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An insight of microRNAs performance in carcinogenesis and tumorigenesis; an overview of cancer therapy

Kosar Babaei[a,1], Shima Shams[b,1], Arman Keymoradzadeh[b,1], Sogand Vahidi[b], Parisa Hamami[c], Roya Khaksar[d,*], Seyedeh Elham Norollahi[b,*], Ali Akbar Samadani[b,e,*]

[a] *Department of Biology, Islamic Azad University of Tonekabon Branch, Tonekabon, Iran*
[b] *Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran*
[c] *Clinical Development Research Unit of Ghaem Hospital, Guilan University of Medical Sciences, Rasht, Iran*
[d] *Department of Biology, Islamic Azad University of Tehran Shargh Branch, Tehran, Iran*
[e] *GI Cancer Screening and Prevention Research Center, Guilan University of Medical Sciences, Rasht, Iran*

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ABSTRACT

Importance of dysregulation and expression of microRNAs (miRNAs) has been confiemed in many disorders comprising cancer. In this way, different approaches to induce reprogramming from one cell type to another in oerder to control the cell normal mechanisem, comprising microRNAs, combinatorial small molecules, exosome-mediated reprogramming, embryonic microenvironment and also lineage-specific transcription agents, are involved in cell situation. Meaningly, besides the above factors, microRNAs are so special and have an impressive role in cell reprogramming. One of the main applications of cancer cell reprogramming is it's ability in therapeutic approach. Many insights in reprogramming mechanism have been recommended, and determining improvment has been aknolwged to develop reprogramming efficiency and possibility, permiting it to appear as practical therapy against all cancers. Conspiciously, the recent studies on the fluctuations and performance of microRNAs,small endogenous non-coding RNAs, as notable factors in carcinogenesis and tumorigenesis, therapy resistance and metastasis and as new non-invasive cancer biomarkers has a remarkable attention. This is due to their unique dysregulated signatures throughout tumor progression. Recognising miRNAs signatures capable of anticipating therapy response and metastatic onset in cancers might enhance diagnosis and therapy. According to the growing reports on miRNAs as novel non-invasive biomarkers in various cancers as a main regulators of cancers drug resistance or metastasis, the quest on whether some miRNAs have the ability to regulate both simultaneously is inevitable, yet understudied. The combination of genetic diagnosis using next generation sequencing and targeted therapy may contribute to the effective precision medicine for cancer therapy. Here, we want to review the practical application of microRNAs performance in carcinogenesis and tumorigenesis in cancer therapy.

1. Introduction

Many studies have indicated that microRNAs are involved in cancer formation and development [1]. In this way, microRNAs depending on their inhibited targets can be either tumor-suppressing or oncogenic. Meaningly, miR-21 causes stimulation, proliferation and cell invasiveness while inhibiting apoptosis [2]. MicroRNA's role is determined upon its interaction with growth, proliferation, differentiation and apoptosis controlling genes and by the same means its direct involvement in cancer progression. Furthermore, studies have indicated abnormal structure and function for the expressed microRNAs in cancer cells and that functional differences in tumors and different cancer stages are linked with microRNAs. MicroRNA expression is associated with clinical and biological characteristics of tumors, such as tissue of origin, differentiation, invasiveness and treatment responsiveness [3]. MicroRNAs can be utilized as diagnostic markers in human serum or plasma measurements. Thus, cancer and tumor microRNAs in serum or plasma can be measured noninvasively, excluding leukemias which is easily accessible to malignant cells [4]. Tissue samples from solid tumors are obtained using biopsy and surgery. Since the procedures are often taken when cancer has considerably developed, such assessments have poor prognostic values. Hence, microRNAs closely associated with malignant

* Corresponding authors.
E-mail addresses: RoyaRokh@gmail.com (R. Khaksar), Elnaz-norollahi2000@yahoo.com (S.E. Norollahi), a_ahormoz@yahoo.com (A.A. Samadani).
[1] These authors contributed equally as the first author.

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phenotypes are invaluable diagnostic markers in the initial stages of cancer. Considering that most screenings fail to identify cancer at its early stages, measuring microRNA expression which presents in blood as cancer progression is an indispensable method for early diagnosis of cancer [4,5]. A series of studies carried out by a group of scientists has indicated oncogenic and anti-apoptotic functions for miR-21 [5]. Any association of cancer stem cells with micro RNAs is interesting and can lead to therapeutic in many cancers [6–9].

The miRNAs mainly contribute to post-transcriptional regulation through interacting with mRNA and subsequently silence gene expression. In other words, these compounds are post-transcriptional regulatory elements that mainly regulate gene expression and are found in a broad spectrum of eukaryotic cells. MicroRNAs are complementary fragment of one or more messenger RNAs (mRNA) [10]. These molecular structures are involved in physiologic and pathologic processes and a large number of these functions as oncogenes and tumor suppressor genes (TSGs); hence any mutation in open reading frames (ORFs) may cause cancer. The various physiologic processes that miRNAs contribute to include development, proliferation, differentiation, and apoptosis [11]. Several endonucleases including Dicer (RNase III endonuclease necessary to produce siRNA and miRNA) and cofactors notably TRBP (the HIV-1 TAR RNA binding protein), PAST (protein activator of dsRNA development protein kinase) eliminate pre-miRNA ring from stem. MicroRNAs influence features of cancer cells and thereby identifying miRNAs and their correspondent target molecules help scientists provide novel insight into the molecular mechanisms underlying cancer. Therefore, the purpose of this research is investigation of these molecular structures and introducing as potential biomarkers in cancer diagnosis, prognosis and treatment. The present study is descriptive experimental research aiming to introduce different kinds of miRNAs, their biogenesis, functions and evolution and surveying their role in cancer diagnosis, prognosis and treatment. So in this review, we have taken advantage of various references and articles. The importance of these molecules as biological regulators had not been recognized when LET-7 was discovered. Ever-increasing attention to the structure and function of miRNAs due to their various effects on different evolutionary and physiological processes notably apoptosis, insulin secretion and hematopoiesis (a small fragment of RNA known as miRNA leads stem cells toward differentiating into red blood cells), tissue differentiation and their involvement in immune system and viral diseases [12]. 90% of miRNAs have been proposed to originate from introns and exons. Loop structure formation is a key event and plays a critical role in their function. The production of miRNAs consists of five steps, two-step occurs entirely in nucleus and the rest are exported to cytoplasm to produce final miRNAs. miRNAs act as oncogenes or tumor suppressor genes (TSGs) by suppressing cancer-associated target genes. The major mechanism of miRNAs changes in cancer cells is ectopic expression which is recognized by abnormal levels of mature miRNAs. Other effective mechanisms in this process include SNPs, mutations in pri-miRNA, and copy number alterations of miRNAs coding sequences and abnormal transcription. Thus, these compounds can be utilized as potential biomarkers in diagnosis, prognosis and treatment of cancer [13]. Human serum and body fluids are rich in biomarkers which can be used in clinical diagnosis. Human serum and body fluids contain sufficient quantities of stable miRNAs, therefore miRNAs profile in bloodstream has been discussed in different studies and has provided a promising perspective as non-invasive biomarkers. miRNAs contribute to control of proteins expression. It should be noted that abnormal expression levels of a particular miRNA can be observed in a large number of cancers. For instance, miR-55, miR-58 and miR-51 are overexpressed in breast cancer, whereas miR-508, miR-8 and miR-1 are underexpressed in these cancer types. In ovarian cancer, miR-500 and miR-141a/b/c are overexpressed. In the other words, any particular miRNAs may have a role in reducing or increasing the chance for specific cancer, for example, miR-19 in reducing breast cancer, miR 15a in reducing non-small cell lung cancer, miR-5 in increasing gastric cancer and MIR-85 in decreasing gastric cancer. OMIC technology has facilitated diagnosis and treatment of cancer. MicroRNA microarray can determine the expression of hundreds of genes in a single tissue sample through hybridization of miRNA with labeled target sequences [14]. miRNA expression is correlated with clinical and biological features of the tumor notably the type of tissue, differentiation, invasion and treatment response. In general, cancer progression can be inhibited by oncogenic miRNAs cleavage by synthetic RNA bound to mRNA, inducing tumor suppressor miRNAs and reducing miRNAs expression by epigenetic agents for example by promoter methylation [15]. Antisense oligonucleotides complementing with miRNAs can be used to reduce miRNAs expression. Among them, Antagomirs as an example of antisense oligonucleotides are produced synthetically. Each miRNA has a unique target, for instance, miR-19 that plays a role in decreasing breast cancer, P1 is its target molecule [16]. Cyclin E, Cyclin D5 and Cyclin D8 are targeted by miR-1 and miR-88, two molecules contributing to decreasing non-small cell lung cancer [17]. miRNAs have a wide range of body functions and play a role not only in cancers but also in cardiac diseases, neurological disorders and cause cardiomyopathy or affect different steps of synapsis and etc. Schizophrenia is an example of their role in pathogenesis of nervous system [18]. Insight into the regulatory mechanism for miRNAs evolution and their role in carcinogenesis and also for optimal use of miRNAs, enhancing their efficiency and reducing adverse effects associated with antisense molecules binding to non-target molecules, extensive research seems necessary in this regard. Since miRNAs can regulate a large number of genes, they can be exploited as novel targets to treat the diseases with complex underlying mechanisms like diabetes [19]. Identifying tumor miRNAs released in bloodstream during gradual progress of the disease is the key strategy for timely diagnosis of cancers. Thus, miRNAs can be employed in cancer treatment and their targets can be influenced by manipulating of these molecules. However, there are some constraints in this regard, for example, a miRNA controls the expression of many target genes, so alterations may also influence the non-target genes. On the other hand, a single gene may be controlled by several miRNAs and thus manipulating a single miRNA would not be sufficient for influencing the gene of interest and subsequent treatment of the disease. Moreover, using antisense oligonucleotide for reducing miRNAs involved in cancer may have some adverse effects due to influencing non-target miRNAs [20].

The human genome encodes > 8000 miRNA transcripts which may include 60% of human and other mammalian cells and are abundantly found in many mammalian cells. miRNA sequences are highly conserved and seem to be critical ancient evolutionary elements in gene regulation. Plant miRNAs often perfectly complement with target mRNAs and subsequently suppress gene expression through cleaving target transcripts [21]. In contrast, animal miRNAs recognize target mRNAs by using a short oligonucleotide (8–6 nucleotides) in their 5′ terminal (seed region). However, this level of complementing is not sufficient to induce target molecule cleavage but stimulate translation inhibition. Combined regulation is one of the characteristics of animal miRNAs, so that a single miRNA might target hundreds different mRNA and a distinct target molecule may be regulated by several miRNAs. Depending on the estimation approach used, the average number of mRNAs targeted by a distinct miRNA. Nonetheless, various procedures have indicated that mammalian miRNAs have ability to target a large number of distinct mRNAs [22] (Fig. 1).

For instance, examining the highly conserved miRNAs in mammals revealed that every miRNA has nearly 400 conserved targets on average. Furthermore, the experiments demonstrate that a single miRNA can lead to decreasing the stability of hundreds of single mRNA or production of hundreds of protein. Nevertheless, this reduction is usually mild (less than two times). miRNAs were initially discovered in early 1990. However, until early 2000 they had not been recognized as a distinct class of biologic regulators [23]. There are different classes of miRNAs expressing restrictively in different cells and tissues. The findings of these researches also imply that miRNAs play different roles

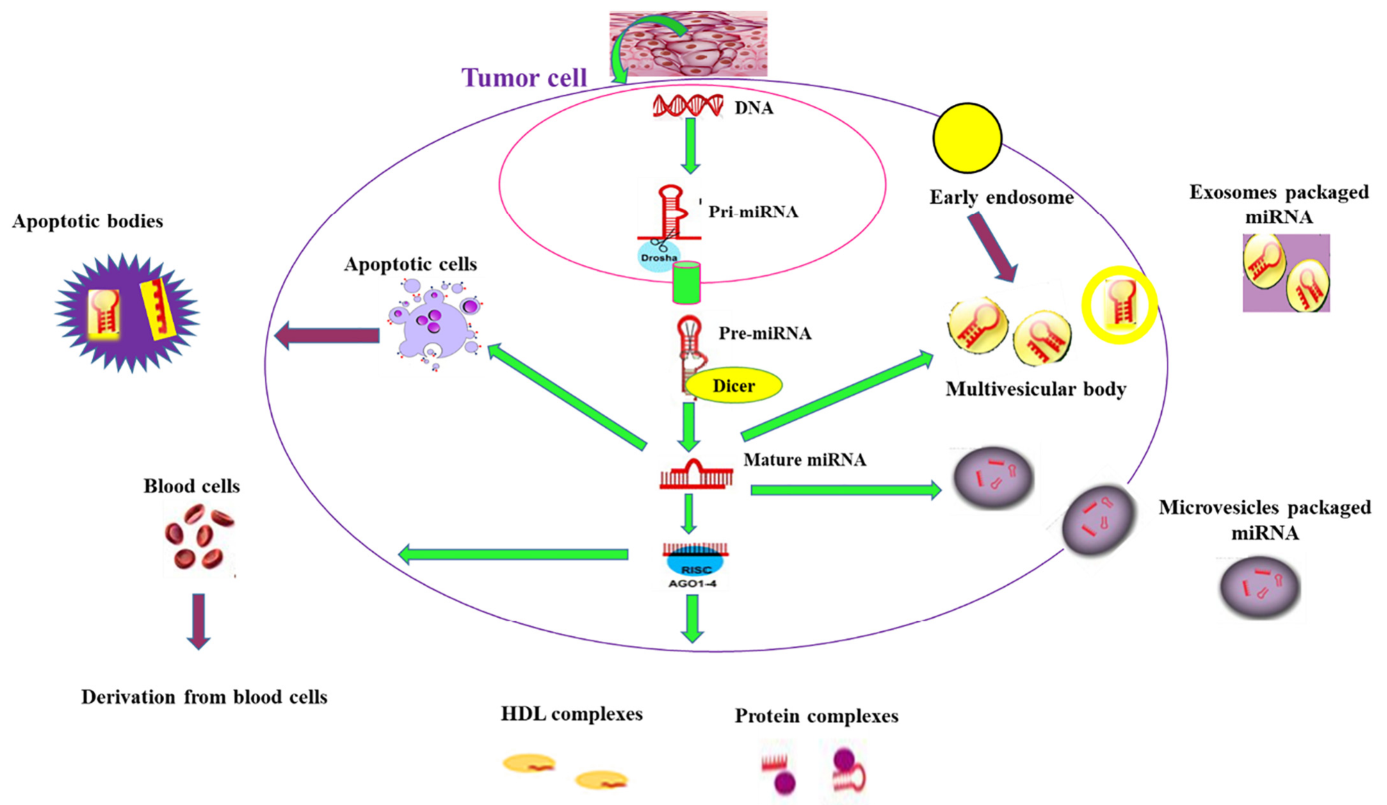

Fig. 1. Extracellular miRNA synthesis pathways in cancer cells.

in animal and plant evolution and also many biologic processes. Ectopic expression of miRNAs has been detected in various diseases and miRNA-based treatments have been investigated. As miRNAs are known to be engaged in the normal functioning of eukaryotic cells, any disturbance in their regulation can cause disease. Mutations in seed region of these regulatory molecules or omitting a class of them can lead to genetic defects [24]. In miR2Disease database, the relationship between disruption of miRNA regulation and human diseases has been documented. The first human diseases identified to be associated with disrupted regulation were lymphocytic leukemia followed by B-cell malignancies [25]. There is a link between many miRNAs and cancer incidence. Overexpression of miRNAs is associated with increased cancer frequency which is known as oncomiR and the ones that their under-expression is associated with increased cancer frequency are known as tumor suppressor miR. Besides, miRNAs expression profile is important in different types of diseases, disease progression and even prognosis. Investigating outcomes of overexpressed miRNAs in cells, tissues and animal models can shed light on the underlying mechanisms of many biologic processes and their pathology and subsequently allow development of miRNA-based therapeutic approaches [26].

2. Biogenesis of microRNAs and RNA interference

The biogenesis of microRNA occurs in the nucleus and the cytoplasm. The initial Transcript of microRNA is several kilobases long and is transcripted by RNA polymerase II and then polyadenylated. The stem-loop structure of this transcript is identified and processed by a 650 kb enzyme complex located in the nucleus. The complex consists of an RNA polymerase III specific for double-stranded RNA excision and a double-stranded RNA binding protein, namely Drosha and Pasha/DGCR8 [27]. The product of this complex, a 60–110 nucleotides long hairpin precursor, is translocated by Exportin-5, a nucleic transport factor and the cofactor, Ran-GTP, into the cytoplasm. The final processing of the microRNA is carried out in the cytoplasm by another RNAse III, Dicer. Dicer together with its ds-RNA binding partner protein (Loqs in drosophila and the homologous form in humans, HIV1-TRBP) cut the terminal loop of pri-microRNA and produces 19–22 nucleotides long (ds-)microRNA [28]. Another TRBP attaches human argonaute protein hAg2(EIF2C2) to the Dicer complex and assembles an RNA-induced silencing complex(RISC). Regularly, only one strand of the mature ds-microRNA, the guide strand, is loaded into the ribonucleoprotein complex which forms miRISC. The sequence of guide strand determines the target mRNA which will be silenced. Necessary components for RISC, are Proteins of argonaute family which contain two conserved regions for RNA binding; PAZ region which binds to 3′ end of single-stranded microRNA and PIWI which is structurally similar to ribonuclease H and interacts with the 5′ end of the guide strand of microRNA [29]. Argonaute proteins are members of a highly conserved family which are involved in RNAi and microRNA pathways. An argonaute protein and a small single-stranded RNA constitute the core of RISC. Ago2 (splicer) is the only member of the commonly found mammalian Ago subfamily (Ago1-Ago4) which functions in RNAi through intra-nucleotidic slicing of target mRNAs [29]. Since, only one of the two strands of microRNA acquires the role of guide strand and guides RISC to 3′ UTR target mRNAs via mRNA pairing, the other strand (passenger strand) is degraded. The strand with the weak base pair bonds in the 5′ end is selected as the guide strand. RISC binding microRNAs pair with the 3′ UTR of their corresponding mRNAs and post-transcriptionally inhibit expression via slicing or translational inhibitor activity. “Gene silencing” is the most dominant mechanism of RNA translation inhibition and is carried out either by employing ribosomal anti-association factor, eIF6 or by the attachment of Ago2 protein to the mRNA cap, preventing the utility of eIF4E and consequently inhibiting the translation. The silenced mRNAs are relocated to process bodies (P-bodies) - cytoplasmic environments where the RNAs are stored or degraded [5]. P-bodies are equipped with decapping

complex Dcp1-Dcp2, 5′ ≥ 3′ exonuclease Xrn1 and deadenylating enzymes to degrade nucleic acids. In addition, Argonaute proteins, microRNAs and silenced mRNAs are also accumulated in P-bodies. In the absence of small RNAs or when Argonaute proteins are not able to attach to microRNAs, Argonaute proteins stay dispersed through cytoplasm. The solidity of P-bodies is maintained with GW182-Argonaute protein interactions. Yet another mechanism of translation inhibition is the trapping of mRNAs in P-bodies; the trapped mRNAs can be released after induction with some natural stimuli and the translation would then take place [28,30]. Hence, translation inhibition by microRNAs can be irreversible. The complexity of these processes is evidence of the profound regulatory significance of microRNAs. A single microRNA can target multiple mRNAs and concurrently a single mRNA can be targeted by multiple microRNAs. Therefore, identifying target mRNAs of a microRNA are crucial for determining its function [31].

3. Identifying target molecules of microRNAs

The key subjects in microRNA research are target molecule identification; establishing a number of complementary base pairs is necessary for a functional interaction between the microRNA and the target molecules' sequence. Often, 6–7 nucleotides are involved in base pairing and are mostly through the seed region which includes the nucleotides 2–9 from the 5′ end of the microRNA. The remaining microRNA nucleotides have limited pairing capacities with 3′ UTR sequences adjacent to the seed region and their transient bonds provide the microRNA with attachments to multiple internal areas within a 3′ UTR. Various computational methods are used for predicting microRNA target molecules which utilize computational algorithms. However, due to the incomplete and limited pairing with the target sequence accurate predictions are constrained. One model of such target molecule predicting algorithms is designed on the basis of base pairing and conservative of microRNA-seed sequences in 3′ UTRs of different species [28].

Remarkably, mRNAs which pair preferentially with 7–8 nucleotides of the seed region are classified on qualities such as their target sequence being evolutionarily conserved and the thermodynamic stability of the interactions between the non-seed region bases and the mRNA's bases on each end in the 3′ UTR. Another form of microRNA-mRNA pairing is an incomplete pairing in the 5′ seed region which is compensated by an additional pairing of one nucleotide in the 3′ end [31]. Numerous bioinformatics studies are conducted and various computer programs are utilized to identify microRNA targets based on seed sequence. Based on the results of studies, 1000 microRNA genes have been identified which make up to 1% of the human genome and it has been suggested that more than a third of the human genome may be regulated by microRNAs (Fig. 2) [27,29,32–36].

4. Performance of microRNAs in cancer progression

Cancer results from the failure in regulatory checks on cell proliferation and differentiation. Tumors become malignant by mechanism such as constitutive activity of growth signal receptors, resistance to growth-inhibiting signals, evasion of programmed cell death, acquiring unlimited proliferation capacity, angiogenesis, tissue invasion and metastasis [3,29,36,37].

Notably, microRNA's role is determined upon its interaction with Growth, proliferation, differentiation and apoptosis controlling genes and by the same means its direct involvement in cancer is established. Hence, microRNA profiles are used for classifications of cancer in distinct groups with regards to cell type and etymology. The incomplete pairing of microRNA with its targets provides for microarrays to identify the expression of hundreds of genes and many pathways with minimal RNA used, thus rendering such classifications more convenient than those based on mRNA profiles [38]. Furthermore, previous studies have indicated that abnormal structure and function for the expressed microRNAs in cancer cells and functional differences in tumors and different cancer stages are linked with microRNAs (Table 1). The difference of microRNA expressions in various cancer cells might be due to the difference in the cell and surrounding origin of tumor tissue. Changes in microRNA expression contribute to tumorigenesis through reducing the expression of key genes regulating proliferation and survival of cells. However, it has not been indicated that microRNAs are directly responsible for tumorigenesis or cancer progression. It has not been yet established that the altered expression of microRNA is a consequence of the pathologic state of cancer or that cancer is initially caused by this expression alterations. Nevertheless, the many occurring changes in cancer cells directly or indirectly influence microRNA expression, genomic rearrangements, disorders of the microRNA gene and the proteins involved in its biogenesis, microRNA epigenetic disorders and gene mutations are all of such changes. However, localization of microRNAs to fragile sites, cancer-associated genomic regions is an important factor in the microRNA expression changes in cancer cells. Furthermore, the impaired mRNA:microRNA interactions resulting from mutated structures of microRNA and mRNA in cancer hinders post-translational processes [5]. Noticeably, epigenetic machinery can deactivate microRNA expression through hypermethylation or histone modifications and vice versa, microRNA can regulate epigenetic agents. Loss of regulation of transcription factors, an increase in its quantity or demethylation in CpG regions of promoter areas can lead to microRNA overexpression. In addition, gene deletion, extra-genic suppression or loss of transcription factor expression in cancer cells leads to a reduction in tumor-suppressing microRNA expression [39].

In addition to post-transcriptional regulations, microRNAs are also controlled by cis-acting sequences adjacent to precursor microRNAs. Thus, mutations in such sequences directly affect microRNA processing and reduce its expression [31].

Tumor-suppressing or oncogene microRNAs are termed Oncomirs. Oncomirs are present in malignancies of various tissues and are often found in regions of genome where deletion, duplication and/or mutation occurs [1,3–5,27–29,32–37,39,40].

Some Oncomirs exhibit their oncogenic phenotypes through reducing the expression of tumor-suppressing genes and/or genes regulating differentiation and apoptosis whereas other Oncomirs inhibit carcinogenesis through targeting proto-oncogenic and mRNAs silencing (Table 2) [1].

5. MicroRNAs influence prominent characteristics of cancer cells

Increase or decrease in microRNA expression which contributes to oncogenesis affects cell growth by the means of interference with cell-cycle regulators. MicroRNAs are the main regulators of programmed cell death in tumorigenesis and the survival of cancer cells is managed through manipulation of these microRNAs. Furthermore, preserving telomeres by a positive regulation on telomerase and adding to the length of telomeres yields immortalization for cancer cells. MicroRNA disorders are the factors that lead to excess telomerase activity in tumors. Also, a number of microRNAs are involved in epithelial-mesenchymal transition which is a key step in tumor invasion and metastasis [22]. Importantly, more than half of the microRNAs are clustered in unstable genomic regions or chromosomal common fragile sites which are associated with various cancers. Chromosome translocation is an essential marker of genomic instability. MicroRNAs have a crucial role in regulating immune responses in cancer. A variety of viral microRNAs is involved in virus-host interactions in tumorigenesis, for example, SV40, a carcinogen in rodents, codes two microRNAs which target and slice the virus T antigen. Since degrading and inhibiting the expression of mRNAs are the main functions of microRNA, microRNA processing enzymes, Dicer and Drosha, aside from engaging in microRNA maturation, inhibit the expression of constitutively turned on angiogenesis genes through their reduced expression (Table 3) [1,3,4,33–37,39].

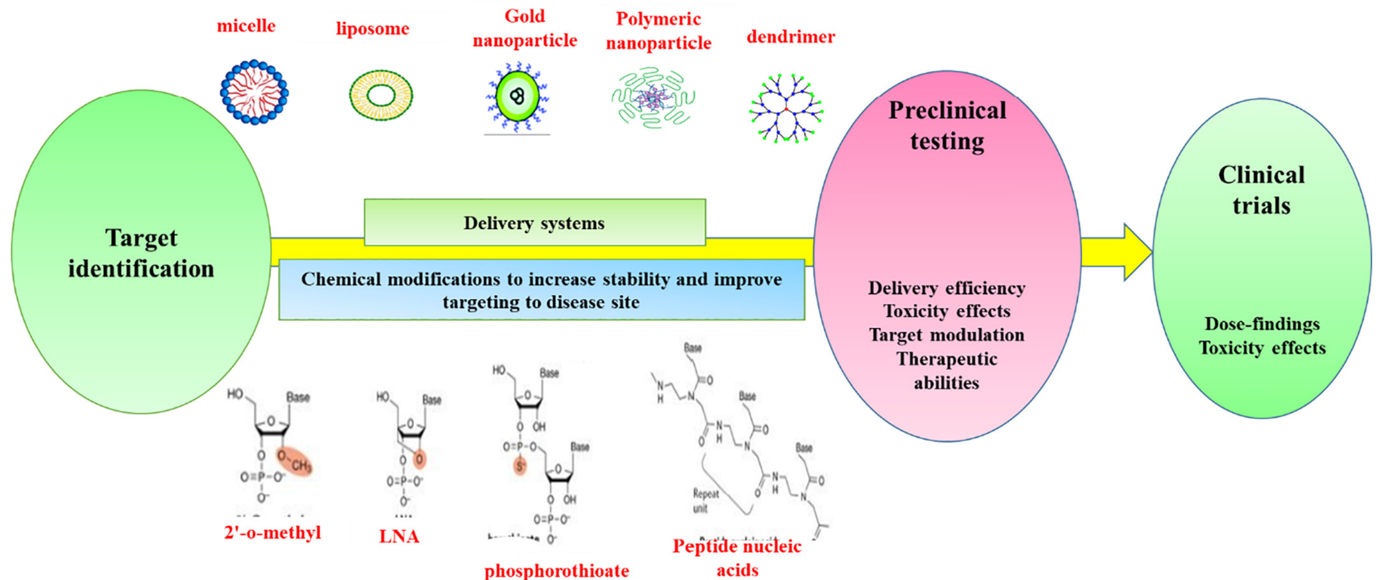

Fig. 2. Various kinds of miRNAs in different diseases.

Table 1
MicroRNAs and their target in cancers.

MicroRNA	Molecular mechanism	MicroRNA disorder in cancer	miRNA target molecules
miR-25	Inhibiting the cip/kip family as cyclin dependent kinas inhibitors through 3′ UTR	Increase the gastric cancer	P_{57}
miR-122	Influencing P_{53} stability and transcription reduced the invasion by adjusting cyclin G_1	Decrease the hepatic cell carcinoma	Cyclin G_1, P_{53}
miR-143	Inhibiting the phosphorylation of kinase 1/2 regulated by external signal in career	Decrease the colorectal cancer	KRAS
miR-145	Inhibiting the cancer cell growth in a mutated cancer by epidermal growth factor receptor	Decrease the lung adenocarcinoma and colon cancer	EGFR-IGF-1R
miR-101	Promoting apoptosis and tumor suppression	Decrease the hepatic cell carcinoma	MCl-1
miR-9-3	The role of P_{53} dependent apoptosis	Decrease the breast cancer	P_{53}
miR-17-92	Facilitating the progression of the cell cycle in S-G_1	Increase the B-cell lymphoma and medulloblastoma	P_{21}–N-MYC
miR-16, miR-15a	Stopping cell cycle in G_0–G_1 collaborate with sonic hedgehog path to increase duplication	Decrease the non-small cell lung carcinoma	Cyclin D_1 Cyclin D_2 Cyclin E_1
miR-512-5p	Inducing apoptosis in cancer cells	Decrease the gastric cancer	MCl-1
miR-128	Inhibition of cell growth	Decrease the glioma	E2F3a

6. MicroRNAs, tools for identification and diagnosis of cancer

"Omics" technologies have made diagnosis and treatment of cancer much easier. Microarrays of microRNA can identify the expression of hundreds of genes within a tissue sample when hybridized with labeled target sequences [39].

MicroRNA expression is associated with clinical and biological characteristics of tumors, such as tissue of origin, differentiation, invasiveness and treatment responsiveness. MicroRNAs can be utilized as diagnostic markers in human serum or plasma measurements. Thus, cancer and tumor microRNAs in serum or plasma can be measured noninvasively. Excluding Leukemias in which the malignant cells are easily accessed [4], in solid cancers tissue sampling is achieved by means of biopsy and surgery. Since the procedures are often taken when cancer has considerably developed, such assessments have poor prognostic values [1], Hence, microRNAs closely associated with malignant phenotypes are invaluable diagnostic markers in the initial stages of cancer [1,3–5,29,37,39,40].

Table 2
Potential mechanism of microRNA expression and modified activity in cancer.

Disruptive mechanism	The impact of the disruptive mechanism
1- The mutation of a non-target mRNA gene	Possible connection of miRNA to non-target mRNA
2- Epigenetic mechanism methylation of the promotor miRNA gene histone charges	Reduction of miRNA formation
3- Mutation/polymorphism of miRNA gene	Increase or decrease of miRNA modified miRNA connection
4- Mutations in the biogenesis of the organization increase the Drosha expression decrease the Drosha expression	miRNA processing
5- Genomic changes Deleted-expanded-displacement	Increase or decrease of miRNA
6- Mutation/polymorphism miRNA attachment site in the aimed target mRNA gene	Modified miRNA connection

Table 3
MicroRNA, and significant features of cancer.

MicroRNA	Significant feature of cancer	MicroRNA functions
miR-17-92 cluster, miR-378, miR-996, let-7f, miR-27b, miR130, miR-126	Inducing angiogenesis	Angiogenesis stimulation Angiogenesis inhibition
Delete or down regulation of micro RNAs such as,miR-20a,miR-17 miR-16-1, miR-15 or let-7	Genomic instability	Proved genomic instability
miR-21, miR-17 cluster, miR-221, miR-222, let-7, miR-519, miR-146a	Resistance to anti-duplicate signal and independence on external growth factor signals	Growth stimulation Growth inhibition
miR-10b, miR-21, miR-373, miR-520c, miR-155, let-7, miR-335, miR-206, miR-126, miR-146a, miR-101, miR-200	Tissue invasion and metastasis	Metastasis stimulation Metastasis inhibition
miR-34 cluster, miR-29, miR-15, miR-16, miR 17-92 cluster, miR-21	Escape from apoptosis	Apoptosis stimulation Apoptosis inhibition
miR-155, miR-17-92 cluster, miR-20a, miR-93, miR-106b, miR-372, miR-373, miR-520c, hcm V-miR-VL112	Escape from immune system	Emancipation from immune surveillance
miR-290, miR-24, miR-34a	Unlimited reproduction potential	Immortal control or aging

7. MicroRNA and cancer treatment

Cancer progression can be halted by inhibition of oncogenic microRNAs and/or slicing them with synthetic mRNA-pairing microRNAs, induction of tumor-suppressing microRNAs and reducing microRNA expression through epigenetic manipulations such as promoter methylation. Anti-sense oligonucleotides which pair with microRNAs can be used to decrease microRNA expression (Fig. 3).

“Antagomir” is such inhibitors which are synthetically produced [34]. This drug RNA molecule is designed to inhibit microRNAs. The exact mechanism of the microRNA inhibition which such oligonucleotides carry out is not understood. However irreversible binding to microRNAs has been suggested to consider for this inhibition. O′2 methylated anti-sense oligonucleotides or LNA anti-sense oligonucleotides are other specimens to this class of drugs [4,39]. These molecules provide stable inhibition and lower toxicity. In “microRNA sponges” strategy, microRNAs are utilized which are derived from transgenes [5]. These RNAs through extensive competitive bindings to targets of microRNAs rescue them from inhibition. Tumor suppressing microRNAs are transferred via viral transporters. Recent developments in AAV vector technology, utilizing self-complementary genome, have yielded an easy and efficient delivery of microRNAs by way of intravenous administration [34]. This technology is yet to be clinically approved. Other methods for delivery of inhibitor microRNAs are plasmids, transposons and liposomes coated with monoclonal antibodies to guide microRNAs into their target organs [37]. Epigenetic drugs such as DNA methyltransferase inhibitors (5-aza-2′ deoxy cytidine) or histone deacetylase inhibitors increase microRNA expression through decreased methylation and increased acetylation respectively. Thus tumor-suppressing functions of microRNAs are restored and cell proliferation arrested [5].

Polymorphisms in microRNAs can lead to drug resistance which concerns “microRNA pharmacogenomics” where predicting microRNA drug resistance is centered for reaching a suitable treatment. MicroRNAs may have effect on drug functions by means of regulating genes which code for some drug-interacting proteins. Drug transporters and metabolizers are such proteins [1,3,4,29,35–37,39,40].

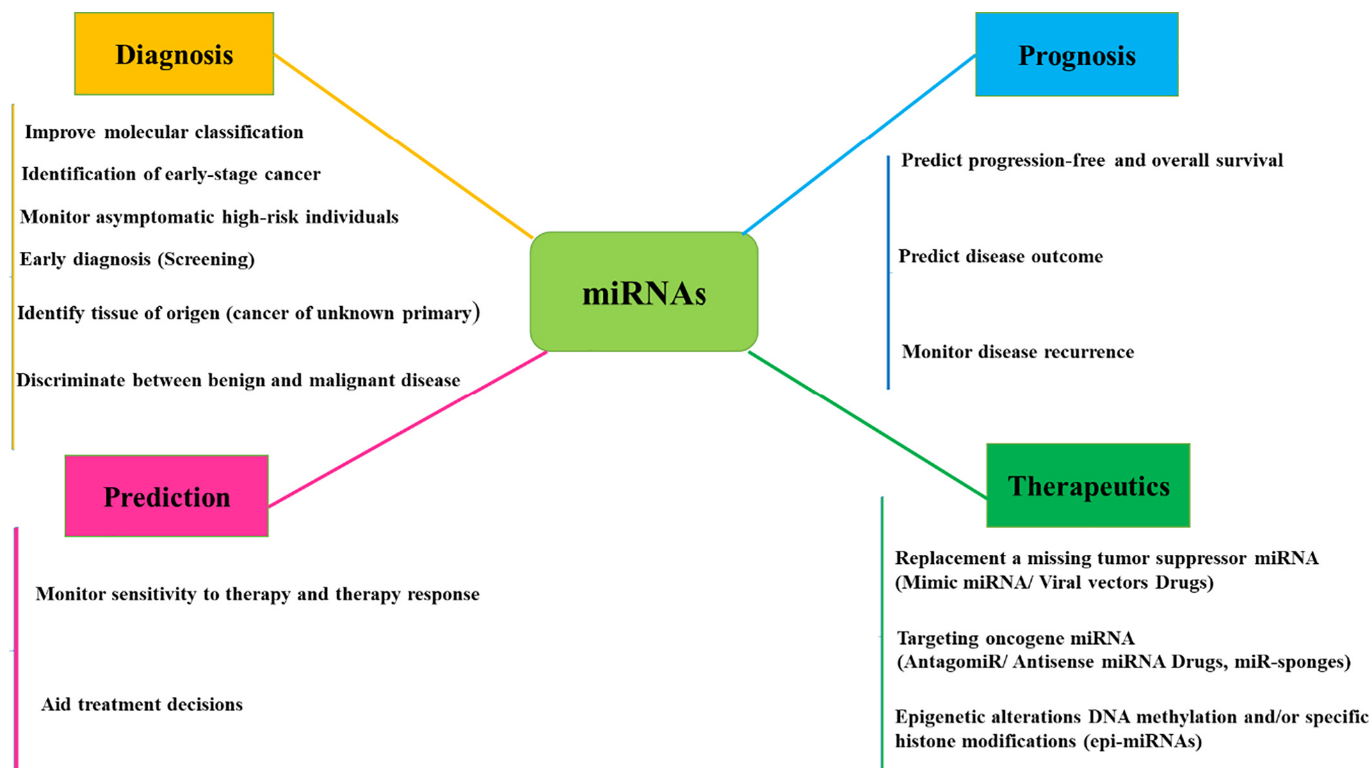

Fig. 3. Methods of transferring miRNAs into cells.

8. MicroRNAs and biological fluids

Biological fluids in human bodies include plasma (serum), urine, saliva, teardrop, CSF, pleural fluid, phlegm, semen, amniotic fluid, milk, colostrum, sweat, and BAL. Considering the low efficiency of RNA extraction from fluids, the concentration of microRNAs, which are a part of the total RNAs, will also be lower. Determining microRNAs' concentration and quality and differentiating them from RNAs' nucleotide fragments is one of the difficulties lying behind the act of separating and extracting microRNAs from body fluids [41]. Regardless of the extraction technique, the amount of total RNAs extracted from the biological fluids is quite different. The amount of total RNAs measured in some samples like CSF is very low (about 100 μg/L) and in some other samples like milk this rate equals 50/000 μg/L). The presence of some mediators in the extraction of biological fluids, particularly in urine sample, causes a reduction in extraction efficiency. In general, urine, CSF, and teardrop contain a small amount of total RNA in comparison with other body fluids [42,43]. Surprisingly, in terms of variety and the number of various RNAs in biological fluids, saliva embodies the most possible variety in microRNAs [43,44]. Saliva contains the most possible variety in the number of microRNAs, which is considerably more than that of plasma and even milk (plasma and milk embody the highest amount of extracted total RNAs concentration). Furthermore, in comparison with other reported samples, there is less variety in the amount of microRNAs in urine, CSF, pleural fluid, and BAL [43,45]. Due to unknown reasons, the amount of particular microRNAs is considerably more than other samples in body fluids. Although the source of these microRNAs has not been pinpointed, the presence of such microRNAs suggests their physiologic and common performance [46]. A few microRNAs are specifically found in somebody fluids, and they are not reported to be present in other fluids or their amount is not close to the current methods' measurement. Considering the element of variety in exclusive microRNAs, plasma has the most possible diversity [47]. About 20 microRNAs have been reported in plasma, which have not been found in other body fluids, for instance, we can refer to miR-224, miR-483-3p, miR-518f, and miR-182 [48]. Due to the presence of multiple cells in the whole blood, which can contaminate the plasma content, one should be very careful in times of separating cells from plasma (such as not using high speed in centrifuges, proper temperature, and a short time). Using particular microRNAs in blood cells, one can verify the fact that plasma is not contaminated by cellular microRNAs. For example, the presence of miR-451 in plasma can show the hemolysis of red blood cells and is a sign of the presence of other red blood cell's microRNAs in the plasma sample. Chah et al. (2016) studied various methods for analyzing hemolysis in serum and demonstrated that measuring miR-451 in plasma is a more sensitive method in comparison with reading serum in 414 nm wavelengths by means of spectrophotometry [49].

The amount of microRNA is low in urine sample and no specific microRNA has been reported in health conditions [42]. In terms of variety in exclusive microRNAs, BAL, teardrop, and urine are weak. It has been mentioned that the low amount of the microRNAs reported microRNAs can be due to the deficiency and low sensitivity in microRNAs' methods of examination and measurement. Although q-PCR is one of the most exclusive and sensitive methods for measuring microRNAs, other employed techniques such as Microarray and RNA-Seq are not as sensitive as q-PCR and need to be verified by q-PCR [50,51].

9. Circulating microRNAs in serum (plasma)

Contrary to other types of RNA, microRNAs are more stable molecules. Several studies have shown that, at least 48 h after separating serum from blood cells, microRNAs are stable in room temperature. Moreover, consecutive freezing and melting of the sample have a little negative effect on the amount of microRNA [52,53]. A change of expression profile in serum's circulating microRNAs has been reported in several studies on malignancies [54,55]. It has been demonstrated in these studies that this change can be proportional to the type of malignancy, the damaged tissue site, and the malignancy development duration. The source of circulating microRNAs in serum is not very obvious. Some researchers believe that circulating microRNAs are a kind of intercellular relationship that is systemically and by means of paracrine signaling responsible for crosstalk fine-tuning [56,57]. On confirming this hypothesis, new findings have shown that microRNAs are selectively secreted into the surrounding environment through the cell's secretion machine, which is reliant on ceramide and sphingomyelinase [58]. These circulating microRNAs are released into the environment in viscosities of a double-layered membrane with various sizes and can tolerate the severe condition of body fluids such as serum, which contain large amounts of ribonuclease, in order to perform their physiological function [59,60].

10. Analyzing circulating microRNAs in blood; serum and plasma dilemma

The amount and variety of microRNAs in serum samples are more than plasma ones. The reason for this increase is that microRNAs are released from the inner part of blood cells such as RBCs, leukocytes, and platelet during the coagulation process. In fact, the coagulation process is a stressful environment for blood cells [61]. In this process, cells are stimulated to secrete microRNAs into the environment.

Moreover, because of the high number of red blood cells and their microRNA's content, it is possible to consider red blood cells as potential sources for serum microRNAs' contamination. Platelets have no nucleus. Nonetheless, despite their small sizes, they are full of RNA and microRNA molecules. More than 500 various microRNAs have been found in platelets [62]. According to what has been said, it seems that the procedure of separating cells without initiating the coagulation process entails less stress for cells. Moreover, it appears that plasma is a more suitable and uncontaminated sample for analyzing microRNAs (Tables 4 and 7).

11. Studying circulating microRNAs in malignancies, autoimmune diseases, and infections

The expression profile of microRNAs in tissues and biopsies were analyzed in early studies [63]. MicroRNAs are considerably resistant in FFPE [64]. The number of researches done on analyzing microRNAs as malignancies' biomarker in tissue samples increased noticeably in a short period of time. MiR-21 is one of the most famous and prominent microRNAs which plays a significant role in the emergence and development of cancer. Preventing the expression of this microRNA causes the activation of caspase enzymes and other apoptosis proteins and accelerates tumor cells death [65]. An increase of miR-21 has been reported in malignancies such as Glioblastoma, breast cancer, HCC (Hepatocellular Carcinoma), and gastric cancer. Similarly, an increase of serum miR-21 has been reported in different malignancies such as ovarian cancer, lung cancer, HCC, laryngeal cancer, and lymphoma, and this microRNA has been presented as a general biomarker for many types of malignancies [66]. In lung cancer, an increase of serum miR-21 has been observed in a number of studies. Furthermore, miR-21 is used as a biomarker in differentiating patients who are at the onset of lung cancer from healthy non-smokers. In addition to miR-21, other microRNAs have been studied in malignancies and proposed as potential biomarkers for cancer diagnosis. The serum concentration of four microRNAs (miR-155, miR-141, miR-34c, and miR-10b) noticeably increases in cancer patients. In addition, in lung cancer, the concentration of serum miR-10b with metastasis is related to lymph nodes [66,67].

Several studies have been done on microRNAs in order to reduce the number of biopsies in the liver. In a chronic infection like Hepatitis C and NAFLD (non-alcoholic fatty liver disease), the amount of serum miR-122 increases in comparison with healthy people. Moreover, the

Table 4
Some of the microRNAs involved in various human cancers have been altered by expression levels [27].

Cancer type	Reduction of expression	Increasement of expression
Colorectal	miR-143, miR-145, let-7, miR30-3p, miR-124a, miR-129, miR133 b,miR328	miR-18, miR-224, miR-10a, miR-17-92 cluster, miR-21, miR-24-1, miR29b-2,miR-31, miR-96, miR-135b, miR-183
Gastro-intestinal	miR-15b, miR-16	miR-106b-25
Pancreas	miR-375, let-7, miR-200, miR200b	miR-221, miR-376a, miR301, miR-21, miR-24-2, miR-100,miR-103, miR107, miR-125b-1, miR-155, miR-181, miR-106, miR-363, miR-301,miR a,miR-212, miR-34a376
Glioblastoma	miR-181a, miR-181b, miR-181c, miR-125a, miR-125b	miR-221, miR-222, miR-21
Gallbladder	miR-29c, miR-26a, miR-30c, miR-30e-5p,miR-145, miR-30a-3p, miR-133a/b, miR-195, miR125b, miR-199a	miR-17, miR-23a,b, miR-26b, miR-103-1, miR-185, miR-203, miR-205, miR-221, miR-223
Acute Promyelocytic Leukemia	miR-181b	miR-15a, miR-15b, miR-16-1, let-7a-3, let-7c, let-7d, miR-223, miR-342, miR-107
Breast	miR-205, miR-143, miR-145, miR10b, miR-125a/b, miR-155, miR17-5p, miR-27b, miR-9-3, miR-31,miR-34 family,let7	miR-21, miR-22, miR-23, miR-29b-2, miR-96, miR-155, miR-191, miR-181, miR-182, miR-27a, miR-210
Acute Lymphoblastic Leukemia	Let-7b, miR-223, miR-100, miR-125b, miR-151-5p, miR-99a	miR-17-92 cluster, miR-125b-1, miR-128a, miR-128b, miR-204, miR218,miR-331,miR-181a, miR-181b, miR-181c,miR-142-3p, miR-142-5p,miR-150,miR-193a,miR-196b, miR30e-5p, miR-34b, miR-365, miR582, miR-708
Hepatocellular	miR-199a/b, miR-195, miR-200a/b, miR-214, miR-223, miR-125a, miR-122a, miR-101, miR-139, miR-150, miR-26a, miR-101	miR-18, miR-21, miR-33, miR-130b, miR-135a, miR-22i, miR-224, miR-301
Chronic Myeloid leukemia	miR-10a	miR-17-92 cluster, miR-17-5p, miR-17-3p, miR-18a, miR-19a, miR-19b-1, miR-20a, miR-92a-1
Prostate	miR-128a, miR-101, miR-125a/b, miR-15a, miR-16-1, miR-143, miR-145, miR-23a/b, miR-200, miR-330, miR-331	Let-7d, miR-195, miR-203, miR-21, miR-181, miR-106, miR-363, miR-221
Chronic Lymphocytic Leukemia	miR-15a, miR16-1, miR-29, miR143, miR-45, miR-30d, let-7a, miR-181a/b, miR-223, miR-92, miR-150	miR-21, miR-23b, miR-24-1, miR-146, miR-155, miR-106b, miR-195, miR-221, miR-221, miR-222
Lung	Let-7, miR-34 family, miR-143, miR-145, miR-124a	miR-17-92 cluster, miR-21, miR-155, miR-191, miR-205, miR-210
Endometrial adenocarcinoma	miR-193a, miR-204, miR-99b	miR-205, miR-449, miR-429
Ovarian	miR-199a, miR-140, miR-145, miR-125a/b, let7	miR-200a/b/c, miR-141, miR-18a, miR-93, miR-429

amount of miR-122 is directly related to the fibrosis level and inflammation in liver cells. However, there is no relationship between the amount of miR-122 and viral loads in infected individuals [68,69]. In HCC, the amount of circulating miR-21 increases in comparison with chronic liver diseases or healthy people. The miR-21 expression in these individuals decreases significantly after their operation, which indicates both the high potential of microRNAs in assessing the success or progress of patients' treatments and their diagnostic efficiency [70].

Even though most studies in case of cancer have been done and published on microRNAs, the number of researches which are being conducted on the relationship between microRNAs and autoimmune diseases and their related illnesses is increasing rapidly [71]. As mentioned earlier, genes' expression changes in the immune cells (in comparison with other cells) are mostly reliant on microRNAs' network regulation. Several studies have shown that survival, proliferation, differentiation and production of cytokines and antibodies are reliant upon the performance of cellular microRNA networks [72].

Which means that any defect in the enzymes involved in the biogenesis of microRNAs in B and T lymphocytes would result in rapid removal of these cells from peripheral blood. Therefore, there is abundant evidence which would, directly and indirectly, emphasize the prominent role of microRNAs in the emergence of autoimmune diseases [73]. Even though most of the microRNAs studied in autoimmune diseases have been intracellular, other microRNAs such as serum (plasma) has been analyzed and measured in extracellular fluids. Due to the inflammatory effects of the microRNAs, it is hypothesized that the mechanism of systemic inflammation in autoimmune diseases may be reliant on the micro-RNAs' changes in body fluids, especially at serum levels [66]. Among the studied microRNAs in the autoimmune process, miR-155 has a more effective and prominent role. In addition to B and T cells, this microRNA's expression increase has also been reported at serum level. A reduction in serum miR-155 causes a decrease in the pathologic effects of autoreactive B cells which produce auto-antibody as well as a reduction in the T-lymphocytes' differentiation against inflammatory phenotypes [74]. An increase of serum miR-155 in SLE (Systemic Lupus Erythematosus) and RA (Rheumatoid arthritis) has been reported in several surveys. Besides miR-155, other microRNAs are also biomarker candidates for autoimmune diseases. For instance, a reduction of serum miR-146a has also been reported in Lupus, Rheumatoid arthritis, and Sjogren syndrome [75]. This microRNA directly prevents the activation of downstream signaling pathways for producing interferon type I. This microRNA's expression increase is related to the systemic reduction of interferon type I production and inflammation control [76]. In Scleroderma-SSc, the microRNAs' expression has been studied in various samples such as serum. In 2013, Tanaga et al. demonstrated that the amount of miR-30b reduced both in the tissue involved with the skin and in the serum level. This microRNA directly prevents the expression of PDGF receptor, which has a significant role in fibrosis development. It was also shown that the amount of this reduction was related to the intensity of fibrosis. Therefore, in addition to the microRNAs' diagnostic role, they can be employed as potential markers in studying disease progress [77]. In 2014, the first study on the serum of those individuals suffering from AITD (autoimmune thyroid disease) was published. Using the microarray technique, 1700 microRNAs in the serum of patients were compared with those in healthy individuals. In this study, a significant increase was reported in serums miR-16, miR-22, miR-375, and miR-451. Furthermore, it was demonstrated that the increase in the abovementioned microRNAs was related to the pathogenesis of GD (Graves' disease) and Hashimoto [78]. In addition to the researches on malignancies and autoimmune diseases done in recent years, there have been several studies on introducing serum microRNAs as diagnostic biomarkers in infectious diseases. For instance, one can refer to the studies done on analyzing serum microRNAs in tuberculosis, latent tuberculosis, pertussis, Hepatitis A and B, and viral diseases like influenza and HIV [79]. The developments achieved in this field made researchers do numerous studies on circulating microRNAs in animals and the infectious diseases associated with them [80,81]. Table 5 shows the results of the studies done on various diseases in order to introduce the recommended circulating microRNAs used for disease diagnosis (Fig. 4).

Table 5
Some of the studies done on different diseases in order to introduce serum microRNAs as diagnostic biomarker candidates.

	Disease	MicroRNA (increase)	MicroRNA (decrease)
Malignancies and Neoplastic diseases	Prostate cancer	miR-16,miR-92 a/b, miR-103	–
	Ovarian cancer	miR-200 a/b/c, miR-21,miR-141	miR-155, miR-127
	Lung cancer	miR-21, miR-30	miR-486, miR146b
	HCC	miR-21, miR-122, miR-34	–
	Esophageal cancer	miR-21	miR-375
Autoimmune diseases	SLE	miR-155	miR-146, miR-200 a/b/c
	Rheumatoid arthritis	miR-24	miR-146, miR-132
	Multiple sclerosis	miR-125a, miR-614	miR-15, miR-223
	Psoriasis	miR-128, miR-1266	miR-19, miR-29
	Inflammatory bowel disease	miR-127	–
	Scleroderma	miR-92a, miR-142a	miR-30b
Infectious diseases	*Mycobacteriumtuberculosis*	miR-93, miR-29a	miR-155
	Hepatitis B	miR-122, miR-16, miR-20a, miR-92a	miR-497, miR-486
	Hepatitis C	miR-122, miR-34a, miR-16	miR-494, miR-483
	Pertussis	miR-202, miR-342	–
	Influenza (H1N1)	miR-150, miR-1260	miR-26a

12. MicroRNA and cancer

The importance of microRNA in cancer was first demonstrated in CLL leukemia. Cytogenetic studies have shown that 13q14 chromosome region is deleted in 50% of the patients suffering from CLL. The following studies determined that this region does not contain the tumor-suppressing protein-coding gene. This region contains two microRNA coding genes (miR-15a and miR-16-1), which are transcribed as polycistronic forms [82].

In 2004, microchip analysis was employed in order to determine microRNA genes in humans and mice. The microchip used contained various microRNA245. These results were also confirmed by RT-PCR and Northern blot techniques. These mechanisms can be employed for microRNA expression analysis in healthy and unhealthy tissues as well as for a change in microRNA expression pattern [83].

13. MicroRNA's performance in cancer

Although microRNA acts as a tumor suppressor in a cell, it has been observed in cancer cells that this type of microRNA undergoes an expression increase and thus tumor suppressors decrease in the cells, which is one of the reasons for tumorization. These microRNAs are called oncomiR [84]. For example, miR-21 undergoes an expression increase in most cancers and tumor suppressors such as PDCD4, PTEN, and TPM1 are among the miR-21targets [85]. On the contrary, there are microRNAs which target is those proto-oncogenes which undergo a reduction or deletion in cancer cells. Therefore, the number of proto-oncogenes in cells increases. For instance, let-7 undergoes an expression reduction in most cancer cells and RAS proto-oncogene is one of the important targets of this microRNA [86]. Studies have shown that in some cancers, those types of microRNAs which targets are DNA methyltransferases undergo an expression reduction, which leads to a decrease in tumor suppressors. Moreover, the microRNAs which target chromatin silencer experience an expression reduction and cause a

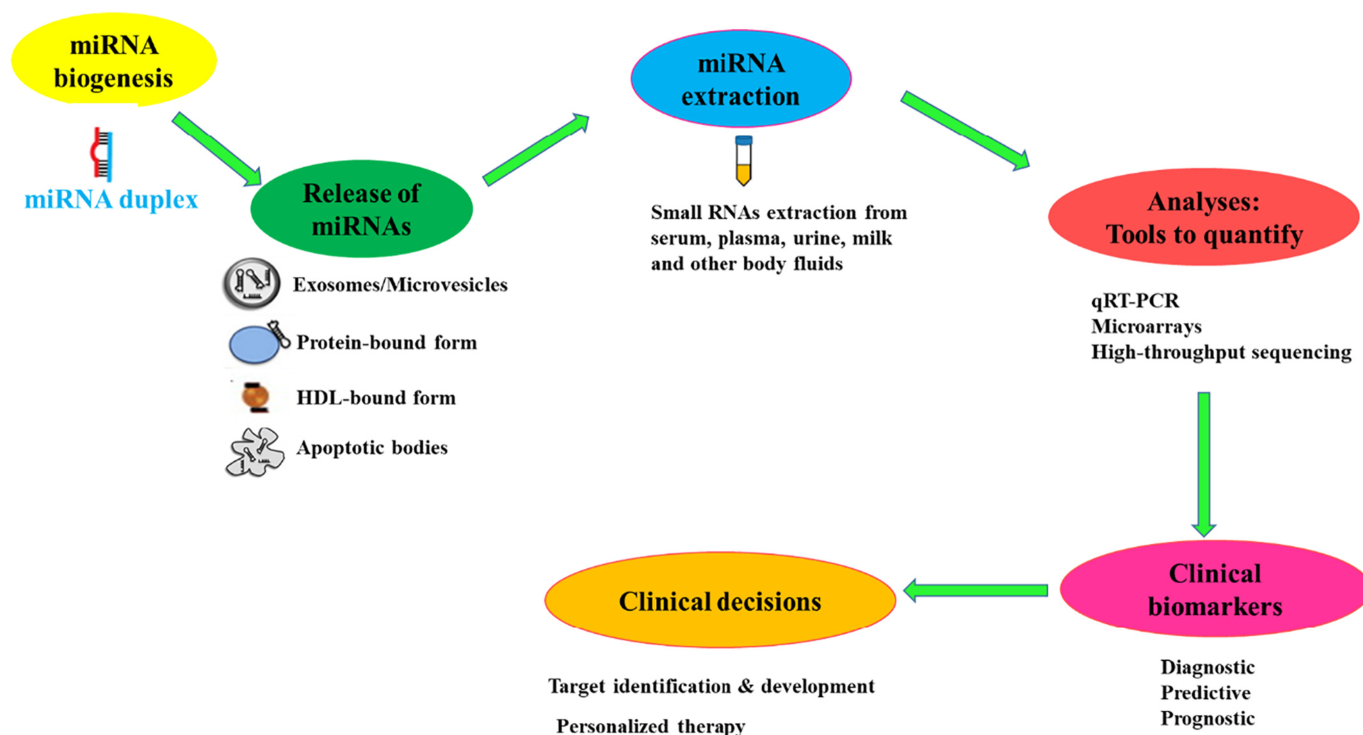

Fig. 4. Different usage of miRNAs in the diagnosis and treatment of diseases.

Table 6
The role of various miRNAs in different stages of tumor development.

Disorders	Main biomarkers of miRNAs
Autism spectrum disorder (ASD)	miR-181b-5p, miR-320, miR-572, miR-130a-3p, miR-19-3p
Biliary atresia (BA)	miR-200b/429, miR-4689, miR-4429, miR-140-3p
Cystic fibrosis associated liver disease (CFLD)	miR-122, miR-21, miR-25
Ewing's sarcoma (ES)	miR-214-3p, miR-214-5p, miR-92b-3p, miR-125b
Hematological malignancies	miR-7, miR-17-92, miR-21, miR-29, miR-30a, miR-30b, miR-34a, miR-125a, miR-125b, miR-126, miR-150, miR-155, miR-181b
Hypercholesterolemia	miR-33a/b
Idiopathic Nephrotic Syndrome (NS)	miR-30a-5p
Inflammatory Bowel Disease (IBD)	miR-484, miR-195
Neuroblastoma (NB)	miR-124-3p, miR-9-3p, miR-218-5p, miR-490-5p, miR-1538
Obesity	miR-486-5p, miR-486-3p, miR-142-3p, miR-200c-3p, miR-190a, miR-221, miR-28-3p, miR-95
Osteosarcoma (OS)	miR-199-5p, miR-199a-3p, miR-195-5p, miR-574-3p, miR-214, miR-335-5p, miR-320a, miR-374a-5p, miR-205-5p, miR-106-5p, miR-16-5p, miR-20a-5p, miR-425-5p, miR-451a, miR-25-3p, miR- miR-139-5p
Retinoblastoma (RB)	miR-17, miR-18a, miR-19b, miR-92a, miR-320, miR-let-7, miR-21
Rhabdomyosarcoma (RMS)	miR-206
Type-1 Diabetes (T1D)	miR-25
Viral Hepatitis B (CHB)	miR-28-5p, miR-30a-5p, miR-125-5p, miR-654-3p
Wilms, tumor (WT)	miR-197, miR-224, miR-100-5p, miR-130b-3p, miR-143-3p, miR-20a, miR-126, miR-144

Table 7
Disturbed microRNAs in cancer.

MicroRNA disorder in cancer	Target gene type	Result of increase or decrease in micro RNA	Example
Up regulation	Tumor suppressor	Decrease PTEN, PDCD4:	miR-21
		Decrease apoptosis and Increase cell growth. [72]	miR-10b
		Decrease HOXD10: increase cell migration and invasion [73]	miR-373
		Decrease CD44: Decrease cell junction to stroma [74]	
Down regulation	Oncogene	Increase RAS: increase duplication [75]	Let-7
	DNA methyltransferase	Increase ER-alpha: increase duplication [76]	miR-206
		Increase DNMT: epigenetics disabling of Tumor-suppressing gene [77]	miR-450a

decrease in tumor suppressors. These types of microRNAs which experience an expression reduction in cancer cells are called tsmiR. Some examples of the microRNAs which undergo disruption in various cancer cells are shown in Table 6 [87,88]. A single microRNA's high expression – for instance, because of gene duplication – reduces its target gene expression and this target gene acts as a tumor suppressor gene in a cancer cell and a single microRNA's low expression – for example, because of gene deletion – increases its target gene expression and this target gene acts as an oncogene in a cancer cell [85].

14. Employing microRNA in cancer therapy

Disruption in the microRNA expression has shown agreement with specific pathological forms and treatment response in various tumors. Recently, microRNAs or AMOs (anti-microRNA antisense oligodeoxyribonucleotide) have been used alone or together with drugs, chemotherapies, and radiotherapy [89]. MicroRNAs are more stable than mRNAs. A single microRNA can have hundreds of target genes. Normally, the targets of a single microRNA are related to mRNAs with similar functions. MicroRNA is found in most body fluids and this feature has motivated experts to employ microRNA in their treatments [90] (Fig. 5).

15. Curative methods with microRNA in cancer therapy

1. Using microRNA-related precursor genes: In this method, the microRNA-related gene is entered into an expression vector which can be viral or plasmid. Factors such as promoter and gene length are taken into account [42]. Antiviruses and adenoviruses are used for differentiated cells which do not divide and for the cells which are being divided. However, due to the fact that adenoviruses do not enter genomes, they are gradually eliminated in the cells which are being divided [91]. The main problem of using expression vectors in invivo experiment is that the host's immune system usually eliminates them [42]. In one experiment, researchers conditionally developed lung cancer in mice by increasing K-ras expression. It was found that adenoviral intranasal injection expressing let-7a reduced tumorigenicity [92].
2. Using microRNA mimic: In this method, a single microRNA, which has the role of tsmicroRNA, is often transferred into the cell in the form of two lines produced by Dicer. Like other methods, this method has been used in both invitro and invivo experiments. In 2010, the LPH nano-particle, which was accompanied by a single-line anti-tumor antibody, was able to purposefully transfer mir-34a into melanoma cells [93].
3. Using AMO (anti-microRNA antisense oligodeoxyribonucleotide): Experts use AMO in oncomir cases; however, due to the fact that AMOs are single-line and affected by intracellular nucleases, these lines' stability can be increased through applying chemical changes [94].
   - 3.1. LNA: In LNA, the end of ribose 2 is connected to the end of ribose 4. AMO, which contains LNA-antimiR-122, causes a reduction of miR-122 in mice and since miR-122 increases cholesterol production in blood, using LNA-antimiR-122 reduces blood cholesterol [95].
   - 3.2. AMO containing 2-O-methoxyethyl: A famous example of AMO is using 2-O-methoxyethyl-antimir-122, which reduces miR-122 and blood cholesterol in mice [96,97].
   - 3.3. AMO linked with cholesterol: Linking with cholesterol causes an increase in AMO's permeability into cells [98].
   - 3.4. Morpholinos: Demonstrates the structure of morpholinos. In this structure, ribose is replaced by morpholine and phosphate is substituted by phosphorodiamidate. Morpholinos has higher stability in comparison with intracellular nucleases [99].
   - 3.5. PNAs: Demonstrates the PNAs' structure in which ribose and phosphate are replaced with glycine N-(2-aminoethyl). PNAs

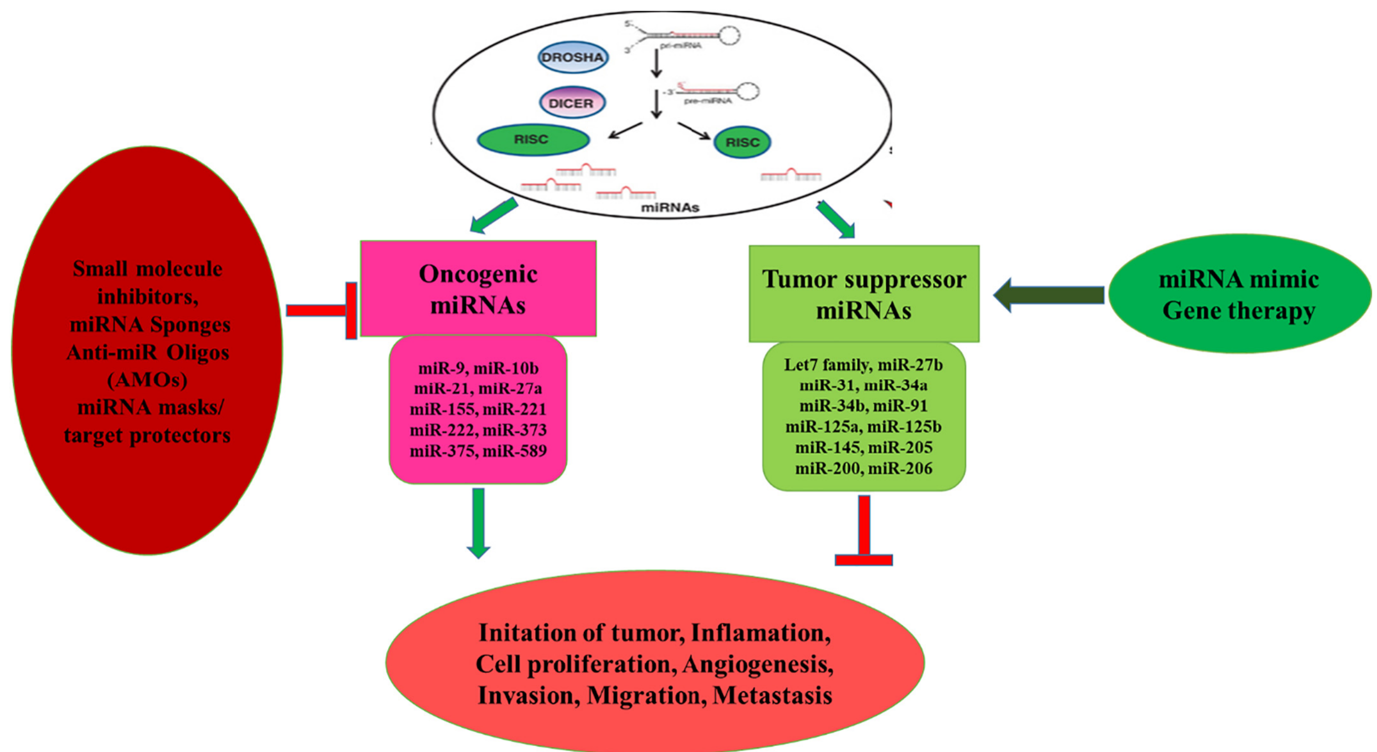

Fig. 5. Different miRNA approaches from synthesis to treatment.

are resistant against protease, nuclease, and PH change [100].

4. MicroRNA trapping: In this method, experts use mRNA, which contains several meeting points with microRNA, in order to prevent the effect of microRNA on its genetic targets. In this approach, mRNA can be expressed stably in the desired cells within the vector and therefore can increase the results of microRNA target genes by connecting to the microRNA itself. This mRNA has been called miRNA sponge [101].

16. CircRNA: natural miRNA sponge

CircRNA is a part of non-coding RNAs and has a regulatory role. CircRNA contains several meeting points for a single microRNA and impedes the performance of that microRNA. For instance, ciRS-7s are ring-structured RNAs expressed naturally in the brains of humans and mice. CiRS-7s contains almost 70 linking sites with miR-7 and increase the expression level of MiR-7's targets within the brain cells. The connection of these sponges with miR-7 in the brain does not lead to the disintegration of the sponges because sequences other than the fundamental sequences are involved in the connection and the sponges are just responsible for trapping miR-7 [102].

17. Protecting the target mRNA

Previous studies have shown that mature microRNAs made by Dicer have different half-lives, which is dependent on the amount of pairing with target genes and the frequency of target genes. When this half-life is rather high (about a week) and it is necessary to express only one target gene among the other ones and prevent the expression of other targets by the related microRNA [103], it is possible to design a protector against a single mRNA in order to stop the inhibition performance of the microRNA on that mRNA [104].

18. Methods of transferring oligonucleotide to cell

One of the most important disadvantages of using traditional gene therapy methods such as viral vectors is the formation of immunogenicity, which usually stimulates the host's immune system in invivo experiments [105]. In recent years, researchers have attempted to employ non-viral vectors such as various lipids, dendrimers, and peptides which can be purposefully transferred to the desired cell by connecting an antibody against the target tissue [106]. Non-viral vectors often contain positive charges and their positive charges are connected with both negative nucleic acids and cells' surface negative glycocalyxes which promote endocytosis. Nonetheless, studies have shown that extra positive charge can also lead to toxicity. All non-viral vectors are categorized into three main groups which include synthetic polymers, natural polymers, and lipids. Most of the efficient non-viral vectors are a hybrid of these three groups [107].

19. Conclusion

Micro-ribonucleic acids (miRNAs) are evolutionary conserved non-coding ribonucleic acids and are 18–25 nucleotides long. miRNAs regulate post-transcriptional gene expression through mRNA degradation and inhibition of translation. These molecular structures play a role in regulating cellular and pathological processes and many of them can be regarded as oncogene and tumor suppressor genes (TSG), so mutations in the open reading frame can cause cancer. Identifying miRNAs and their targets, has provided a new opportunity to recognize the pathways leading to cancer. Therefore, these compounds can be employed as potential biomarkers for diagnosis, prognosis and treatment of cancer. In this review, miRNAs biogenesis, the underlying mechanism of their synthesis and function and the way the target molecules are recognized will be described. Furthermore, this article will discuss novel findings of the role of miRNAs in the function of cancer cells and their application in cancer diagnosis and treatment.

Author contributions

KB, SHSH, AK, SV, PH, RKH and AEN accomplished the data processing, investigated the informatics database and also performed the

statistical analyses. AAS wrote the whole manuscript, revised and managed the manuscript. All authors revised the article comprehensively and confirmed the final edited version of the manuscript.

Ethical issues

There are no ethical problems for this review article.

Declaration of competing interest

There is no conflict of interest.

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