Chapter

MicroRNA: A Signature for Cancer Diagnostics

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Abstract

Various tools and techniques are being used for the diagnosis of cancer, but not a sole technique provides powerful result at the very early stages of cancer. This provides the need for type of tools which could detect cancer at early stages so that survival rate could be augmented. There are various diagnostic ways to identify cancer, but in each case, there are always circumstances to compromise on the sensitivity. In this framework, a new and more advanced approach of diagnosis for cancer is microRNA (miRNA). miRNAs are conserved regions among humans and animals, and their synthesis takes place in the nucleus and cytoplasm. There are several types of microRNAs that could be upregulated and downregulated in various cancers. A cancer cell could be identified by measurement of the expression pattern of miRNA. By examining the expression level for different types of cancers, miRNA can be used as biomarker for early detection of cancer in human beings.

Keywords: microRNA, cancer biomarker, diagnostic, colorectal, upregulation, downregulation, breast cancer, cervical, liver, prostate

1. Introduction

MicroRNAs (miRNAs) are a small, non-coding, single-stranded RNA consisting of around 22 nucleotides [1]. More than 3% of the human genome (gene portion) encodes for microRNA, and their number is around 1000 [2–4]. This small RNA can regulate gene expression posttranscriptionally [5–7]. This small RNA can regulate gene expression posttranscriptionally by binding to its cognate RNA target at the 3^0 untranslated region (UTR) [8–11]. A small microRNA was discovered for the first time in *C. elegans* and is encoded by the Lin-4 gene [12] providing evidence for its evolutionary conservation. This conserved microRNA was found to be involved in many important biological processes including cell proliferation, growth, apoptosis, etc. [13, 14], and many cell-based factors have been known to regulate its expression [15]. The genes transcribing the miRNA are considered to belong to the set of tumor suppressor genes, and the serum level of miRNA can be detected [16, 17]. There are certain miRNAs that can behave as either oncomiRs (whose expression can cause the cancer) or tumor suppressor depending on the context "Several miRNAs cannot be clearly and unequivocally categorized as tumor suppressors or oncomiRs because data in our hands are quite intricate and conflicting since they could act as tumor suppressors in one scenario or as oncomiRs in the other" [18].

2. Synthesis/biogenesis of miRNA

Synthesis of miRNA takes place in the nucleus as well as in the cytoplasm. Genes encoding miRNAs are present in the form of a cluster and contain introns (**Figure 1**). These genes are transcribed by polymerase II with the generation of the primary precursor pri-miRNA. This precursor miRNA consists of a 3′ poly-A tail and a 5′ end cap [19, 20] with a stem-loop structure. RNase 3 Drosha cleaves this structure with the help of its Pasha cofactor DGCR8. This resultant cleaved, precursor structure is known as pre-miRNA and consists of ∼70–90 nucleotides [21]. This ∼70 nt precursor is exported to the cytoplasm by Exportin-5.

In the cytoplasm, the whole pri-miRNA is recruited by a RNA-induced silencing complex (RISC) and is converted into mature miRNA. These are mediated by an RISC leaching complex (RLS), which is basically a multiprotein complex and consists of a double-stranded RNA domain protein (DICER), tar RNA-binding protein (TARB), and the Ago 2 protein. The RNAse 3 DICER along with its cofactor yields duplex miRNA (19–25 nucleotide duplex miRNA with 2 nucleotide overhangs at each 3′end). During the process of cleavage, two strands are formed, namely, a functional and a passenger strand. The functional strand along with the Ago protein (RISC) is involved in gene silencing function, while the passenger strand is degraded due to its instability. This miRISC incorporates one strand of miRNA (functional strand and guide strand) so that it takes the guidance from this complex to target mRNA (complementary) for its degradation or inhibition at the translational level [22]. miRNA is processed in the cytosol and transported to the blood. It is resistant to degradation because it is carried by complexes of lipoprotein inclusions [23] or in the form of exosomes [24, 25].

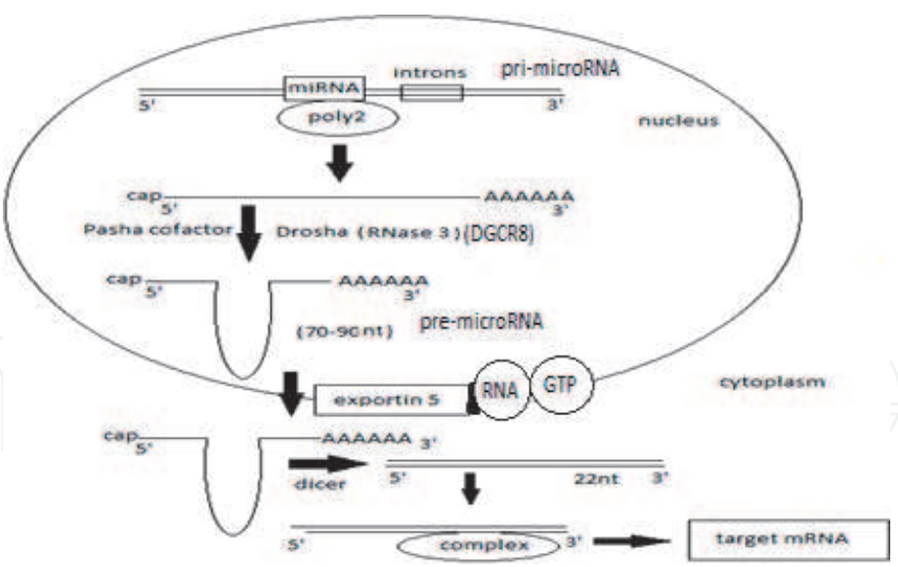


Figure 1.
Biogenesis of microRNA.

3. Mechanism of action

The mechanism of action of microRNA is such that it binds to its partial complementary sequence in the target mRNA (that codes for protein). Hence, the expression is repressed (**Figure 2**) and no product is synthesized [7].

In another scenario, the microRNA may bind to the complementary sequence of target mRNA that codes for protein and initiates RNA-mediated gene silencing, with the resultant cleavage of the target RNA (**Figure 3**) [26].

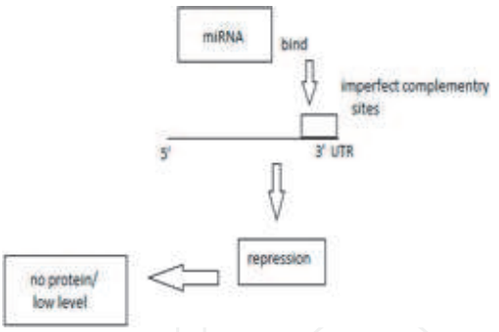


Figure 2.
Mechanism of action of miRNA.

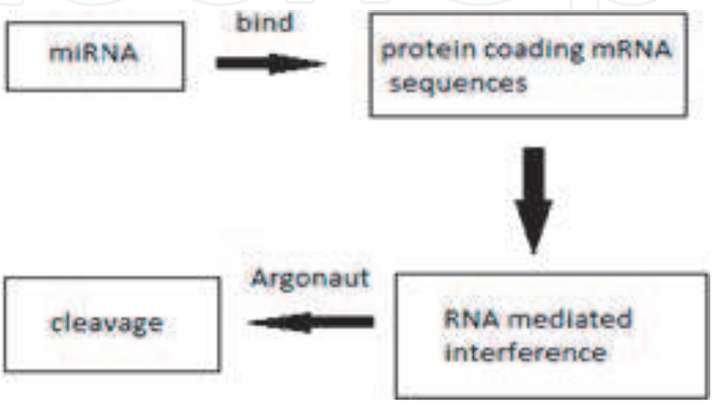


Figure 3.
Mechanism of miRNA.

4. Diagnosis of cancer

There are reported differences in the expression pattern of miRNA in normal and cancer cells [27]. Some miRNAs are overexpressed, while the others are downregulated in different kinds of cancers [28]. Due to its small size and resistance to RNase-mediated degradation, they have the potential as powerful biomarkers for cancer diagnosis [29]. miRNA expression is involved with the rearrangement of chromosomes, methylation of the promoter region, and transcriptional regulation. miRNA-mediated aberrations in one or more of these processes can culminate in alterations in protein and mRNA expression [30].

5. Types of miRNA and cancer according to organs

Different miRNAs are involved in different types of cancers:

5.1 Breast cancer

Breast cancer is the most prevalent form of cancer in women. Among 12.7 million cancer cases globally, breast cancer is most frequently diagnosed, that is, 23 and 14% deaths due to breast cancer have been reported [1, 31]. The alarmingly increasing mortality data coupled with increases in relapses warrants an improved molecular understanding of the etiology and mechanistic details that contribute to the chemoresistance. There are four subtypes (intrinsic) of breast cancer. These are ErbB2^{+} (epidermal growth factor receptor 2-positive (also called HER2)), luminal A

(hormone receptor positive for estrogen and progesterone, HER2), luminal B (hormone receptor positive for estrogen and progesterone and positive or negative for HER2), and basal like (hormone receptors negative for estrogen, progesterone, and HER2) showing its heterogeneity. Many of the microRNAs play a role in the inhibition of breast cancer. The upregulation of miR-21 (**Table 1**) results in the increased expression of BCL-2 protein and chemoresistance in breast cancer [38]. MiR-125b shows the resistance to chemotherapeutic agents 5-fluorouracil, and it has higher expression in the patients that are nonresponsive to this agent (**Table 2**). Many promote the prognosis of breast cancer by targeting the tumor suppressor at the gene level and activating the transcriptional factors that are oncogenic in nature [32, 38].

The Rab protein is a member of the Ras superfamily (**Figure 4**). This protein is a G-protein-coupled receptor and is involved in many cellular processes including fusion, budding, synthesis of vesicles, and motility [55]. A member of the Rab class is Rab11a, and this protein has many functions including cellular migration and phagocytosis [56]. In breast cancer there is overexpression of Rab11a protein [57] and is regulated by miRNA 320a. This miRNA can downregulate Rab11a protein, thereby mediating the inhibition of breast cancer progression.

MiR-320a has an important role in tumor suppression [58] and can be a biomarker for breast cancer. This miR-320a results in a 15% increase of cells in G0/G1,

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-10b	Homeobox D10	Promotes cellular invasion, migration, and metastasis by targeting the RhoC	[32]
2	miR-21	Programmed cell death protein 4, hypoxia-inducible factor-1α	Promotes cellular invasion, metastasis, epithelial-to-mesenchymal transition and migration	
		Phosphatase and tensin homolog, programmed cell death protein 4, tropomyosin 1	Promotes cellular invasion	[33]
		Metalloproteinase inhibitor 3	Promotes cellular invasion	[34]
3	miR-155 (chemosensitive determinant by targeting the FOXO3)	Suppressor of cytokine signaling 1	Promotes cell proliferation and growth	[35]
		Tumor protein p53 inducible nuclear protein	Promotes cell proliferation	[36]
		Forkhead box protein O3	Promotes cell proliferation and cell survival	[37, 38]
4	miR-373	CD44 (inversely correlated)	Promotes cellular invasion and migration	[39]
			Promotes cellular invasion and metastasis	[40]
5	miR-520c		Promotes cellular migration, invasion, and metastasis	[39]

Meta-analysis or Cochrane reviews documenting the involvement of a specific miRNA or a battery of miRNAs contributing to relapse or recurrence can be displayed as a separate table for each of the cancers.

Table 1.
MicroRNAs upregulating the breast cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-125b	Erythropoietin, erythropoietin receptors (positive correlation with ERBB2/HER2 expression)	Inhibition of cellular differentiation and proliferation	[41]
		Glutamyl aminopeptidase or aminopeptidase A, casein kinase 2-alpha, cyclin J, multiple EGF-like domains 9	Inhibition of cellular proliferation	[42]
		Receptor tyrosine-protein kinase erbB-2 (human epidermal growth factor receptor 2) (induction of miR cause the downregulation of ERBB2/ERBB3)	Inhibition of invasion and migration	[43, 44]
2	miR-205	High-mobility group box 3 gene	Suppression of invasion and proliferation	[45, 46]
3	miR-17-92	Mitogen-activated protein kinase kinase kinase 2	Promotes the antitumoral activity of natural killer cells and reduction in metastasis	[47]
4	miR-206	Cyclin D2, connexin 43	Reduction in invasion, migration, and metastasis	[48]
5	miR-200	Zinc finger E-box binding homeobox 1/2, snail family zinc finger ½	Reduction in tumor growth, EMT through E-cadherin, and metastasis	[49]
6	miR-146b	Nuclear factor kappa B, signal transducer, and activator of transcription 3	Reduction in survival and metastasis via interleukin 6	[50]
7	miR-126	Insulin-like growth factor-binding protein 2, c-Mer tyrosine kinase, phosphatidylinositol transfer protein, cytoplasmic 1	Reduction in angiogenesis and metastasis	[51]
8	miR-335	SRY-related HMG-box 4, tenascin C	Suppression in migration and metastasis	[52]
9	miR-31	Ras homolog gene family	Targets various steps of metastasis and invasion for inhibition	[38]
		WAS protein family, member 3, Ras homolog gene family	Reduction in the metastasis and progression of cancer	[53]
		WAS protein family, member 3	Reduction in the metastasis and progression of cancer	[54]

Table 2.
MicroRNAs downregulating the breast cancer.

and the population of cells in the S phase is decreased. Apart from the G0/G1 cell cycle arrest, miR-320a also increases the activity of caspase resulting in the induction of apoptosis [59]. The potential target of miR-20 is Rab11a; it has two binding sites at the 3′UTR region for miR-320a and can mediate its posttranscriptional repression. This protein is also necessary for the activation of Akt via phosphatidylinositol-4-kinase (PI4K3) in breast cancer—a pro-survival signal [60]. Further, overexpression of Rab11a protein results in the reversal of cell cycle arrest and apoptosis mediated by miR-320a by targeting the MTDH at 3′UTR [61]. The gene coding for the Rab coupling protein (RCP) (a Rab11-FIP1C (Rab coupling protein))

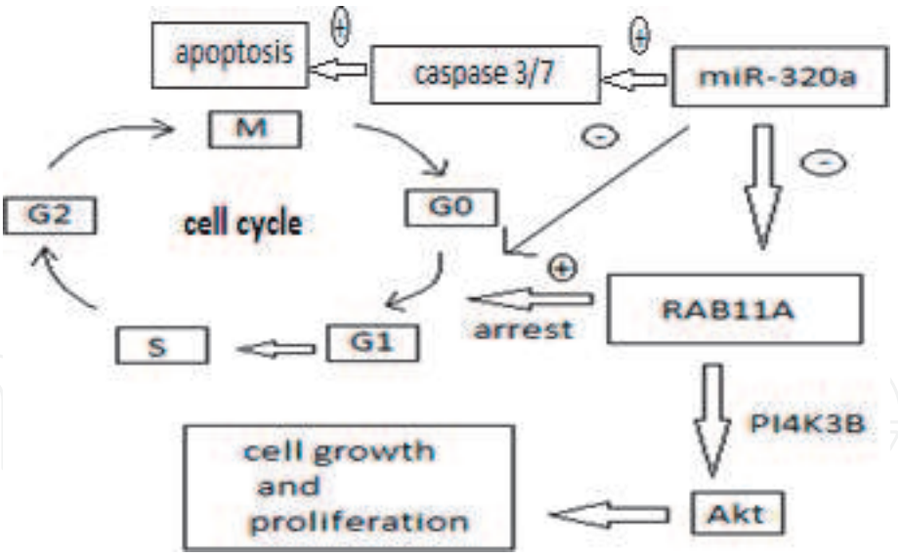


Figure 4.
MicroRNA and breast cancer.

is amplified in breast cancer and aids in the sorting of epidermal growth factor receptor (EGFR) [62, 63]. For the metastasis or migration of cancer, the cell critical factor is RCP which mediates this effect via cell surface integrin alpha-5-beta-1 demonstrating that Rab11a is a protein that is involved in the metastatic or invasive phenotype of breast cancer [64, 65].

5.2 Colorectal cancer

Colorectal cancer is the third most common cancer around the world. The incidence rate is increased up to 6% [66]. Survival rate can increase to 90%, if it is diagnosed at an early stage. Survival rate is inversely proportional to the stage of cancer [67].

In a study, the cluster of miR-17/miR-92 (chromosomal region 13q31.1 with miR-20a as one of its members). The region encompassing this cluster is under the regulation of the oncogenic Myc transcriptional factor and TGF-β [68, 69]. Overexpression converts a benign tumor to colorectal cancer [70].

Mir-20 acts as a potential colorectal cancer cell biomarker [71]. Induction of miR-20-mediated EMT is a critical factor contributing to the increases in tumor cell migration, metastasis, E-cadherin downregulation, and upregulation of matrix metalloproteinases (**Figure 5**) [72, 73]. This microRNA can cause a delay in TGF-β-mediated G1/S transition. However, cell cycle progression occurs due to an inactivating mutation in this pathway [74]. Normal TGF-β-mediated signaling can be a cytostatic response and inhibit tumorigenicity in colorectal cancer cells [75].

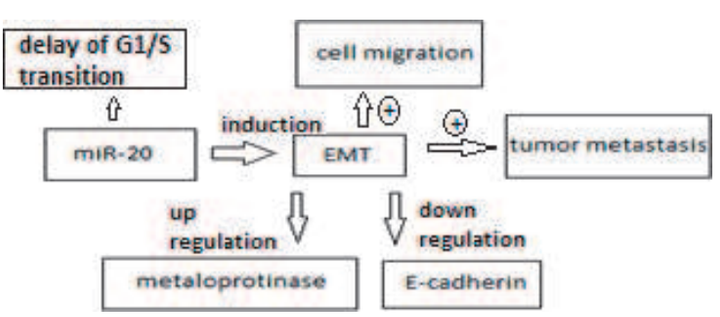


Figure 5.
MicroRNA and colorectal cancer.

miR-20 may be degraded by a bacterial strain that is dominant in the lumen of the bowel of colorectal patients. Hence, expression of miR-20a is reduced in patients having colorectal adenoma [76–78].

In another study, miR-34a modulates EMT and MET processes. There is methylation in CpG islands (cancer specific), and these are repressed by *IL-6/STAT3* pathway which is mediated by *interleukin-6 receptors* (*IL6R)* and *inactivation of TP53*. This results in downregulation of miR-34a [79]. miR-34a inhibits SIRT and activates *TP53.* A positive feedback loop has been suggested between miR-34a (**Table 3**) and TP53 [81]. In many cancers, TP53-inducible microRNA is miR-34a [82].

In another study, miR-200 is downregulated in primary colorectal cancer (invasive stage) correlatable with the disruption of the basement membrane [83]. The miR-200 family consists of five members and is encoded in two clusters. One cluster is present on chromosome 1 and encodes for miR-200a, miR-200b, miR-200c, and miR-141. The other cluster is present on chromosome 12 and encodes for miR-141. The potential target of miR-200 family is ZEB1/ZEB2 which is a repressor of CDH1 (**Table 4**). Expression of all members of this family can be repressed following methylation of CpG islands in the regulatory region of their genes [84, 85]. Strong expression of miR-200 results in metastatic colorectal cancer [83]. Another study shows that miR-155 and miR-21 are overexpressed in colorectal cancer [86]. In another study involving colorectal cancer patients, the expression of miR-195 and miR-497 is reduced [87].

5.3 Cervical cancer

Cervical cancer is the most common cause of death among women in the developing countries [88, 89]. Cervical cancer can cause the death of 270,000 women per year [90]. Human papillomavirus (HPV) is the causative agent, with the E6 and E7 proteins targeting p53 and pRb, respectively [91].

Sr. no.	MicroRNAs	Potential target	Function
1	miR-185	Ras homolog gene family, member A, and cell division control protein 42 homolog	Reduction in the proliferation, induction of cell cycle arrest at the G1 stage, and promotion of apoptosis
2	miR-192	cyclin-dependent kinase inhibitor 1	Regulating the p53
3	miR-215		
4	miR-34a	Tumor suppressor p53	Modulate the EMT transition

Table 3.
MicroRNAs suppressing the colorectal cancer [80].

Sr. no.	MicroRNAs	Potential target	Function
1	miR-130a	Mothers against decapentaplegic homolog 4 (SMAD4)	Enhances the cell proliferation and migration
2	miR-301a		
3	miR-454		
4	miR-200	Zinc finger E-box-binding homeobox ½	Promotes metastasis

Table 4.
MicroRNAs promoting the colorectal cancer [80].

Type of miRNA	Function	Ref.
miR-491-5p	Downregulated; suppress cervical cancer by telomerase reverse transcriptase and regulate the PI3K/AKT pathway	[92]
miR-142-3p	Inhibit the proliferation of cell Frizzled_7 receptor (FZD7)	[93]
miR-142-3p	Inhibit the growth of cell via downregulation of its FOXM1 target	[94]

Table 5.
AmiRNA involved in cervical cancer.

Several miRNAs are upregulated and downregulated during cervical cancer (**Table 5**). miR-135b is a biomarker for cervical cancer. Suppression of this biomarker results in the inhibition of cell growth.

Downregulation of miR-135b results in the percentage of G1 cells with a concomitant decrease in those in the S phase. The expression of cyclin-dependent kinases (p27 and p21) is increased and that of cyclin D1 is decreased. Cyclin D1 (nuclear protein) is responsible for the regulation of cells (proliferating) that are at the G1 phase of the cell cycle [72, 73].

There seems to be an inverse relationship between miR-135b and FOXO1 protein. When FOXO1 protein is downregulated, cervical cancer is promoted. When FOXO1 protein is expressed, then there is an increase in the p27 and p21 expression with a decrease in cyclin D1 level and cell cycle is arrested [95, 96]. So, when miR-135 is downregulated, FOXO1 is upregulated with the resultant inhibition of cell growth (**Figure 6**).

In cervical cancer, miR-196a is upregulated and its targets are $p27^{Kip}$ and FOXO1. It promotes the transition of cells from G1 phase to S phase, enhances the cellular proliferation by involving the PI3K/Akt pathway, and is involved in tumorigenesis [97].

In one study, miR-10a is overexpressed in cervical cancer (Long et al., 2012; [28]). The target of miR-10a is transmembrane protein type 1 close homolog of L1 (CHL1) that is downregulated. A decrease in CHL1 protein dysregulates PAK and MAPK pathways resulting in increases in cell growth followed by migration and invasion [98].

In another study, miR-21 is upregulated in cervical cancer, and it is located at the 17q23.21 locus (**Table 6**). The pri-miR-21 is transcribed by the intronic region of TMEM49 (protein-coding gene). This miRNA targets the p53 and Cdc25 (regulators of the expression of genes), TPM1 and RECK (suppressing the metastasis), and PTEN and PDCD4 (inducing the apoptosis of metastasized cell). Hence, decreases in this miRNA can result in the PDCD4 gene providing signals for the activation of the RAS pathway. This activation, in turn, activates the transcription factor AP-

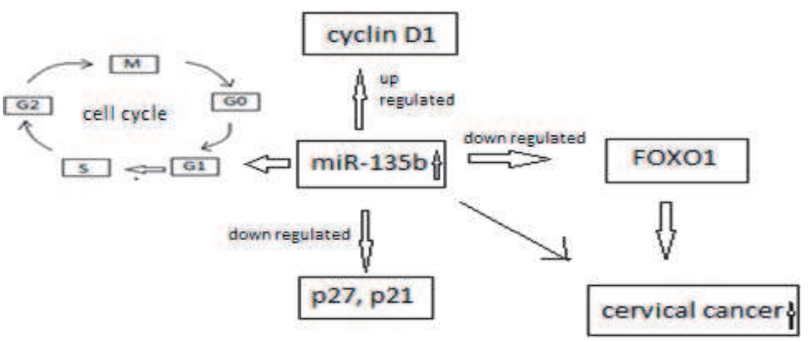


Figure 6.
MicroRNA and cervical cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-196a	Binds to the 3′UTR of $p27^{Kip}$ and FOXO1 and inhibits their translation	Increases in cell proliferation and tumorigenesis	[97]
2	miR-10a	Has an inverse relation with the expression of close homolog of L1 (CHL1) transmembrane protein type 1—a cell-adhesion protein	Cell growth followed by migration and invasion	[91]
3	miR-21	Negatively regulates p53 and Cdc25, TPM1 and RECK, and PTEN and PDCD4	Enhances the expression of genes associated with cell proliferation, metastasis, as well as those involved in the antiapoptosis effect	[91]
4	miR-886-5p	Negatively regulates the Bax gene	Dysregulation of the gene involved in apoptosis (miR-10a, miR-106b, miR-21, miR-135b, miR-141, miR146, miR-148a, miR-214, and miR-886-5p)	[91]
5	miR-20a	TNKS2 oncogene is upregulated (by binding at 3′UTR of mRNA of TNKS2 results in enhanced translation)	Migration, colony formation, and invasion	[91]

Table 6.
MicroRNAs activating the cervical cancer.

1gene. This AP-1 binds to a specific site on the promoter of miR-21 and as a result miR-21 gene is transcribed [99], thereby providing a plausible mechanism for a positive feedback loop.

It was reported that miR-886-5p targets and negatively regulates Bax gene expression via inhibition of translation, and hence, this form of control may be significant for the development of cervical cancer. When there is a death signal, the proapoptotic protein coded by Bax gene is inserted into the outer membrane of mitochondria. As a result, cytochrome C is released, and the initiator caspase-9 is subsequently activated with the initiation of apoptosis (**Table 7**) [91].

5.4 Liver cancer

Liver cancer is rising very rapidly globally with aflatoxins also contributing to its etiology. Specific miRNA may be expressed in the case of liver cancer. One of the

Sr. no.	MicroRNAs	Potential target	Function
1	miR-143	Target k-Ras, Bcl-2 and Macc1, specifically downregulation of Bcl-2	Inhibition of apoptosis and uncontrolled cell proliferation
2	miR-129-5p	Downregulates HPV18 E5 and E7 expression as well as inhibits the translation of SP-1 transcriptional factor	Suppressing the progression of cervical cancer
3	miR-34a	Cyclin E2 and D1, CDK6, E2F3, CDK4, E2F1, E2F5, P18, Bcl-2, and SIRT1	Aberrations in cell proliferation and differentiation—cell transformation

Table 7.
MicroRNAs suppressing cervical cancer [91].

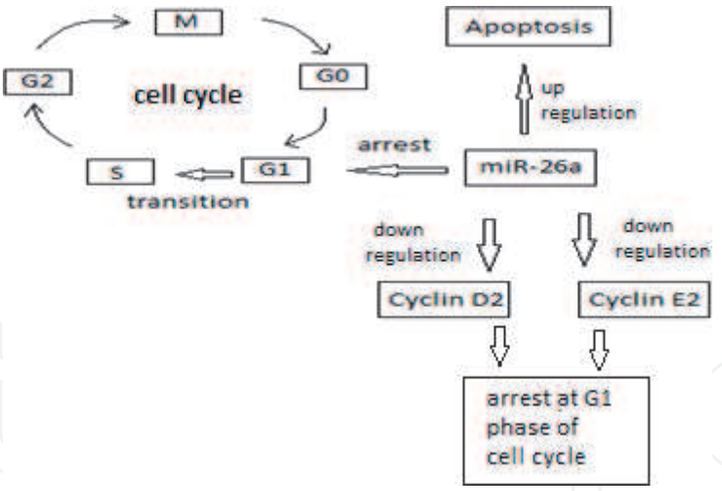


Figure 7.
MicroRNA and liver cancer.

miRNA biomarkers in liver cancer is miR-26a. Its expression is reduced in liver cancer unlike normal hepatic cells, where its expression level is increased [100].

miR-26a and miR-34a cause an increased number of cells in the G1 phase of the cell cycle, while there is a decrease in the cells in the S phase of the cell cycle. miR-26 causes cell cycle arrest at the G1 phase [84]. In the 3′UTR region of cyclins E2 and D2, there is a conserved binding site for miR-26a. miR-26a binds to these binding sites and represses the expression of both cyclins (**Figure 7**). miR-26 causes the induction of apoptosis in the tumor cells and suppresses hepatic cancer [101].

Kim et al. studied the expression of miR-31 in liver cancer (**Table 8**). The main target of miR-31 is CDK2 protein and HDAC2, with these proteins suppressed in the livers of normal individuals. There is an enhanced expression of CDK2 protein and HDAC2 in liver cancer. When HDAC2 is suppressed, $p21^{WAF1/Cip1}$ and $p16^{INK4A}$ are activated, and positive regulators of the cell cycle (cyclin D1, CDK2, and CDK4) are suppressed simultaneously [102].

In another study, the expression of miR-9 enhances the formation of tumor spheres in the liver. The direct target of the miR-9 is PPARA and CDH1 genes and regulates them via binding to the 3′UTR region of these genes. Upregulation of miR-9 enhances the level of vimentin (mesenchymal marker) and deregulates the CDH1 (**Table 9**). The transcriptional factor PPARA has been implicated in the metabolic homeostasis of the liver by regulating the nuclear factor-4 alpha (hepatocyte HNF4A) gene, which is a tumor suppressor. In liver cancer, miR-9 suppresses the CDH1 and also suppresses the PPARA at their mRNA level by binding to the 3′UTR of these genes [103].

In one study, there is overexpression of miR-525-3p in liver cancer, and its potential target is a zinc finger protein (Krüppel C2H2 type family) ZNF395. This

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-26a	Cyclin E2 and D2	The arrest of the cell cycle at G1 phase	[84]
2	miR-31	CDK2 protein and HDAC2	Suppress the positive regulators of cell cycle and promote those proteins involved in EMT-related processes	[102]

Table 8.
MicroRNAs suppressing the liver cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-9	Influences the PPARA/ CDH1pathway	Suppress the tumor suppressor	[103]
2	miR-525-3p	Downregulates ZNF395	Enhances cell growth and prevent apoptosis	[104]

Table 9.
MicroRNAs activating the liver cancer.

zinc finger protein was originally a transcriptional factor and binds to the promoter region of the human papillomavirus (HPV). This protein mediates the regulation of PI3K/Akt pathway and causes the inhibition of cell growth via the induction of caspase-3 and the promotion of apoptosis. The expression of miR-525-3p enhances cell growth and prevention of apoptosis [104].

5.5 Prostate cancer

In countries in the West, prostate cancer is a more prevalent form of cancer among males with an increasing incidence rate [105]. Prostate cancer is the result of undesirable genomic alteration [106, 107]. CD9 is inactivated during prostate cancer and may cause its progression [108].

In the prostate cancer, serum level of miR-141 is elevated [109]. So it acts as the biomarker of prostate cancer. In the progression or repression of prostate cancer, miR-141 function is understood poorly [110]. One other study is done by Waltering et al. in which miR-141 is castrated and results in upregulation and activation (**Figure 8**). This causes the LNCaP cell growth to increase. This miRNA is also involved in the regulation of signaling of the androgen. This androgen has a crucial role in the growth of prostate cancer (castration-resistant and androgen-dependent). So it may be involved in the progression of prostate cancer [111, 112].

In a study involving prostate cancer, miR-888 was found to be upregulated. Its target is the tumor suppressors SMAD4 and RBL1. Binding of this miRNA to the 3′UTR causes their downregulation. RBL1 is the member of the RB (retinoblastoma) family and blocks the progression of cells at the G1-S phase following its binding and inhibition of the transcription factor E2F. SMAD4 protein binds to SMAD receptors and transduces the signal initiated by TGF-β/BMP ligands in order to regulate differentiation and cell growth [113].

In another study, there is the downregulation of miR-23a, b (**Table 10**). There is upregulation of the-Myc gene which causes the repression of these miRNAs at the transcriptional level. Mitochondrial glutaminase protein is expressed in the prostate

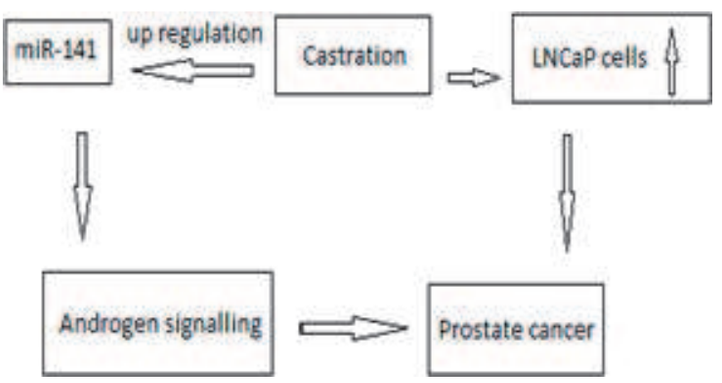


Figure 8.
miRNA and prostate cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-141	LNCaP cells	Promote cell growth Decreased growth in response to anti-miR-141 treatment	[112]
2	miR-888	Downregulates SMAD4 and RBL1	G1-S phase transition	[113]

Table 10.
MicroRNAs activating the prostate cancer.

cancer cells. Consequently, glutamine catabolism is increased, providing a growth advantage to the cancer cells [114].

In another study, miR-34a is suppressed in prostate cancer. The target of miR-34a is deacetylase sirtuin (SIRT1) and cyclin-dependent kinase 6 (CDK6). CDK6 regulates cyclin D, which, in turn, regulates cell cycle progression and G1-S phase transition, while p53 protein-dependent apoptosis is regulated by SIRT1 via deacetylation and stabilization of p53. The target of the p53 gene is miR-34a. It is suggested that there is a positive feedback loop in which SIRT1 mediates the activation of miR-34a via stabilization of p53 and induces the apoptosis and blocks the cell cycle transition. This activation of p53 causes the upregulation of miR-34a which in turn suppresses the SIRT1 (**Table 11**) [114].

5.6 Lung cancer

The leading cause of death around the world is lung cancer by tobacco smoke. This environmental lifestyle-related factor may cause undesirable epigenetic and genetic modifications [115]. The key role in lung cancer is the alteration and mutation in tumor suppressor genes (p53 and *RB/p16pathway)* and less frequent is the genetic alteration of *FHIT*, *K-ras*, *MYO18B*, and *PTEN* [116].

Five miRNAs were differentially expressed in lung cancer tissues, and these include miR-21, miR-155, miR-145, miR-17-3p, and hsa-let-7a-2. Specifically, hsa-miR-155 levels were increased, while that of hsa-let-7a-2 was downregulated [117].

There is a functional interaction of let-7 with the Ras as a target gene is overexpressed associated with protein kinase and resulting intracellular pathway of signaling [118]. The molecular mechanism is unclear involving miRNA in lung cancer. Alteration in the somatic genes resulted in the defective miRNA expression in lung cancer. This reduced expression of miRNA (has-let-7a-2) in the lung cancer is due to epigenetic modification and results in the silencing of tumor suppressor gene and many others (**Figure 9**) [119, 120]. The expression of hsa-miR-21 is upregulated in cancer cell and causes the inhibition of product of gene which initiates apoptosis and causes lung cancer [121]. In a report miR-17∼92 cluster is overexpressed in the lung cancer. This cluster consists of six miRNAs.

Sr. no.	MicroRNAs	Potential targets	Function
1	miR-23a,b	Glutaminase protein (indirect)	Glutamine catabolism
2	miR-34a	SIRT1 and CDK6	Progression of cell cycle, G1-S phase transition, and antiapoptosis

Table 11.
MicroRNAs suppressing the prostate cancer [114].

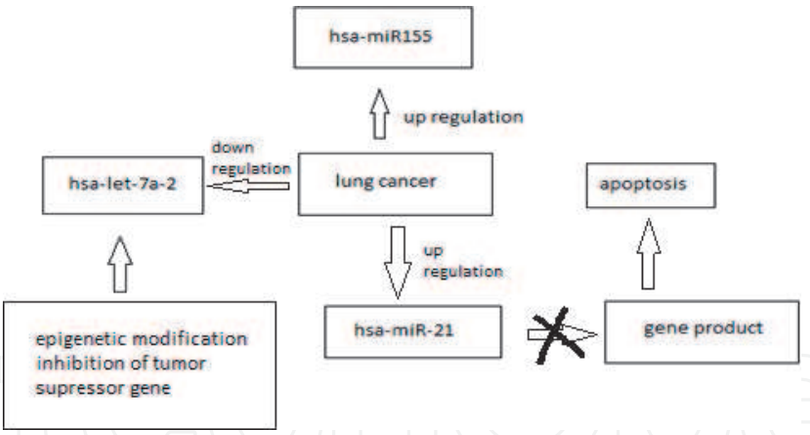
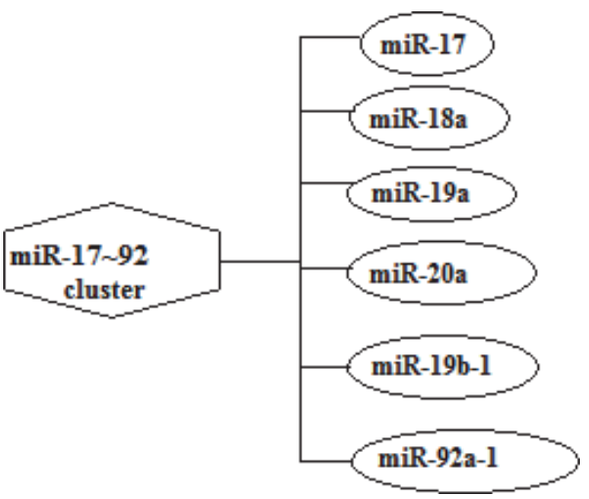


Figure 9.
miRNA and lung cancer.



This cluster in lung cancer is transactivated via MYC and members of the E2F family. The direct target of this cluster is HIF-1α. Upregulation of MYC causes the downregulation of HIF-1α and affects proliferation of cell in normoxia without affecting the hypoxic condition. Overexpression of this cluster causes knockdown of retinoblastoma gene and results in the formation of reactive oxygen species. Another direct target of this cluster is RAS-related protein 14 (RAB-14), and it is downregulated by this cluster and results in the initiation and development of cancer [122].

In another study, miR-21 is upregulated in the lung cancer. Its direct target is tumor suppressor gene PTEN that is repressed by overexpression of miR-21 (**Table 12**), which results in cell growth enhancement and non-small cell lung carcinoma invasion [123]. miR-21 is upregulated by RAS via PI3K and RAF/MAPK pathways [122].

In another study, miR-34 is downregulated in the lung cancer. This miRNA is directly regulated by p53 and regulates the apoptosis and arrest of the cell cycle in cancer [81].

The miR-34/miR-499 is downregulated in lung cancer and its direct target is E2F and p53 (**Table 13**). Both miRNAs suppress the E2F and upregulate the p53 via SIRT1 so cell growth is increased [124].

The miR-15/miR-16 is downregulated in lung cancer. There is upregulation of cyclin D1 with the downregulation of miR-15/miR-16. The overexpression of miR-15/miR-16 causes the arrest of the cell cycle at G1 phase [122]

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	let-7	Ras	Protein kinase-associated signaling pathway	[118]
2	miR-17∼92	HIF-1α and RAB14	ROS and initiation and development of cancer	[122]
3	miR-21	PTEN	Cell growth enhancement and invasion	[122]

Table 12.
MicroRNAs activating the lung cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-34	p53	Regulate the apoptosis and arrest of cell cycle	[81]
2	miR-34/miR-499	E2F and p53	Cell growth and proliferation	[124]
3	miR-15/miR-16	Cyclin D1	The arrest of the cell cycle at the G1 phase	[122]

Table 13.
MicroRNAs suppressing the lung cancer.

5.7 Gastric cancer

The second malignancy that is widely prevailed is the gastric cancer which results in 12% deaths around the world [125]. Gastric cancer is the result of a series of steps. When transforming growth factor (TGF-beta) resistance is developed and E2F1 is upregulated, then gastric cancer is developed [126, 127].

In gastric cancer, there is upregulation of cluster of miR-106b-25 present on Mcm gene [128]. The transition of the G1/S phase of the cell cycle is targeted by Mcm gene. It ensures that DNA is replicated only one time when replication fork is assembled on the DNA during each cycle [129]. When cells exit from the mitosis, then expression of cluster of miR-106b-25 is activated by E_2F1 (**Figure 10**) and gains the reentry in the G1 phase of the cell cycle. The cell cycle inhibitor is p21 [130].

The cytokine TGF-beta causes the cell cycle arrests by activating p21 and causes the apoptosis [131]. As this cytokine is activated it causes the downregulation of miR-106b-25 cluster, reduces the expression of E2F1, causes the cell cycle arrest at G1/S phase of cell cycle, and causes the induction of apoptosis. The key target of miR-93 and miR-106b is E2F1 [132]. The key target of miR-25, the biomarker of gastric cancer, is TGF-beta cytokine [133]. The target of cytokine in mediating the apoptosis is Bim protein that in turn causes the activation of proapoptotic Bax and Bad molecules acting as an antagonist of Bcl2 and BclXL antiapoptotic factors (**Figure 11**) [134].

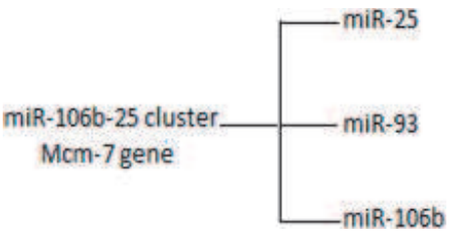


Figure 10.
miR-106b-25 cluster.

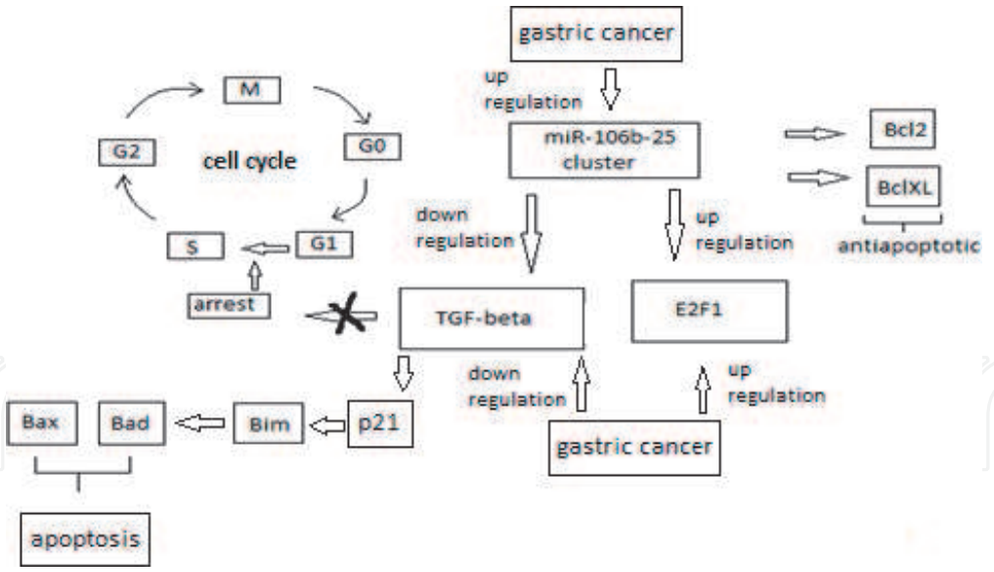


Figure 11.
miRNA and gastric cancer.

Lim found that miR-196b is upregulated in the gastric cancer (**Table 14**). This miRNA is present in chromosome 9 at HOXA cluster. There is a positive association of expression of miR-196b with the expression of HOXA10. Unmethylation of CpG islands results in the expression of miR-196b. The HOXA10 expression results in hematopoietic stem cell proliferation and progenitor cell proliferation leading to the development of cancer via expression of genes that codes for integrin-β3, TGFβ2, and dual-specificity protein phosphatase 4 [135].

We studied miR-375 is downregulated in gastric cancer (**Table 15**). Its expression in cancer cell causes the decrease in cell viability by downregulation of PDK1 and JAK2 revealing that miR-375 is a tumor suppressor in gastric cancer [136, 137].

In another study, miR-135a is a tumor suppressor in gastric cancer. Upregulation of miR-135a causes the suppression of gastric cancer via suppression of proliferation of cell via E2F, metastasis, and EMT. In gastric cancer, lymph node metastasis is associated with proliferation, metastasis, and EMT which is suppressed by overexpression of miR135a [138].

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-106b-25	E2F1	Antiapoptosis and cell proliferation	[132]
2	miR-196b	HOXA10	Progenitor and hematopoietic stem cell proliferation	[135]

Table 14.
MicroRNAs activating the gastric cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-375	PDK1 and JAK2	Decrease the cell viability	[136, 137]
2	miR-135a	E2F	Suppress cell proliferation, metastasis, and EMT	[138]

Table 15.
MicroRNAs suppressing the gastric cancer.

5.8 Bladder cancer

In males, bladder cancer is an important malignancy present in two forms that are muscle invasive and non-muscle invasive (benign) [139]. There are two microRNAs associated with bladder cancer. They are miR-21 and miR-129 [140].

In the bladder cancer, miR-129 and miR-21 both are upregulated. The direct target of miR-21 is the tumor suppressor genes that are TPM1 and PTEN (**Figure 12**) [141, 142]. The known targets of miR-129 are the genes involved in the regulation of transcription and processing of miRNA that are TAMTA1 and EIF2CA [143]. The mir-129's pathway of death effectors leads to the tumor as its target is also SOX4 [144].

According to one study, miR-19a is frequently upregulated in the bladder cancer. The expression of miR-19a is related to PTEN expression (**Table 16**). PTEN is a tumor suppressor gene. When miR-19a is overexpressed, it causes the downregulation of PTEN and increases the cell level of phosphatidylinositol-3,4,5-trisphosphate in AKT/PKB pathway. When growth factors are released, then the AKT pathway is initiated and cell growth is increased [145].

Zhang studied that miR-125b is downregulated in bladder cancer. The expression of miR-135b causes the inhibition of formation of colony and development of cancer via suppression of E2F3 which is overexpressed in bladder cancer [74].

In another study angiogenesis in the bladder cancer is suppressed by miR-34a (**Table 17**). The target of miR-34a is CD44 and causes the suppression of CD44 when upregulated which results in the regulation of transcription of the various

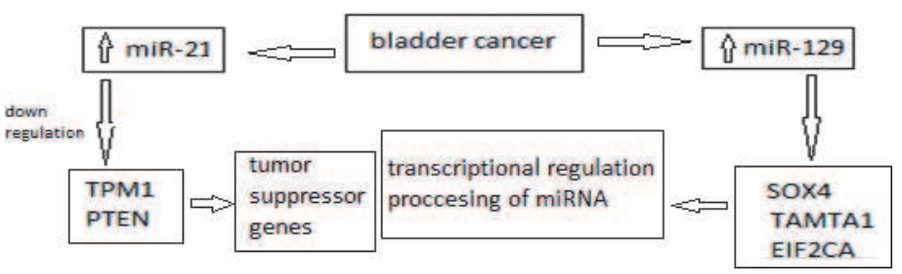


Figure 12.
miRNA and bladder cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-129	TAMTA1 and EIF2CA	Regulation of transcription	[143]
2	miR-21	TPM1 and PTEN	Growth of tumor cell	[141]
3	miR-19a	PTEN	Increase in the cell growth	[145]

Table 16.
MicroRNAs activating the bladder cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-125b	E2F3	Inhibition of formation of colony and development of cancer	[74]
2	miR-34a	CD44	Inhibition of invasion, metastasis, migration, tube formation, and angiogenesis	[146]

Table 17.
MicroRNAs suppressing the bladder cancer.

genes in bladder cancer. Over expression of miR-34a causes the inhibition of invasion, metastasis, migration, tube formation, and angiogenesis by targeting the CD44 [146].

5.9 Glioblastoma

Glioblastoma is the tumor of astrocytes, star-shaped cells that form the supportive tissues (glue-like) of the brain. This is readily metastasizing tumor because it is surrounded by large blood vessels. Glioblastoma is a complex and heterogeneous tumor that comprises on neoplastic cells, endothelial cells, stemlike cells, neural precursor cells, microglia, reactive extracellular components, and peripheral immune cells [147].

The biomarker in glioblastoma is miR-21 that is upregulated in this cancer (**Figure 13**). It mediates its effect in two ways: acting at the translational level and acting at the transcription level. It binds the 3′UTR region of the target gene (for apoptosis) [148] and causes the inhibition of transcription of apoptotic genes by decreasing the stability. It also resists the caspases 3 and 7 that are important apoptotic agents so apoptosis does not occur [149].

Upregulation of miR-221 and miR-222 was in glioma cells. These two miRNAs present as a cluster on Xp11.3 and have the same target. Functional studies revealed that there is an association of these two miRNAs with the progression of the cell cycle. Their direct target is cyclin-dependent kinase 1B/p27. The overexpression of these miRNAs cause the activation of quiescent glioblastoma cells and the progression of these cells from G1 phase to S phase of the cell cycle. miR-221/miR-222 also targets the p57 and p27 (inhibitors of cell-dependent kinase) to prevent the quiescence at G1 phase and cause their entry to S phase of the cell cycle. The miR-221/miR-222 also targets the PUMA, a proapoptotic protein, to prevent the apoptosis (**Table 18**) [150].

Another biomarker miR-128 is found to be downregulated in glioblastoma. The expression of miR-128 causes the regulation of proliferation of glioblastoma multiform (GBM) cells via targeting the PDGFR-α and EGFR, the oncogenic kinases

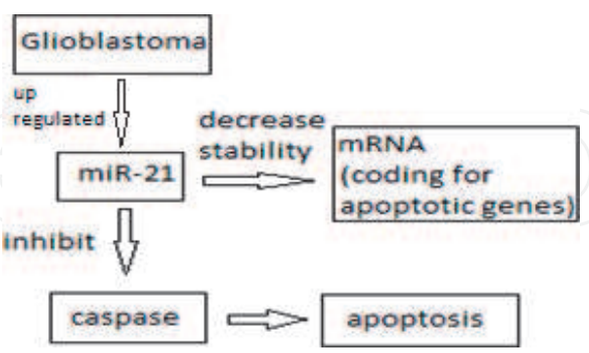


Figure 13.
miRNA and glioblastoma.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-21	Caspases 3 and 7	Antiapoptotic	[149]
2	miR-221/miR-222	Cyclin-dependent kinase 1B/p27	Prevent the apoptosis	[150]

Table 18.
MicroRNAs activating the glioblastoma.

(receptor tyrosine kinases) (**Table 19**). It suppresses the GBM by enhancing the differentiation of neuronal cells. It also targets the signaling molecules in the PI3-kinase/AKT pathway which causes the tumor cell proliferation [147].

In other study miR-7 is downregulated in glioblastoma. Its target is EGFR and causes the inhibition of AKT pathways and EGFR and results in the reduction of cell viability of GBM via direct binding to mRNA of EGFR or via targeting to IRS1 and IRS2 (insulin receptor substrate). The major regulators EGFR and IRS are at upstream site of AKT pathway [151].

5.10 B cell chronic lymphocytic leukemia

This is the cancer of B lymphocytes (antibodies), and it is a prevalent form of leukemia in the adult around western countries [152].

In B cell leukemia, the expression of three microRNAs is seen as cancer biomarker. These are miR-15a, miR-16-1, and miR-19a (**Figure 14**). Two microRNAs are present at 13q14.3 chromosomal location; these are miR-15a and 16-1 [153]. The expression of these two is decreased in this leukemia, whereas the expression of miR-19a is increased [152]. The region encoding for miR-15a and miR-16-1 was deleted. This leads to the presence of the genes of IgV_H that were mutated [154]. The potent target of miR-19a is PTEN, and there is down-expression of this PTEN gene; hence its protein is not properly synthesized because the promoter of the gene is hypermethylated [155].

The miR-16-1 and miR-15a (located on chromosome 13) are downregulated in B cell lymphocytic leukemia (**Table 20**). These miroRNAs target the p53 gene which

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-128	PDGFR-α and EGFR	Enhancing the differentiation of neuronal cells	[147]
2	miR-7	EGFR	Reduction of cell viability	[151]

Table 19.
MicroRNAs suppressing the glioblastoma.

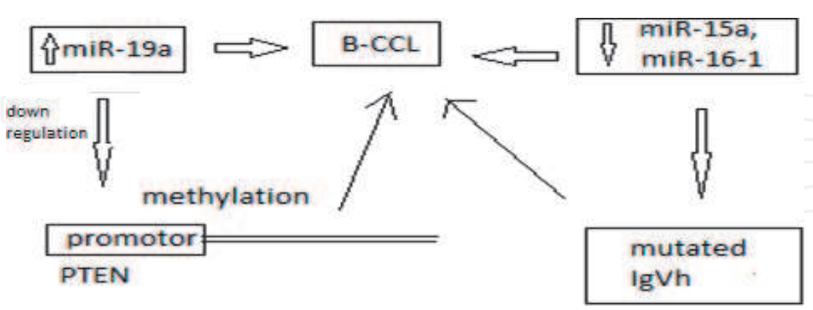


Figure 14.
miRNA and B cell lymphocytic leukemia.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-15a	p53	Prevent the apoptosis and cell survival is increased	[153]
2	miR-16-1	p53	Prevent the apoptosis and cell survival is increased	[156]

Table 20.
MicroRNAs suppressing the B cell lymphocytic leukemia.

is a tumor suppressor gene. When these miRNAs are downregulated, then the expression of p53 is reduced or inhibited, and expression of BCL-2 is increased which prevent the apoptosis and cell survival is increased [156].

In one study, miR-17/miR-92 cluster is overexpressed in the B cell lymphocytic leukemia (**Table 21**). The direct target of this cluster is PTEN and Bim. The PTEN is a tumor suppressor gene, and Bim is proapoptotic protein. Overexpression of this cluster causes prevention of apoptosis and progression of tumor [157].

In other study, miR-155 is overexpressed in the B cell lymphocytic leukemia [159]. The potential target for miR-155 is SHIP1. Expression of miR-155 causes the alteration of BCR response in signaling pathway via the modulation of SHIP1 expression in chronic lymphocytic leukemia. Scr homology-2 domain comprising the inositol 5-phosphatase is encoded by SHIP1. This phosphatase causes the inhibition of BCR signaling and surface immunoglobulin [158].

5.11 Pancreatic cancer

Pancreatic tumor is most of the time identified at the last stages when therapy does not save life. Li et al. characterize the pancreatic cancer stem cells (PCSCs) for the very first time [160].

In one study, there is overexpression of miR-1290 in pancreatic cancer. The direct target of miR-1290 is FoxA1 which has an effect on the transition of epithelial mesenchyma. The overexpression of miR-1290 results in the growth of cell and invasion [94].

In another study there is overexpression of miR-194 in pancreatic cancer. The target of miR-194 is DACH1 and results in the formation of the colony, the proliferation of cell, and migration (**Table 22**), so miR-194 causes the progression of the tumor [161].

The growth and differentiation of the cell are regulated by LIN28, a protein that binds to the RNA [162]. The protein that is encoded by LIN28 is 25 kDa and has two binding sites for RNA: cold shock domain (CSD) and a pair of zinc fingers. In pancreatic cancer, the expression of LIN28 is increased which in turn suppresses the biosynthesis of family let-7 of microRNA (**Figure 15**). This family targets the genes involved in the growth and differentiation regulation [163]. This LIN28 causes the inhibition by binging to the loop present at the terminal region of let-7 family, so

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-19a	PTEN	Cause the tumor	[155]
2	miR-17/miR-92	PTEN and Bim	Prevention of apoptosis and progression of tumor	[157]
3	miR-155	SHIP1	Inhibition of BCR signaling and surface immunoglobulin	[158]

Table 21.
MicroRNAs activating the B cell lymphocytic leukemia.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-1290	FoxA1	Cell growth and invasion	[94]
2	miR-194	DACH1	Progression of tumor	[161]

Table 22.
MicroRNAs activating the pancreatic cancer.

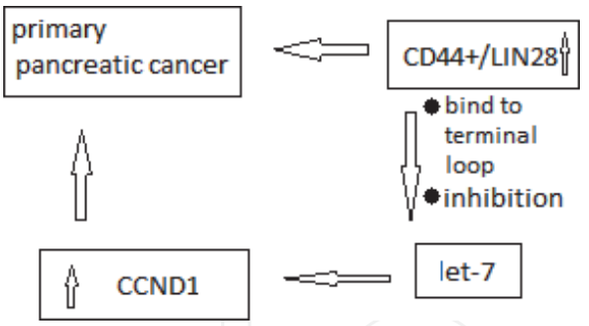


Figure 15.
miRNA and pancreatic cancer.

their processing is blocked [45, 46, 164]. This family is involved in the regulation of tumor by cyclin D1 (CCND1) inhibition [165, 166].

In one study there is downregulation of miR-145 in pancreatic cancer. The decreased expression of miR-145 is due to activation of the K-ras gene. Expression of miR-145 causes the inhibition of expression of insulin growth factor-1 receptors (**Table 23**). Its expression causes the downregulation of genes related to cancer (SET, MCM2, SPTBN1). These genes cause growth and carcinogenesis of pancreatic cancer [161].

5.12 Acute myeloid leukemia

In the myeloid leukemia, malignant blast cells are synthesized in comparison to mononuclear cells of healthy bone marrow [167]. In myeloid leukemia the hypermethylation of the DNA is involved in tumor suppression [168]. In one study, there is overexpression of miR-204 in acute myeloid leukemia. The target of miR-204 is MEIS1 and HOXA 10 genes which disturbs the differentiation of myeloid cells. Its overexpression causes tumorigenesis [169].

In another study, miR-125b (located on chromosome 1) is overexpressed in acute myeloid leukemia. The target of miR-125b is BCL2-antagonist/killer 1 (Bak1) which enhance the proliferation of AML cell and prevent the apoptosis [169].

In another study, miR-155 (located on chromosome 21) is overexpressed in the acute myeloid leukemia. This miR-155 is located in B cell integration cluster (BIC) gene. This BIC correlated to MYC to initiate lymphomas. Overexpression of miR-155 causes the inhibition of WEE1, a regulator of the cell cycle, and hMLH1, hMLH6, and hMLH4, the genes for mismatch repair (**Table 24**). The result of this inhibition is increased in mutation rate in progenitor and hematopoietic stem cells [169].

The known biomarker for the acute myeloid leukemia is miR-29b [167]. miR-29b causes the hypomethylation of the DNA. Sp1 transcriptional factor has the binding site for both miR-29b and DNMT1. In DNMT, it binds to its promoter and 3′UTR for miR-29b of Sp1 (specificity protein 1). Binding to the 3′UTR causes the reduced expression of Sp1, so DNMT (DNA methyltransferase) expression is also

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	let-7 family	cyclin D1 (CCND1)	Regulation of tumor	[166]
2	miR-145	K-ras	Growth and carcinogenesis	[161]

Table 23.
MicroRNAs suppressing the pancreatic cancer.

Sr. no.	MicroRNAs	Potential targets	Function
1	miR-204	MEIS1 and HOXA	Tumorigenesis
2	miR-125b	Bak1	Enhance proliferation and prevent apoptosis
3	miR-155	WEE1, hMLH1, hMLH6, and hMLH4	Increase mutation rate in progenitor and hematopoietic stem cells

Table 24.
MicroRNAs activating the acute myeloid leukemia [169].

reduced (**Figure 16**). In acute myeloid leukemia, miR-29b results in the apoptosis when it directly targets the MCL (induced myeloid leukemia cell differentiation protein) [170]. So the expression of miR-29b is reduced in acute myeloid leukemia which leads to cancer progression as apoptosis has been decreased with reduced expression of miR-29b (**Table 25**).

5.13 Ovarian cancer

In ovarian cancer, the biomarker that is used is miR-214 and it is upregulated in cancer. It binds to the 3′UTR region of phosphatase and tensin analog (PTEN) gene and causes its hypermethylation. So this is inactivated. The direct target of PTEN is Akt protein kinase B and mediates its activation by the help of PI4K3B [171]. Akt causes the downstream effects such as activation of glycogen synthase. So when PTEN is inhibited, it activates the expression of Akt. This miR-214 resists the cisplatin-mediated cell death, so it is antiapoptotic in nature (**Figure 17**). Cisplatin is an important factor in mediating cell death [172].

In a study, there is overexpression of Hsa-miR-182 in ovarian cancer. The potential target of Hsa-miR-182 is forkhead box 3 (FOXO3) and forkhead box 1 (FOXO1) which promote the differentiation and inhibition of growth (acting as a tumor suppressor). These tumor suppressor genes are suppressed, and growth and proliferation of ovarian cell are increased (**Table 26**) [173].

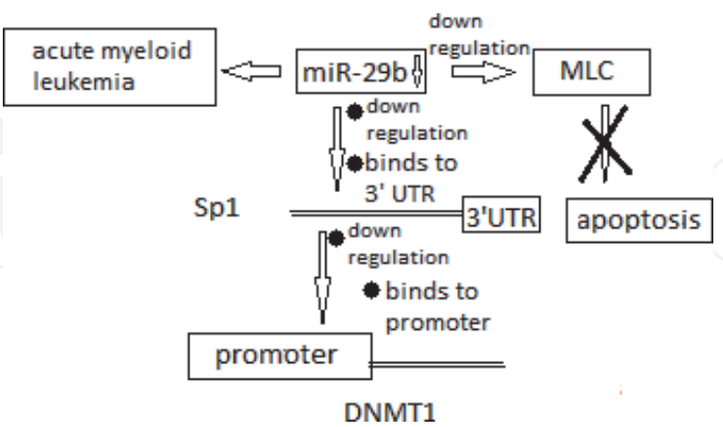


Figure 16.
miRNA and acute myeloid leukemia.

Sr. no.	MicroRNAs	Potential targets	Function
1	miR-29b	DNMT	Apoptosis
2	miR-29b	MCL protein	Apoptosis

Table 25.
MicroRNAs suppressing the acute myeloid leukemia [170].

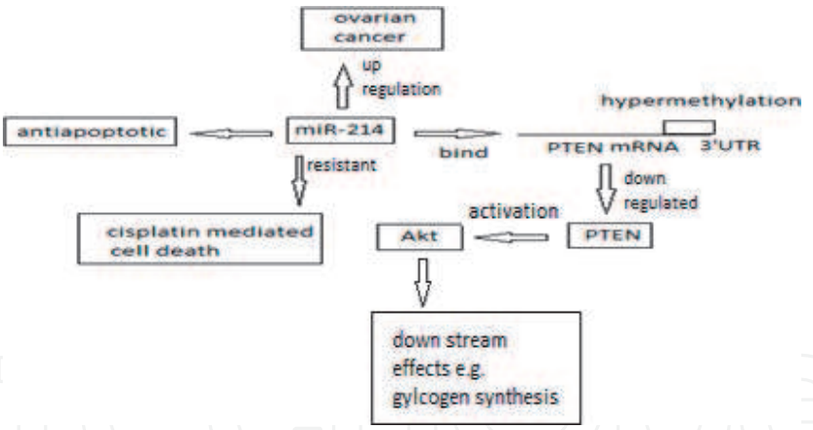


Figure 17.
miRNA and ovarian cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-214	PTEN	Antiapoptosis	[172]
2	Hsa-miR-182	FOXO3 and FOXO1	Increased proliferation and growth	[173]

Table 26.
MicroRNAs activating the ovarian cancer.

Sr. no.	MicroRNAs	Potential targets	Function	Ref.
1	miR-200	ZEB1 and ZEB2	Prevent the EMT, metastasis, invasion, and migration	[174]
2	miR-506	SNAI2, CDK4/ CDK6-FOXM1 axis	Inhibition of cell invasion and migration and proliferation; initiates the senescence	[175]

Table 27.
MicroRNAs suppressing the ovarian cancer.

In another study, there is downregulation of miR-200 family in ovarian cancer. The direct target of miR-200 is zinc finger E-box-binding homeobox 1 and 2 (ZEB1 and ZEB2). It prevents the EMT, metastasis, invasion, and migration of tumor cell. Interleukin-8 and CXCL1 (released from tumor epithelial cells) are also the target of miR-200 and prevent the angiogenesis of tumor cell [174].

In another study there is downregulation of miR-506 in ovarian cancer, so there is cell migration invasion of the cancer cell. When this miRNA is overexpressed, it causes the expression of E-cadherin and results in inhibition of cell invasion and migration and proliferation of ovarian cancer and, via targeting SNAI2 (E-cadherin transcriptional factor), prevents the EMT induction by *TGF-β* (**Table 27**). The miR-506 directly targets the CDK4/CDK6-FOXM1 axis and initiates the senescence [175].

6. Conclusion

MicroRNAs (miRNAs) could be used as potential tool for early detection of cancer. It may upregulate or downregulate multiple targets through various mechanisms. It is upregulated as an oncogene (miRNA) and downregulated as a tumor suppressor. microRNA targets the PTEN, interferon (tumor suppressor genes), and

also to the cell cycle along with the regulation of these genes [172]. MicroRNA is of vital importance because of its resistance to degradation and could be a potential candidate for clinical applications. However, its expression level can be screened in the serum/plasma (blood) by high-throughput sequencing technology. Further research for identification of novel microRNA will warrant the development of microRNA-related cancer prognosis [176–180].

Abbreviations

miRISC	microRNA-associated RNA-induced silencing complex
DGCR8	DiGeorge syndrome chromosomal [or critical] region 8
EGFR	epidermal growth factor receptor
FOXO1	forkhead box protein O1
PTEN	phosphatase and tensin homolog
TPM1	tropomyosin alpha-1 chain
SOX4	SRY-related HMG-box
CCND1	cyclin-D1
DNMT	DNA methyltransferase
MCL	induced myeloid leukemia cell differentiation protein Mcl-1
PKB	Akt (protein kinase B)

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