a marker for diagnosis and prognosis of NPC [40].

4.5 miRNA for the detection of *Hepatitis B Virus*

HBV infection is widely spread in African, Asian and Western countries. The prevalence of HBV is transitional (2–7%) in Southern and Eastern Europe where the cause of infection is through perinatal transmission, tattooing, making

cut outs, and nosocomial transference, by sexual contact and by needle exchange between drugs users [41].

Generally, hepatitis B vaccinations strategy for new born and teenage has been started that reduce the prevalence of HBV infection. The defensive immune response that demolish virus-infected liver cells causes acute liver injury and due to the lack of immune response, virus infected cells were not destroyed and infection turned into chronic. This case is related with antenatal acquired HBV infection that is concerned to chronicity up to 95% [42].

From a global view point, majority of the hepatocellular carcinoma is due to chronic HBV infection. Elders with chronic hepatitis B get HCC about 5% for decades, that is about 100-fold greater than the rate between uninfected populations [43]. The high death rate is because of recognition at its last stage with few therapeutic choices. Actually insufficient diagnostic markers and poor treatment plan makes it a crucial challenge.

In case of HBV infections, circulating miRNAs are attaining attention for the diagnosis and prognosis of HCC [44]. Until now, two miRNAs exhibit extremely high potential to diagnose HCC which were miRNA-21 and miRNA-122. miRNA-122 was a liver miRNA while miRNA-21 is created by different tissues containing heart, liver and colon that were severally involved in cancer growth and coronary disease development. MiRNA-21 activates phosphatases (e.g., ATK and MAPK) which inhibits the tumor suppressor pathways while miRNA-122 hinders the cancer growth, being a tumor suppresser gene. A direct association was seen between enlarge miRNA-21 level and cell proliferation. Additionally, high level of circulating miRNA-21 was linked with increasing HCC therefore, specify a poor prognosis [45]. Level of serum miRNA-122 is inversely associated with the extremity of liver fibrosis. The antitumor characteristic of miRNA-122 has been effectively utilized in preclinical model to stop HCC development. The diagnostic precision of miRNA-21 somewhat surpassed that miRNA-21 have sensitivity and specificity up to 87% and 80% as compared to miRNA-122 which have 68.0% and 73.3% so they were the potential biomarker for the diagnosis of early HCC [46].

During recent years, many other miRNAs were also found to play crucial functional roles. miR-106b and miR-181b may serve as a biomarker for diagnosis of liver cirrhosis [47]. Up regulation of miR-885-5p was observed in the serum of HBV, LC and HCC patients and may represent as a biomarker for liver diseases. Let-7c, miR-23b, miR-122, miR-150 and miR-122-5p, miR-192-5p acted separately as a potential biomarker for HBV infection. MiR-143 and miR-215 present in the serum could act as a potential biomarker for CHB and HCC [48]. MiR-21-5p may act as a marker for viral hepatitis [49] and after liver transplantation MiR-146a-5p may serve as a marker for acute rejection. All these findings would help us to understand the expression mechanism of circulating miRNAs in various phases of HBV driven infections and furthermore to the production of diagnostic tools for the recognition of CHB and LC.

4.6 miRNA for the detection of *Human T-cell Leukemia Virus* (*HTLV*)

HTLV is a retrovirus, representative of Delta retrovirus genus that was identified in early 1980s by two-separate groups in America [50] and in Japan [51]. Though, there are four types of HTLV and HTLV-1 is the utmost pathogenic and has the perception that it may be the 1st oncogenic retrovirus discovered in humans. HTLV approximately infects 15–20 million populations worldwide and involved as a pathogen in different kinds of diseases like adult T-cell leukemia or lymphoma (ATL) and tropical spastic papaparesis or HTLV-1 associated myelopathy (TSP/HAM). HAM/TSP was 1st identified in 1969 over the decade before the revelation of HTLV-1 [52].

As many studies have shown that miRNAs were involved in progression and prognosis of disease, in case of HTLV many miRNAs were concerned with the survival of HTLV-1 infected cells. One key discovery was that up-regulation of miR-93 was found in HTLV-1 infected cells. Moreover, various kinds of tumors including HTLV-1 have increased expression of miR-93 which shows that miRNA play a vital role in cellular alteration [53, 54]. Additionally miR-223 demonstrated to be upregulated in HTLV-1 infected cells in adult T-cell leukemia patients [20]. MiRNA-155 has also been recognized as it supports the cellular transformation of HTLV-1 and it has also been seen in another oncogenic virus like EBV [55] and that miRNAs might be involved in the progression of disease.

In order to check whether miRNAs were involved in detection of disease, an experiment was conducted by isolating CD4-positive cells from two healthy individuals, three acute and three chronic ATL patients and microarray was used to profile cellular miRNAs. Five miRNAs were screened which were miR-155, let-7g, miR-126, miR-130a and let-7b. Because a huge variation was seen in their expression in diseased patients' v/s healthy individuals. The expression level prior to 5 miRNAs was re-measured by RT-qPCR and it wasn't repeatedly consistent in cells and plasma. The increased and decreased level of miR-155 and miR-126 altered with ATL phase. So this study showed a quantitative variation between plasma miRNAs and cellular miRNAs. The increased level of plasma miR-155 and decreased level of miR-126 associated with their bad prediction, showed their functionality as a unique biomarker for the analysis of disease stage [56, 57].

4.7 miRNA for the detection of *Human Papillomavirus* (*HPV*)

Human Papillomavirus (HPV) preferably affects mucosa epithelial cells that effectuate non-cancerous and sometimes malignant tumor. Different species of HPVs, like HPV16, 18, 31, and 45, were recognized usually in anogenital cancers, especially cervical cancer and anal cancer, and hence they were counted to be oncogenic [58]. HPV16 infection appears to be common in colorectal cancer-tissues. McNicol and Dodd first detected HPV DNA in prostatic tissues using polymerase chain reaction (PCR). Cervical cancer is most usual cancers in female with high mortality about 233,000 deaths per year [59]. The prevalence is lesser in emerging states because of cervical screening tests and so many health education paths. The causal link in high-risk HPV (HR-HPV) infection and cervical cancer has been well recorded in epidemiological and functional research. High-risk HPVs, such as HPV16, HPV18, and HPV31 have been identified in up to 99.7% of cervical squamous cell carcinomas and 94–100% of cervical adeno- and adenosquamous carcinomas. The high-risk HPV oncoproteins, E6 and E7, lead to cervical cancer by severely immobilizing the cellular tumor repressor proteins p53 and pRb [60].

Throughout the world, cervical cancer remains one of the leading causes of death in women. It is a contagious disease having genes associated with complicate biological processes, so closely linked with constant infection of high-risk human papilloma virus (HPV) [61]. Chromosomal mutation and alteration of single nucleotide polymorphisms; these were the key factors to cause the malignant alteration of cervical epithelial [62].

Over recent years, the analysis of small RNAs (miRNA) modulation of gene expression begins to be a hot spot. Above 1000 human miRNAs were estimated to regulate around 60% of protein-coding genes, specifying their substantial role in many biological processes. In cervical cancer tissues, up regulation of miR-21 was seen [63], accumulating affirmation about change in the expression of miR-21 in cervical cancer demonstrates that it might play a vital role in tumor biology.

In order to check the clinical value of miR-21, a group of scientist performed RT-PCR assay to examine the expression mechanism of miR-21-3p and miR-21-5p in HPV associated carcinoma [64]. There data confirmed that the expression of miR-21-3p and miR-21-5p particularly increased in cervical carcinoma as compared to normal tissues, which shows that miR-21 could play a crucial role in the progression and poor diagnosis of human cervical cancer. MiR-21 was discovered for the 1st time as a marker for prognosticating the clinical result of cervical cancer patients. Similar to this, many experiments were done to check the increased or decreased level of miRNAs in cervical cancer. Up regulation of miRNA-182 was seen in cervical carcinoma, and a significant association in high expression of miR-182 and developed phase of cervical cancer was discovered. So this finding show that miR-182 plays an oncogenic role in cervical cancer [64].

Decreased expression of microRNA-218 was also seen in serum of cervical cancer patients and up regulation of miR-224 in cervical cancer were linked with the assertive development and poor prognosis of cervical cancer. Lately [65] investigate that particular miRNA signature would differentiate between normal colon and colon cancer and specifically mir-21 was seen to be over expressed in colon cancer patients up to 87% while mir-143, miR-145 [66] let-7a-1 [67] miR-16, miR-125b miR-31, miR-133b, miR-96 and miR-145 was found to be low expressed in colorectal cancer. Additionally, tumor suppressor miRNA, miR-34a was showing low level in CRC tissues so it can be used for diagnosing CRCs. Patients having metastatic prostate cancer have high level of miR-141 in serum [68]. Similar study examines the miRNAs expression level in plasma and reveals that miR-141 is a novel biomarker for the detection of prostate cancer [68].

4.8 miRNA for the detection of *Merkel Cell Polyomavirus* (*MCPyV*)

Polyomaviruses (PyVs) were linked with malignancies containing Merkel cell carcinoma (MCC). With the discovery of PyVs in 2008, Epidemiological studies have recognized MCPyV, as a usual virus that causes the infection in human population. Enzyme linked immunosorbent assays particularly used for the immunogenic determinative of MCPyV, the main capsid protein VP1, have been utilized to govern that up to 80% of the grownup population carry serum antibodies to MCPyV [69].

The MCPyV genome consist of 22 nucleotides viral miRNA (MCV-miR-M1-5p) that probably causes the auto regulation of initial viral gene expression over the late stage of infection, as it was manifest to decrease the level of reporter transcripts comprising MCPyV initial region sequences [70]. One research revealed that miRNAs expressions are conserved in almost 50% of MCPyV-positive MCC tumors, and there is an association between viral genome copy number and expression level of miRNA in tumor [70]. The existence of MCPyV miRNA in MCC tumors surely assures more observation to check its role in the pathogenesis of MCC.

As previous studies have suggested that MCPyV encodes a MicroRNA which may control the regulation of cellular and viral genes. A group of scientist performed an experiment to check whether the MCPyV encodes a miRNA which is expressed in MCC tumors. More than 30 million small RNAs from 7 MCC tumors which were

cryopreserved and 1 sample that was perilesional were sequenced. By using RT-qPCR, 45 extra MCC tumors were observed to check the expression of MCPyV-encoded mature miRNA [70, 71].

Through direct sequencing between two out of three MCPyV-positive MCC tumors, "MCV-miR-M1-5p" was identified. However MCV-miR-M1, a precursor miRNA had been identified in silico [71]. Particularly, the sequence of MCV-miR-M1 was similar in 79 reads which were obtained after in vivo but it varies from the in silico identified mature miRNA with two nucleotide alteration, which results in the specific seed region and a distinctive set of prognostic target genes. This mature microRNA was identified in MCPyV-positive MCCs (n = 38) and in 0% of MCPyV-negative MCCs (n = 13) by the help of real-time PCR. So this result concluded that in 50% of MCPyV-positive MCCs, expression level of MCV-miR-M1-5p is low, which shows that virus miRNA plays vital role in developing immune elusion and controlling viral DNA reproduction.

Xie and co-workers check the miRNA account between MCPyV-positive and negative MCC. MiR-23 remarkably expressed lower in MCPyV-positive MCC as compared to MCPyV-negative MCC. The increased expression of miR-203 in MCPyV-negative MCC prevents the cell growth and persuades cell cycle arrest [72]. This result demonstrates that MCPyV may lead to the cell proliferation by suppressing the expression of miR-203, but the exact process by which MCPyV regulates this miRNA, is not clarified yet.

4.9 miRNA for the detection of *Human Herpes Virus 8* (*HH8V*)

Human Herpes Virus 8, also known as *Kaposi sarcoma-associated herpes virus* is a representative of gamma-herpes virus family which progress to sustain long-lived latent infection in the independents [73]. KSHV is responsible for Kaposi sarcoma, B-cell lymphoma and some Castleman diseases [74]. Kaposi's sarcoma (KS) is a multitudinous tumor of mesenchymal genesis which was first represented by Moritz Kaposi in 1872 [75].

Past researches lead to the discovery of many viral coded miRNA that play vital role in controlling the regulation of herpes virus latent infections [76]. Viral miRNA can regulate the gene expression in both host and viral cell during infection without producing any toxoid viral protein which can be identified by the host defense system [77]. In plasma and serum sample, variation between the expression level of viral and cellular miRNA demonstrated particular patterns in different diseases like sepsis, cancer, atherosclerosis etc. [78]. These miRNAs stay in circulation in a secure form, being extremely resistant to severe changes in pH, endogenic RNase activity, and difference in temperature [79].

Moreover, many mature miRNAs, obtained from 12 precursor mRNAs from KSHV genome, play vital roles in KSHV-induced cell modification [80]. Furthermore, this study reported that increase levels of KSHV miRNAs in plasma were linked with a poor clinical outcome in the patients having sepsis. Identified virus encoded miRNAs might indicate a high sensitive assay to persuade the accurate prevalence of various viral infections, including latent KSHV infection.

One study reveal that there is an upregulation of miR-143/145 in KS that act as a biomarker as compared miR-221/222, miR-155, and the let-7 family, which were down regulated in KS [81]. Other scientist also clearly recognized 170 deregulated miRNAs, from which 69 miRNAs were up regulated and 101 miRNAs were down regulated when contrast with KS and healthy tissues [82]. Specifically, miR-126-3p and the 13 were upregulated which were KSHV-linked miRNAs.

Another study revealed that from 17 FFPE Kaposi's sarcoma samples and 3 Kaposi's sarcoma linked herpes virus (KSHV) negative standard Formalin fixed paraffin embedding (FFPE) samples, 185 miRNAs were present which were differently expressed, from which 76 miRNAs were up regulated in sample and 109 were showing down regulation [83]. So this report suggests that the deregulation of miRNAs helps in the existence and progression of KS.

Several studies have showed that miR-126-3p hinder the development of cancer by direct targeting IRS1, Sox2, VEGF p85β (PIK3R2), and many other genes [40, 84, 85]. One more study have revealed that miR-126-3p can hinder cell growth, persuade cell apoptosis, stops the cell invasion, arrest cell cycle development and downregulate the expression level of gene PIK3R2 in SLK cells. So this miR-126-3p by targeting PIK3R2 gene in KS cells act as a tumor suppressor miRNA. These studies will help us about understanding the profiling of KS and gives a powerful base for the analysis of PIK3R2 in KS.

5 Conclusion

The result from the present study strengthens a foundation and gives a logic to investigate the ability of miRNAs as circulating biomarkers in various type of cancers. Nevertheless, majority of the studies includes in this review have been organized in small and finite patient population. Thus, in order to show the practical efficacy of miRNAs in disease diagnosis, further attestation in huge and separate cohorts is required. Since the level of miRNAs in one type of cancer can differ in the other type, making a fingerprint, which represents signature of many miRNAs as contrary to a single miRNA or two of miRNAs that would be a more valid, precise and sensitive tool for diagnosing

cancer status. Furthermore, the present study has well elaborated the circulating miRNAs in population beside they acquire cancer, and so facilitating the future studies to profile miRNAs in population with lineage of cancer and their diagnosis on earlier basis.

With each of the passing day, more and more knowledge will be obtained regarding miRNAs function and their part in different biological pathways as well as in disease diagnosis. Moreover, with extending technological approaches, promoting simple and cost-effective techniques for the identification of miRNAs, the purpose of utilizing the enormous potential of miRNAs being diagnostic biomarkers seems to be very promising.

Acknowledgements The authors are truly thankful to the University of Central Punjab for providing the facilities to carry out research.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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