Review Article on Tumor Immune Microenvironment in Cancer Progression and Cancer Therapy

MicroRNAs: potential biomarkers for diagnosis and prognosis of different cancers

Prakash Chand Sharma, Alisha Gupta

University School of Biotechnology, Guru Gobind Singh Indraprastha University, New Delhi, India

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Correspondence to: University School of Biotechnology, Guru Gobind Singh Indraprastha University, Dwarka Sector-16C, New Delhi 110078, India. Email: prof.pcsharma@gmail.com.

Abstract: A thorough understanding of the tumor environment and underlying genetic factors helps in the better formulation of cancer management strategies. Availability of efficient diagnostic and prognostic biomarkers facilitates early detection and progression of the disease. MicroRNAs affect different biological processes participating in tumorigenesis through regulation of their target genes. An expanding list of unique RNAs and understanding of their regulatory role has opened up a new field in cancer research. Based on a comprehensive literature search, we identified 728 miRNAs dysregulated in sixteen cancer types namely bladder cancer (BC), breast cancer (BrC), cervical cancer (CC), colorectal cancer (CRC), esophageal cancer (EC), endometrial cancer (EnC), gastric cancer (GC), hepatocellular cancer (HCC), head and neck squamous cell cancer (HNSCC), lung cancer (LC), ovarian cancer (OC), pancreatic cancer (PC), prostate cancer (PrC), renal cell cancer (RCC), skin cancer (SC), and thyroid cancer (TC). Expression of 43 miRNAs was either upregulated or downregulated in six or more of these cancers. Finally, seven miRNAs namely mir-18a, mir-21, mir-143/145, mir-210, mir-218, mir-221, showing maximum dysregulation, either up- or down-regulation in the majority of cancers, were selected for a detailed presentation of their expression and evaluation of their potential as biomarkers in the diagnosis and prognosis of different cancers.

Keywords: miRNAs; dysregulation; biomarkers; tumorigenesis; cancer therapy

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Introduction

Cancer is a generic term assigned to a group of diseases, which affect different parts of the body. In the majority of cancers, normal cells are transformed into cancer cells involving a multistage process, ultimately turning a pre-cancerous tissue into a malignant tumor. These changes involve interaction of genetic factors present in an individual with external agents, including physical and chemical carcinogens, and biological infections. Ageing, consumption of tobacco and other food carcinogens also constitute major risk factors for the development of cancer.

Cancer is the second leading cause of human death globally with an estimated 9.6 million deaths in 2018. Worldwide, about one in six deaths is due to cancer. On the basis of number of incidences, the common cancers include lung, breast, colorectal, prostate, skin and stomach cancer. On the other hand, the majority of cancer deaths occur due to lung, colorectal, stomach, liver, and breast cancer. An increase in the span of life expectancy and deterioration of the global ecosystem has contributed substantially towards a spurt in the cancer incidences in recent times. The number of cancer cases is expected to reach 23.6 million by 2030 (1).

About one third of cancer incidences can be prevented by implementing prevention strategies such as avoidance of risk factors, vaccination against infectious agents, and

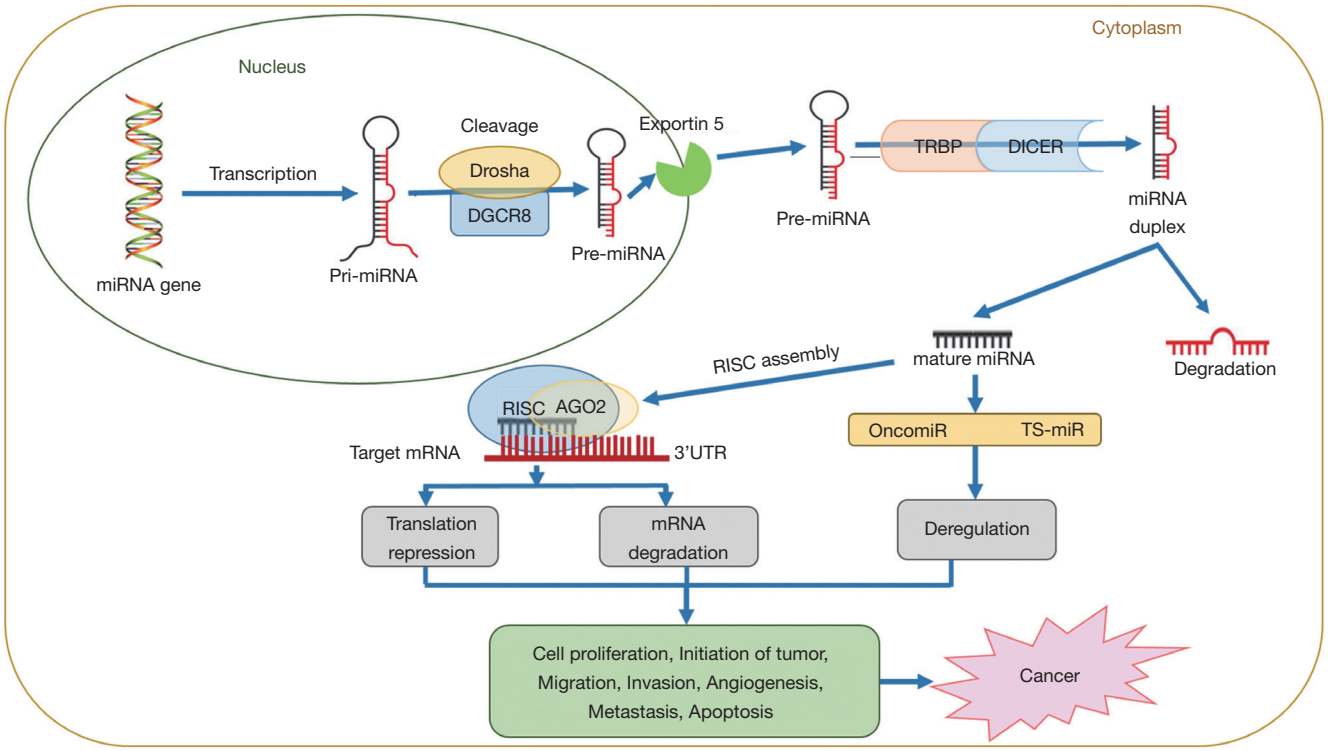

Figure 1 Biogenesis of microRNAs and their implication in the occurrence of cancer.

reduction of exposure to environmental carcinogens such as pollutants and radiations. Moreover, cancer burden can also be reduced through early detection of cancer and effective management of cancer patients. When diagnosed early, cancer is more likely to respond better to treatment allowing greater probability of survival, less morbidity, and reduction in the cost of treatment. Moreover, a correct diagnosis helps in the effective cancer treatment since every cancer type requires a specific treatment regimen. Furthermore, resistance to chemo- and radio-therapy has recently become another major concern in cancer treatment. Therefore, a comprehensive understanding of the tumor environment and underlying genetic factors is required to facilitate personalized treatment of cancer ensuring prolonged and better quality of life (2).

MicroRNAs, abbreviated as miRNAs or miRs, are small non-coding RNAs approximately 19–25 nucleotide in length. miRNAs post-transcriptionally regulate the expression of various target genes by binding to their 3'-UTR affecting a variety of downstream biological processes such as cell cycle, differentiation, proliferation, apoptosis, stem cell maintenance, stress tolerance, energy metabolism, tumorigenesis and immune response (3). Approximately, 2,000 miRNA sequences account for about three percent of human genome (4). The mechanisms of miRNA dysregulation mainly include amplification or deletion of miRNA genes, epigenetic regulations, dysregulation of transcription factors, and key genes/proteins participating in miRNA biogenesis and processing (5). An overview of the process of miRNA biogenesis, maturation and the mechanism of regulation of their target gene expression leading to cancer is shown in *Figure 1* and described elsewhere (6).

miRNAs regulate nearly 30% of human genes, particularly tumor associated genes, through different mechanisms (7,8). The dysregulation of miRNAs in tumor cells suggests their modulatory effects on target genes expressed in the tumor environment (9). In fact, some miRNAs are tumorigenic (oncomirs), and others are tumor suppressors (TS-miRs). In general, a rise in the expression of an oncomir will lead to a decrease in the target tumor suppressor, whereas a reduction in the expression of a TS-miR will trigger a rise in the target oncogene. Interestingly, some miRNAs can act both as oncomir and TS-mir, depending on the time and tissue specific expression (3,5,10,11). A large number of studies have indicated

that many of the target genes regulated by miRNAs mediate response of tumor cells to chemotherapy (12). Experimental tools like next-generation sequencing (NGS) and microarrays coupled with computational methods have facilitated rapid, precise, reproducible and deeper analysis of miRNAs engaged in the oncogenic processes. The importance of miRNA research has also been emphasized considering the indication that more than 90% of cancer deaths are associated with chemotherapy drug resistance, and miRNAs play a key role in inducing such resistance (13).

Various studies on tissue specific dysregulation of miRNAs have suggested that miRNA expression levels may be considered as cancer biomarkers. Analysis of miRNA expression through invasive cancer screening, including formalin-fixed tissues and non-invasive diagnostic screening based on circulating cell-free miRNAs has been possible in different human and animal systems (14,15). Two approaches of miRNA-based treatments involve the use of miRNA mimics (miRNA substitute treatment) and miRNA antagonists. MiRNA mimics utilizes the reintroduction of tumor suppressive miRNAs into cancer cells. In contrast, when abnormal expression of the target oncomirs is of interest, chemically altered miRNA proteins (antagomirs or anti-miRs) perform important function and prevent oncomirs from binding to one of their targets (16,17).

MicroRNAs in cancer

Accumulating studies have demonstrated that abnormally expressed miRNAs play pivotal roles in the development of different types of cancers. A comprehensive literature search of miRNAs implicated in different cancer revealed 728 miRNAs dysregulated in 16 cancer types namely bladder cancer (BC), breast cancer (BrC), cervical cancer (CC), colorectal cancer (CRC), esophageal cancer (EC), endometrial cancer (EnC), gastric cancer (GC), hepatocellular cancer (HCC), head and neck squamous cell cancer (HNSCC), lung cancer (LC), ovarian cancer (OC), pancreatic cancer (PC), prostate cancer (PrC), renal cell cancer (RCC), skin cancer (SC), and thyroid cancer (TC). Many of these 728 miRNAs have been found exclusively dysregulated in only one type of cancer. However, it is highly likely that these miRNAs are dysregulated in other cancer types also, where their role is yet to be ascertained. Thus, considering dysregulation of miRNAs in different cancers, 43 miRNAs were selected that are either upregulated or downregulated in six or more of the cancers listed above. These miRNAs and their expression status in different cancers are presented in *Table 1*.

Next, out of the 43 miRNAs (*Table 1*; *Figure 2*), seven miRNAs showing maximum dysregulation, either up- or down-regulation in majority of the 16 cancer types, were selected for detailed analysis of their role in different cancers assuming that these miRNAs have potential application as a biomarker in cancer research and therapy. These seven miRNAs are listed in *Table 2* and discussed in detail in the following text.

miRNA-18a

MicroRNA-18a is a member of miR-19-72 cluster, along with six other miRNAs including miR 17-3p, miR-17-5p, miR-19a, miR-19b-1, miR-20a, and miR-92-1. This miRNA cluster is located on chromosome 13q31.3 (18). The oncogenic role of this cluster of miRNAs has been demonstrated in various reports for a variety of cancer types, for instance, LC (19). miR-18a alone has been shown upregulated in different types of cancer with fold change of 3.98: EnC (20), 3.52: HNSCC (21), 3.33: HCC (22), 2.9: BC (23), 2.9: SC (24), 2.0: CRC (25), 2.0: GC (26), 1.94: RCC (27), 1.46: TC (28), OC (29) and PC (30), and regarded as a potential biomarker in some of these cancers (27,31,32). Taqman qRT-PCR assay conducted on 147 plasma samples representing 82 GC patients and 65 healthy controls revealed significantly elevated expression level of miR-18a in GC patients compared to their corresponding healthy controls, suggesting potential diagnostic value of miR-18a in GC. Since the 5-year overall survival of GC patients with higher miR-18a levels in plasma was worse than in patients with lower miR-18a levels, expression of miRNA-18a was also considered of prognostic potential in GC. Moreover, miR-18a expression levels were also correlated significantly with lymph node metastasis status and pathological grade (27). Similar results were reported in another qRT-PCR based study on 104 GC patients and 65 healthy controls showing higher miR-18a expression in GC tissues and cell lines (31). Presence of miR-18a and other elevated miRNAs in urine has been suggested to be a potential biomarker in bladder carcinoma (32). In the case of PC patients, the aberrant expression of miRNAs has been observed in systematic circulation also, in addition to pancreatic cells and tissues, and the enhanced level of miRNA-18a in the blood of pancreatic ductal adenocarcinoma (PDAC) patients has provided

Table 1 List of 43 miRNAs differentially expressed in six or more types of cancer

S. No.	miRNA	Upregulated in cancer(s) (↑)	Downregulated in cancer(s) (↓)	Both upregulated and downregulated in cancers (↓↑)
1	miR-1	GC	BC, CC, CRC, EnC, HNSCC, PrC, RCC, TC	
2	miR-7	BC, BrC, EC, EnC, HNSCC, RCC	CC, TC	
3	miR-17-5p	BC, CRC, GC, HNSCC, RCC, TC	CC	
4	miR-18a	BC, EnC, GC, HCC, LC, OC, PC, RCC, SC, TC		CRC, HNSCC
5	miR-19a	BC, CRC, GC, HNSCC, RCC, TC		
6	miR-19b	BC, BrC, HNSCC, RCC, SC, TC		
7	miR-20a	BC, BrC, CC, CRC, GC, HNSCC, OC, RCC	PC, SC	TC
8	miR-21	BC, BrC, CC, CRC, EC, EnC, GC, HCC, HNSCC, LC, OC, PC, PrC, RCC, SC, TC		
9	miR-23b	OC	BC, CC, CRC, EnC, HNSCC, PrC,	RCC
10	miR-26a		BC, CC, HCC, HNSCC, SC, TC	
11	miR-30a		BC, CC, CRC, HNSCC, RCC, SC,	
12	miR-30a-5p		BC, GC, HNSCC, LC, RCC, TC	
13	miR-93	BC, BrC, GC, HCC, HNSCC, OC, PC, SC	CC, CRC	
14	miR-96	BC, CRC, EnC, HNSCC, OC, TC	PC	
15	miR-101		BC, CC, CRC, EnC, GC, HCC, HNSCC	
16	miR-106a	BC, CC, CRC, EnC, GC, HNSCC, RCC, TC		
17	miR-106b	BC, BrC, CC, GC, HNSCC, LC, SC, TC,	HCC, OC	RCC
18	miR-125b	CRC	BC, BrC, HCC, HNSCC, OC, RCC, SC, TC	CC, LC
19	miR-133a		BC, CC, EnC, HNSCC, OC, RCC	
20	miR-133b	CC	BC, CRC, EC, EnC, HNSCC, LC, RCC	
21	miR-135b	CRC, CC, EnC, HNSCC, OC, SC,	RCC	
22	miR-137	TC	BC, CC, CRC, EnC, LC, OC,	
23	miR-139-5p		BC, BrC, EnC, HNSCC, OC, SC	
24	miR-141	BC, CC, EnC, HNSCC, OC, TC	PC, RCC	
25	miR-143		BC, BrC, CC, CRC, EC, EnC, HNSCC, LC, OC, PC, PrC, RCC, TC	SC
26	miR-144	HNSCC	BC, CC, CRC, EC, PrC, TC,	
27	miR-145		BC, BrC, CC, CRC, EC, EnC, HNSCC, LC OC, PC, PrC, RCC, TC	SC
28	miR-155	BrC, CC, CRC, HNSCC, PC, RCC, TC	BC	
29	miR-182	BC, CRC, EnC, HNSCC, OC, PrC, SC, TC,		CC
30	miR-183	BC, BrC, EnC, HNSCC, RCC, TC	CC	
31	miR-195	OC	BC, BrC, CC, CRC, EnC, HCC	HNSCC

Table 1 (*continued*)

Table 1 (*continued*)

S. No.	miRNA	Upregulated in cancer(s) (↑)	Downregulated in cancer(s) (↓)	Both upregulated and downregulated in cancers (↓↑)
32	miR-200a	BC, CC, EC, EnC, HNSCC, OC, PC, TC,	HCC, RCC	
33	miR-200b	BC, EC, EnC, LC, OC, PC	RCC	CC, TC
34	miR-204		BC, BrC, CC, HNSCC, RCC, SC	
35	miR-210	BC, BrC, CC, CRC, EnC, GC, HCC, HNSCC, LC, PC, RCC, SC	EC, OC	TC
36	miR-214	CRC, GC, TC	BC, CC, EnC, HCC, HNSCC, OC, PC, SC	
37	miR-218		BC, CC, CRC, GC, HNSCC, LC, PC, PrC, RCC, TC	
38	miR-221	BrC, CC, CRC, GC, HCC, LC, OC, PC, RCC, SC	BC, PrC	HNSCC, TC
39	miR-222	CC, GC, HCC, PC, SC, TC,	BC, HNSCC	
40	miR-224	BC, CC, CRC, EnC, HCC, HNSCC, RCC, TC		
41	miR-375	TC	CC, CRC, EC, GC, HNSCC, PC, RCC	BC
42	miR-497	SC	BC, BrC, CC, EnC, HNSCC, RCC	
43	miR-Let-7a		BrC, CC, EnC, GC, RCC, SC	

novel diagnostic value (30). The miRs in circulating exosomes have the ability to serve as novel diagnostic biomarkers (33) and the expression levels of a few exosomal miRNAs along with miR-18a was found significantly higher in hepatocellular carcinoma patients than that in corresponding normal subjects (34). In anaplastic thyroid carcinoma, an undifferentiated type of TC, all the seven miRNAs of the miR-17-92 cluster were found upregulated as compared to those in normal thyroid tissues. Inhibition of these miRNAs in order to check their role in tumorigenesis led to the activation of caspase 3 and 9, and as a result, cell growth was suppressed and apoptosis was induced. These observations suggest a crucial role of miR-17-92 cluster in thyroid tumorigenesis (28). In colorectal carcinoma, miR-18a is reported as a downregulated tumor-suppressive miRNA that specifically targets the oncogene, *KRAS*, suppressing the proliferation and growth in colon adenocarcinoma HT-29 cells, suggesting miR-18a to be a potential therapeutic target for cancer therapy (35). Exosomal tumor suppressor miR-18a was over-expressed in CRC patients with metastasis as compared to those without metastasis. miR-18a has a crucial role in HCC cell migration and invasion by inhibiting Dicer I expression (36), in promoting liver cancer by targeting a tumor suppressor gene, *TSC-1* (37), and in cell proliferation by targeting *IRF2* and *CBX7* genes (38). Another group of researchers found miR-18a along with members of other miR-17-92 cluster upregulated in BC (39). Microarray based miRNA profile analysis showed differentially expressed miRNAs in samples representing endometrial serous adenocarcinoma (ESC). A total of 120 miRNAs were found to be dysregulated with at least 2-fold expression change (66 upregulated, 54 downregulated). miR-18a was upregulated with a fold change of 3.98 in ESC (20). Upregulation of miR-18 in SC tissues was observed in the biopsies of seven patients with basal cell carcinoma of the skin (40). Apart from these studies, miR-18a was observed upregulated in renal cell carcinoma (26) and high-grade serous ovarian cancer (HG-SOC) (29) also. In HNSCC, miR-18a was upregulated in case of hypopharyngeal SCC (21) and oral cavity larynx cancer (41), and downregulated in case of oropharyngeal cancer with fold change of 0.52 (42), where miRNA expression was significantly associated with HPV status.

miRNA-21

miR-21, a very important miRNA located on chromosome 17q23.2 (43), is the most consistently over expressed

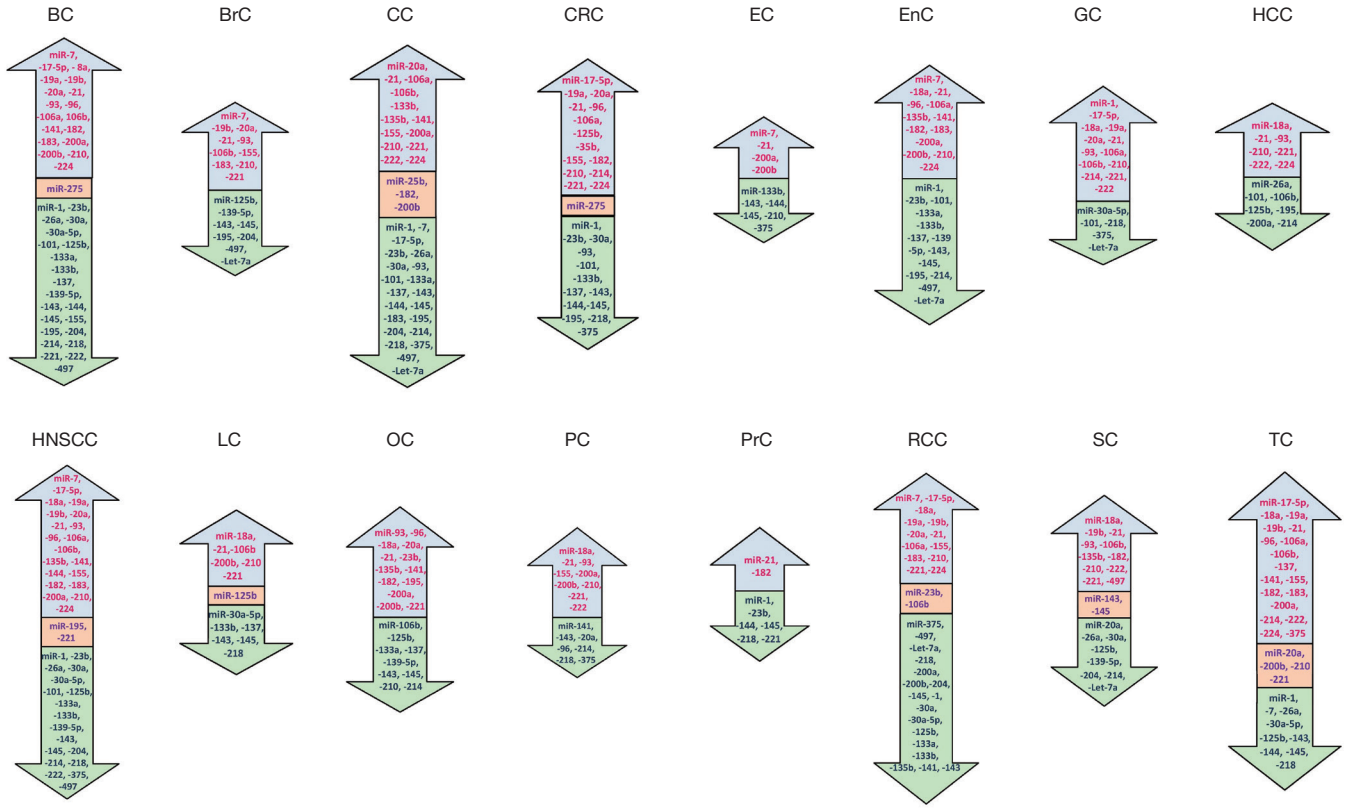

Figure 2 Differential expression of microRNAs in different cancers. The upwardly pointed arrows represent upregulated microRNAs (red font), whereas downwardly pointed arrows represent downregulated microRNAs (blue font). microRNAs showing both up- and down-regulated expression are presented in the middle blocks.

Table 2 Potential miRNA biomarkers showing dysregulation in the majority of cancers

S. No.	miRNA	Cancer(s) ↑ (upregulated) or ↓ (downregulated) or ↑↓ (both)
1	miR-18a	(BC, EnC, GC, HCC, LC, OC, PC, RCC, SC, TC) ↑, (CRC, HNSCC) ↑↓
2	miR-21	(BC, BrC, CC, CRC, EC, EnC, GC, HCC, HNSCC, LC, OC, PC, PrC, RCC, SC, TC) ↑
3	miR-143	(BC, BrC, CC, CRC, EC, EnC, HNSCC, LC, OC, PC, PrC, RCC, TC) ↓, (SC) ↑↓
4	miR-145	(BC, BrC, CC, CRC, EC, EnC, HNSCC, LC, OC, PC, PrC, RCC, TC) ↓, (SC) ↑↓
5	miR-210	(BC, BrC, CC, CRC, EnC, GC, HCC, HNSCC, LC, PC, RCC, SC) ↑, (EC, OC) ↓ (TC) ↑↓
6	miR-218	(BC, CC, CRC, GC, HNSCC, LC, PC, PrC, RCC, TC) ↓
7	miR-221	(BrC, CC, CRC, GC, HCC, LC, OC, PC, RCC, SC) ↑, (BC, PrC) ↓, (HNSCC, TC) ↑↓

oncomir in the maximum number of cancer studies. Elevated expression level of miR-21 has been reported in all the 16 cancers. The list of the different cancers with decreasing order of fold change in mir-21 expression include PrC: 9.77 (44), CC: 9.6 (45), SC: 8.6 (46), HNSCC: 7.77 (47), PC: 5.63 (48), HCC: 5.57 (49), CRC: 5.3 (50), BC: 4.7 (44), TC: 4.3 (51), LC: 3.17 (52), EnC: 2.985 (53), OC: 2.88 (54), EC: 2.68 (55), RCC: 2.5 (26), GC: 2.19 (56), and BrC: 1.55 (57). Presence of miR-21 in the serum exosomes of serous adenocarcinoma of ovary (58) and in the urine samples of BC patients (59,60), supports its potential as biomarker for OC and BC, respectively. miR-21 expression

was directly linked to disease-free as well as overall survival rate, advanced clinico-pathological features, stage and grade and poor prognosis in RCC patients, and could significantly differentiate among oncocytoma, ccRCC, pRCC and chRCC affirming the possibility of its use as diagnostic biomarker in renal cell carcinoma (61). Other workers have further suggested the ratio of miR-21 expression to either miR-216 expression (62) or miR-10b expression (63) as prognostic biomarker for RCC progression. A correlation of miR-21 expression level with higher tumor-grade and poor overall survival rate has been observed in melanoma patients (64). Wang *et al.* [2009] demonstrated that aberrant miR-21 and other plasma miRNAs in PDAC patients could distinguish them from their corresponding healthy patients (65). Prognostic and diagnostic value of serum exosomal miR-21 expression has been established in children with hepatoblastoma (66). Furthermore, miR-21 elevated level was found associated with clinic-pathological features, poor survival, and poorer 5-year survival rate in various HNSCC subtypes (67-70). Similarly, an unfavorable poor survival rate was predicted for BrC patients (71). In GC, miR-21 has been confirmed as a diagnostic biomarker for early GC-detection as well as for high risk of GC post *H. pylori* eradication (72-75), and as a prognostic biomarker associated with poor prognosis, tumor size, TNM and progression stage and lymph node metastasis also (76-79). All these observations have been obtained from qRT-PCR, and microarray based experiments performed on serum/plasma samples of GC patients. Moreover, miR-21 present in gastric juice of the subjects was considered valuable for differentiating between benign gastric disease and GC (80). miR-21 level was upregulated in hormone resistant prostate cancer (HRPC) patients as compared to that in patients with localized PrC and androgen dependent PrC resulting into docetaxel resistant chemotherapy. Further, miR-21 serum expression level was found related to prostate specific antigen level in metastatic PrC patients. These results implicate miR-21 as a crucial biomarker for PrC patients during tumor progression (81). On the other side, Shi *et al.* [2010] using *PDCD4*-microarrays demonstrated that significantly upregulated miR-21 expression enhanced docetaxel resistance in wild-type PC3R cells, whereas inhibition of miR-21 expression through transient transfection eventuated sensitivity towards docetaxel, thereby suggesting miR-21 to be an excellent regulator of docetaxel drug resistance in PrC patients (82).

miR-21 regulates a large number of genes participating in different pathways. Some of the anti-oncogenic target genes reported include *PTEN* (53), *PDCD4* (83), *VEGFA* (84), *TGFBR2*, *RAB6 A* and *RAB6 C*, *SKI*, *RASA1*, *RHOB*, *BCL2* (85), *TIMP3* (86), *SMAD7* and *NRF2* (87), *TPM1* (88), *MMP9* (89), *FasL* (90), *TCF21*, *GRHL3* (91), *BTG2* (92), *FBXO11* (93), *IGFBP3* (94), *p85*α (95), *RECK* (96), *CLCA3P*, *SATB1*, *MALT1*, *C17*, *SLC35F5*, *SPRY1/2*, *CDC25A*, *TIAM1* (97), *hMSH2* (98), *CTNNB1*, *BRAF*, *SFRP1*, *ZFHX3* (99,100), *HIF-1a* (101), *ANXA1* (45), and *CCL20* (102). It also influences the expression of CDK-4, cyclin-D1 dependent on *NF-κB* and *IKK*β (103), and CDK-5 (104), hence, aggravating cancer cell proliferation. CDK-5 over expression was due to STAT3-miR-21 pathway, promoting EMT, while EMT reversal was observed with STAT-inhibitor (104). miR-21 sustains tumor invasion and proliferation by targeting a tumor suppressor, *PTEN*, an inhibitor of *PI3K*-Akt phosphorylation (53) and downstream activator of mTORC1 (105) by binding to the complimentary sequence in 3'-region of the PTEN-mRNA. In addition to *PTEN*, upregulated miR-21 activates mTORC via reducing *PDCD4*-rictor interaction in mTOR signaling pathway to augment Akt-phosphorylation (83), thus, increasing the potential of cancer cells to metastasize. Darido *et al.* [2011] have presented the view that mice lacking *GRHL3* gene in their keratinocytes were susceptible to chemically induced, spontaneously developed cutaneous squamous cell carcinoma (CSCC). miR-21 down modulates *GRHL3*, a gene that activates *PTEN* transcription, by directly binding to its promoter's conserved site. As a result, signaling pathway PI3K/Akt/mTOR is activated and RAS/MAPK/ERK is repressed inducing aggressive CSCC (91). VEGF is a key regulator of embryonic as well as tumor angiogenesis and is regulated by *HIF-1a* via transcriptional activation. Due to the lost inhibition of Akt and *ERK-1/2* through *PTEN*, *HIF-1a* and *VEGF* expressions are enhanced, leading to induced tumor angiogenesis (101) and inhibition of anoikis (43). Higher expression levels of miR-21 along with miR-203 and miR-205 elevated further with 5-AZA, a demethylating agent. Hence, Iorio *et al.* [2007] suggested regulation of miRNAs by methylation (106). Since elevated level of miR-21 in cancer secreted microvesicles induced myoblast apoptosis, leading to cachexia through TLR-7, Nakamura *et al.* [2016] opined that blocking the binding between TLR-7/8 and miR-21 or inhibiting the secretion of microvesicles by suppressing fusion between microvesicles and muscle cells might prove to be a potential therapeutic target for cancer induced cachexia (107). In BC, *SNAIL1* regulated by Akt/GSK/3β-pathway, is reported to promote miR-21 expression

transcriptionally (108). Additionally, the generation and upregulation of miR-21 are reported to be promoted by environmental stimuli such as UV-radiations and smoking, enforcing downregulation of its TS-targets and ultimately causing melanomagenesis (109). miR-21 contributes to the induced tumor activating environment by increasing cancer cell invasion and metastasis via involvement of CAFs (110) and its high expression level is associated to gemcitabine chemo-resistivity (111) and 5-FU chemotherapy resistance (112). According to Valeri *et al.* [2010], miR-21 down modulates the expression of tumor suppressor *hMSH2* (human DNA MutS homolog-2) consequently reducing apoptosis and G2-M damage arrest induced by 5-FU (98). Passadouro *et al.* [2014] in an effort to find the potential therapeutic cancer targets, demonstrated that co-delivery of human serum albumin-1-palmitoyl-2-oleoyl-sn-glycerol-3-ethylphosphocholine cholesterol with an anti-miR oligonucleotide efficiently suppressed the upregulation of miR-21, miR-10, and miR-221/222 in PC (113). CRC tumor derived miR-21 exosome (TEX) transfer into liver cells has been speculated to contribute to liver metastasis. A negative correlation between expression of miR-21 and one of the tumor suppressor gene, *BTG2*, was found associated with hepatocarcinogenesis (92). Genistein, an active small biological flavonoid, inhibited cancer cell migration and expansion by silencing oncomirs, including miR-21, which mediate their function through RAC1/VEGF related angiogenesis, silencing NOTCH-signaling and upregulating *RHOA*, a tumor suppressor gene (114).

miRNA-143/145 cluster

miRNA-143 and miRNA-145 are clustered together on chromosome 5q32-33 (115). The members of this cluster act as TS-miRs independent of the cancer type and often show reduced expression in a broad range of human cancers The fold changes reported for miR-143 and miR-145, respectively for different cancers are PC: 0.04, 0.002 (48,116), BC: –13.7, –15.9 (23), EnC: –8.6, –7.15 (20), CC: –8, –14.1 (117), EC: –5.87, –5.63 (55), HNSCC: 0.177, 0.167 (118), LC: 0.28, 0.3 (52,119), CrC: 0.3, 0.3 (50), PrC: –2.78, –3.45 (120), OC: –1.85, –3.38 (54), TC: 0.6, 0.7 (28), SC (BCC): 0.62, 0.75 (121), RCC: 0.714, 0.45 (122), and BrC: 0.9, 0.42 (57). However, the expression of miR-143 was found elevated in CSCC along with miR-145 (121), which was also elevated in melanoma (24). Both CSCC and melanoma are other kinds of SC. The expression levels of certain miRNAs including miR-145 have been used to predict the risk of early relapse after nephrectomy in non-metastatic RCC patients (123). Bobryshev *et al.* [2015] by analyzing the regression of cox proportional-hazard of global miRNA-expression, recognized that upregulated miR-143 is connected with overall poor survival of esophageal adenocarcinoma (EAC) patients (124). Potential diagnostic roles of miR-143 in CC (125), and miR-143 and -145 in BrC (126) have also been reported. Chung *et al.* [2013] delineated miR-145 as a potential biomarker in OC patients (127). Similarly, Iorio *et al.* [2008] showed the prognostic value of miR-145 along with tumor grade, lymph node propagation and invasion degree (128). TS-miR-145 in EAC investigated by Derouet *et al.* [2014] was found upregulated by eight folds post chemoradiotherapy, and miR-145 expression levels were associated with shorter disease-free survival (129). miR-145 accelerated anoikis resistance, a key step in cancer progression that helps tumor cell migration into bloodstream, by delaying PARP (poly-ADP-ribose polymerase) and caspase-3 cleavage. In addition, miR-145 could increase wound healing, cell invasion and cell adhesion to fibronectin, however, had no effect on cell proliferation or on response towards chemotherapy drugs including 5-FU and cisplatin. Contrarily, in ESCC cell line, miR-145 improved anoikis and repressed cell proliferation advocating for its participation in specific functions depending upon the histological subtype of EC (129). miR-143/145 expression level is substantially reduced in endometrioid than in non-endometrioid EnC cells and both these miRNAs target *DNMT3B* in endometrioid tumor cells but not in the non-endometrioid ones. Thus, downregulated miR-143/145 and overexpressed *DNMT3B* seem to be a negative prognostic factor in EnC patients. Since DNMTs play a key role in gene expression regulation and their dysregulation is related to malignancies, miR-143/145 is suspected to be associated with prognosis of endometrioid carcinomas (130). Golgi membrane protein-1 (GOLM1) is a reported target of this cluster in HNSCC (131) and PrC (132). It represses the c-MYC oncogene directly by participating in TP53 regulatory pathway, where antitumor miR-145 is regulated by tumor suppressor TP53 transcriptionally via direct interaction with its promoter (119,133). Other reported target genes of this miRNA cluster include *HK2* (134), *FSCN1* (131), *GEF1*, *GEF2*, *MMP-1* and *MMP-2* (135), *BRAF* (136), *KRAS* (135,136), *NEDD9*, *ANGPT2*, *ADAM17* (137), *ERK5* (138), *Akt*, *IGF1R* (139), *PAI-1* (140), *PAK1* (141), *OCT4* (142), *DNMT3B* (130), *SWAP70* (143), *ZEB2* (144),

HIF-1α (145), *Bcl-2* (146), *SIP1* (147), *CTNNB1*, *TCF4*, *VIM*, *SNAIL1*, and *CDH1* (148). In PC cells, miR-143/145, oncogenic KRAS-G12D and RREB proteins are reported to work in synchronization via feedback regulation, where downregulation of miR-143/145 is mediated by mutated KRAS-G12D through RAS-responsive element binding protein (116). miR-145 targeting *ADAM17*, *ANGPT2*, and *NEDD9* genes, is one of the cell matrix related micro-RNAs involved in RCC progression and metastasis. These genes are involved in the HIF-2α/VEGF/MMP9/CCND1/ARE signaling pathways. Zhou *et al.* [2015] reported that miR-143 functions as a tumor suppressor by regulating the expression of HK-II, a glycolytic enzyme phosphorylating glucose to glucose-6-phosphate in glycolysis, and its downregulation by 62.5% in PrC tissues influenced the cell apoptosis, cell viability and cell cycle arrest at G1/S phase transition (134). Downregulation of miR-143/145 aggravates tumor cell invasion and metastasis by suppressing E-cadherin and promoting EMT-phenotype. miR-145 and ZEB2 are in negative feedback loop, where miR-145 represses ZEB2 as an EMT stimulator and ZEB2 directly down modulates miR-145 expression (144). Wild-type p53 mediated over expression of miR-145 was observed to knockdown *FSCN1* and *SWAP70* genes suppressing tumor cell migration and invasion in PrC (149). The results of a study by Zhao *et al.* [2017] suspect that miR-143 modulates the HeLa cells proliferation and apoptosis via targeting HIF-1α (145). Pagliuca *et al.* [2013] observed that miR-143 and -145 are amongst the most important TS-miRNAs involved in EGFR-pathway and their combined action of targeting several EGFR-pathway members such as *KRAS* and *BRAF* reduces cell proliferation and migration (136). An inverse correlation between lost function of miR-145 and the over expression of various EMT genes including *CTNNB1*, *VIM* and *SNAI*, and the down regulation of *CDH1* expression was also seen in SW480 cell-line (148). All these studies are based on qRT-PCR and microarray experiments. Skinner *et al.* [2014] created a MEP (miRNA expression profile) score by combining four miRNAs (mir-145, mir-451, mir-99b and mir-505) that provided a robust platform for identifying patients for whom chemoradiotherapy/surgery/alternative therapies would be appropriate for treatment (150). In PC cells, adenovirus-mediated transduction of miR-143/145 (116) and miR-143 (135) inhibited tumorous growth by blocking metastasis. Significant shift in the miR-145 expression was observed in caki-1 renal cancer cells under the impact of sunitinib and everolimus (151). miR-143/145 is also considered as one of the HPV-positive cancer related microRNAs (152). Down modulation of OCT4, a protein participating in the self-renewal of embryonic stem cells, by miR-145 induces differentiation in endometrial endothelium. Since the expression levels of miR-145 and OCT4 in EAC cells are negatively associated with tumor grade, Wu *et al.* [2011] suggested that miR-145 might serve as a useful therapeutic target and an EAC grading tool (142). Xu *et al.* [2011] opined that *in vitro* upregulation of miR-143 suppressed PrC cell migration and miR-143 treated PrC cells showed promoted sensitivity to chemotherapy using docetaxel, suggesting a beneficial role of miR-143 in chemotherapy (153).

miRNA-210

miRNA-210, an oncogenic microRNA located on chromosome 11p15.5 (154), is a hypoxia-regulated miRNA (155) having significant role in different cellular processes such as DNA repair, cell proliferation, angiogenesis in endothelial cells (156), mitochondrial-respiration, and vascular biology. miR-210 has been reported to be upregulated with variable fold change in twelve cancer types including BC: 19.6 (23), TC (follicular type): 9.6 (157), SC: 9.0 (158), HCC: 7.6 (159), CC: 7.3 (117), RCC: 4.3 (26), EnC: 3.17 (20), PC: 2.78 (48), GC: 2.39 (160), LC: 2.32 (161), HNSCC: 2.21 (162), and BrC: 1.43 (57). Interestingly, it has been reported downregulated also in OC (163), TC (anaplastic type) (28) and EC (164). miR-210, along with other three miRs, which are highly overexpressed in the serum and cancer tissues of the mouse model of DGC (diffuse-type GC) compared to the controls, have been exploited as diagnostic biomarkers for early DGC detection (165). In BrC, miR-210 is considered as an independent overall survival predictor (166), and a diagnostic and prognostic biomarker (167) since its high expression level is associated with poor survival rate (71). Hypoxia reduces the miR-210 expression in melanoma cells, allowing an escape from cell lysis by antigen-specific cytotoxic T-lymphocytes (168). Since the level of miR-210 was higher in metastatic melanoma than in primary melanoma, it was considered a good indicator of early melanoma recurrence (158). Wang *et al.* [2009] reported that the aberrant expression of miR-210, along with three other miRs in the plasma, can distinguish PDAC patients from healthy controls (65). Greither *et al.* [2010] conducted a study on 56 PDAC patients and determined a correlation between elevated levels of four miRNAs including miR-210, and an increased mortality by 6.2 folds compared to that in patients with low

level of these miRNAs (156). The potential role of miR-210 as biomarker for early tumor diagnosis has been highlighted by analyzing healthy subjects and cancer patients pre- and post-nephrectomy (169), and the diagnostic value has also been validated (170). Since VGF-HIF has a key role in RCC, miR-210 upregulation can be a major factor in the oncogenesis of RCC. Furthermore, high levels of miR-210 in serum can be exploited as a diagnostic biomarker for PC (171) and clear cell RCC (172). Serum exosomal miRNAs have been reported to act as biomarkers for hepatocellular carcinoma (112), and higher miR-210 level in the serum correlates with high microvessel density in HCC tissues (159). Moreover, salivary miRNA-210 expression discriminates HPV-positive HNSCC from HPV-negative HNSCC (173). Hess *et al*. [2018] divided the patients into high- and low-risk groups based on the expression of miRNA-210 and four other miRNAs such that the high-risk group had a 70% chance of recurrence of HNSCC, whereas the low-risk group had a chance of 30% only. These miRNAs were suggested to have future potential in framing guidelines for selecting chemotherapy, radiotherapy and (or) surgery of cancers with different aggressiveness (174). miR-210 targets genes such as *ISCU* and *COX10* (137), *FGFRL1*, *RAD52*, *BDNF*, *PTPN1*, *NCAM1*, and the lncRNA XIST (175), and is involved in cell proliferation, migration, and invasion.

miR-210 stimulates angiogenesis by targeting two negative regulators of VEGF i.e., receptor tyrosine kinase ligand ephrin A3 and phospho-tyrosine phosphatase 1B (176). In CRC, its upregulation is well correlated with poor prognosis and stimulates angiogenesis by promoting RBM3 (RNA binding motif) protein expression (177). Upregulated miR-210 plays a role in the development of CRC and its progression, and can be triggered by the KRAS pathway activation (178). However, miR-210 was reported downregulated in stage III/IV epithelial ovarian carcinoma (163), anaplastic thyroid carcinoma (ATC) (28), and primary EAC tissues by using quantitative RT-PCR (164).

miRNA-218

miRNA-218 represents an important tumor suppressor miR-family with members miR-218-1 and 218-2, located between chromosome region 4p15.31 and 5q34 (179). This miRNA has shown downregulated fold changes in ten cancers namely BC: 0.006 (180), PC: –10.43 (181), RCC: 0.130 (182), CC: –5.6 (45), LC: –4.4 (183), CRC: –3.6 (184), GC: –3.108 (185), HNSCC: 0.322 (21), TC: –2.3 (186), and PrC: –1.96 (187). To the best of our knowledge, the regulation in the remaining six cancers is not known yet. Considering the conspicuous role of miR-218 in tumorigenesis, it was presumed to have prognostic and diagnostic biomarker potential. Plasma samples of GC patients showed down-regulated miR-218 as a potential biomarker for the diagnosis of distance and no-distance metastasis (72). Xin *et al.* [2014] found significantly reduced expression level of miR-218 in the serum samples of GC patients associated with metastasis, tumor stage and grade, TNM stage and 3-year survival rate, suggesting it as a prognostic biomarker implicated with poor overall survival (185). miR-218 inhibits metastasis pathways and related genes, for example, metastasis promoting *LOXL2* (188), *LAMA3*, *LAMB3* and *LAMC2* in head and neck cancer (189), *RICTOR* and *PXN* in oral cavity cancer, *ROBO1* and *BIRC5* in nasopharyngeal cancer (190). PCR, western blotting, and luciferase assay have been used for the validation of these targets. miR-218 is among the anti-oncomiRs in the tumorigenesis of renal cell carcinoma, targeting *Caveolin-2* and *CXCR7* genes and involved in the cell viability, invasion, migration and cell-adhesion pathway (137). In PrC, miR-218 keeps a check on the transcription of *LASP1*, a gene that encodes for LIM and SH3 domain protein1, an oncogenic protein regulating cell-migration (191). Restoration of downregulated miR-218 via directly targeting *LASP1* mRNA-3'-UTR inhibited cell invasion and migration (190,192). miR-218, as a tumor suppressor, targets *BMI1* gene in *p53* mediated apoptosis and cell cycle arrested HT29 and HCT116 human colon-cancer cell lines (184). miR-218 is also downregulated in papillary thyroid carcinoma (186). miR-218, along with other differentially expressed micro RNAs in TPC-1 cell line bearing mutated *RET-PTC1*, compared to *RET-PTC1* transfected normal thyroid cell-line Nthy-ori was suspected to regulate thyroid functional genes. The dysregulation of these micro RNAs is associated with the progression of thyroid carcinoma (193). Over expressed miR-218 in He La cell line targeted AKT/mTOR signaling pathway, enhancing the cell sensitivity to cisplatin via reduced proliferation and induced apoptosis (194). On the other hand, downregulation of miR-218 aggravated CC tumorigenesis, by targeting *CCN1* and *MMP3* genes (45), tumor suppressor *APC* gene and *Wnt*-β catenin signaling pathway leading to suppressed apoptosis and increased cell-proliferation (195). *SFMBT1*, *DCUN1D1* targeting by microRNA-218 in CC was reported to induce EMT and metastasis (196). These studies on CC were based on

qRT-PCR and microarray experiments involving human models. Efforts to find any correlation between miRs expression levels and HPV genotypes suggested that high-risk human papillomavirus infections cause low expression levels of miR-218 leading to CC pathogenesis (197). The expression level of miR-218 gradually declined during PC progression and lymph node metastasis (181).

miRNA-221

miRNA-221 is a component of miR-221/222 cluster located on the X-chromosome. miR-221 and miR-222 are homologous, having identical seed sequences (198). It is often reported as an oncomiRNA, upregulated in cancers such as FTC: 46.9 (157), PTC: 12.3 (51), OC: 9.0 (199), CC: 7.0 (200), LC: 5.9 (201), HCC: 3.79 (22), PC: 3.78 (48), SC: 3.0 (202), RCC: 2.8 (203), GC: 2.5 (204), BrC: 2.3 (205), HNSCC: 1.4 (206), and CRC: 1.16 (207). In contrast, miRNA-221 has been shown downregulated in BC: –5.8 (23), HPV-positive HNSCC cell lines: –3.38 (208), PrC: –2.67 (187), and anaplastic type TC: 0.51 (28). These results indicate the dual role of miR-221 in tumorigenesis. Yilmaz *et al.* [2015] implied miR-221 as a biomarker in their study of plasma samples of larynx cancer patients, as its elevated expression level in tumor patients reversed to normal after tumor excision (206). Exosomal miRNAs, including miR-221 have been considered novel biomarkers for hepatocellular carcinoma on the basis of a study conducted on 20 patients each of chronic hepatitis-B, liver cirrhosis and HCC (34). Over expression of miR-221 has also been confirmed to be used as a practical way of PTC diagnosis (209). The potential biomarker application of miR-221 for early GC diagnosis and prognosis has been confirmed through qRT-PCR based multistage studies on plasma and serum samples (210,211). Upregulated expression of miR-221 in dysplasia cases was correlated with poor GC differentiation suggesting its potential role as diagnostic and prognostic biomarker for GC detection with high specificity and sensitivity, even 5-year before the clinical diagnosis (211). Later, Smid *et al.* [2016] reported that high expression of miR-221 is associated with TTP and OS in GC patients, indicating that it can be used as a biomarker to predict treatment effectiveness (212). Similarly, suppression of miR-221 is reported to sensitize estrogen receptor-alpha (*ER*-α) positive MCF-7 BrC cells towards tamoxifen (213) and fulverstrant, since miR-221/222 modulates *ER*-α negatively (214). In the RCC transcriptome, most highly up- and down-regulated miRs including miR-221, were advanced as serum early diagnostic biomarkers in another study performed on 44 RCC patients and 34 healthy controls using real-time PCR (203). In an effort to check the prognostic association of miR-221, Khella *et al.* [2015] in their analysis of miR-expression of metastatic RCC patients, having long (≤12 months) and short (>12months) progression free survival (PFS) and administered with sunitinib as a first line therapy, observed a negative connection between miR-221 expression and its target *VEGFR2*. Patients with poor PFS were characterized by higher miR-221 expression, whereas longer PFS was associated with higher *VEGFR2* (215). Additionally, miR-221 is reported to temper the expression of genes involved in the AKT-PI3K signal-transduction pathway which is related to cell proliferation and survival. *PTEN*, a tumor suppressor gene preventing cell proliferation by negative-regulation of AKT-PI3K, is targeted by miR-221 in various human malignancies including HCC (216), PDAC (217), SC (218), CC (219), and BrC (220). This interference resulted in the decreased sensitivity of CC cells to gefitinib (219). Other targets of miR-221 include *TIMP-2* (tissue inhibitor of metalloproteinases-2), *p27* (kip1), *p57* (kip2), and *PUMA* (217). miRNA-221 inhibition in PC cells and in TPC-1 cell line using 2'-O-Me-221 antisense oligonucleotide (221) resulted in the elevated expression levels of tumor suppressor genes *p27*, *p57*, *PUMA* and *PTEN* (96). Here, no significant variation in the expression of p27- kip1 mRNA was observed, suggesting strongly that miR-221 over expression might be responsible for post-translational negative regulation of p27 expression in malignant thyroid cells, inducing cells to enter S-phase of cell cycle thereby promoting cell growth (221). In HCC, it targets *TGF-b* also, resulting in liver fibrosis (216). Additionally, over expression of miR-221 influences some cyclin-dependent kinases and cyclin-complexes controlling progression of cell cycle. CDK inhibitor *CDKN1B*, which encodes for p27 (kip1) and *CDKN1C* are putative targets of miR-221 in various cancer cell lines such as TC and PDAC (221,222). In cervical carcinoma, miRNA-221 is reported to target another gene namely *ARID1A*, leading to an increase in *c-Myc*, *E2F4*, *E2F5* expression and suppression of p21 and *p53* expression (223). Another target of miR-221 is an oncogene, *c-KIT*, a receptor tyrosine kinase playing a key role in melanocyte differentiation through tyrosinase and MITF (microphthalmia associated transcription factor) (224). Hence, *c-KIT* variant screening might help in case of patients at high-risk and to predict patients more responsive to receptor tyrosine kinase treatment. miR-221 expression

was shown upregulated up to 11–19 folds (51), and up to 70 folds (225), when miR-expression profiles of normal thyroid tissues were compared to those of PTC tissues, where its expression was only weakly detectable in healthy tissues and thus the over expression was associated with extra-thyroidal invasion. Based on their analysis of microRNAs extracted from FEPE samples through laser micro-dissection, Jikuzono *et al.* [2013] reported that miR-221 expression is significantly upregulated in metastatic minimally invasive as well as widely invasive kind of FTC, characterized by distant metastasis and poor prognosis (226). Avissar *et al.* [2009] reported that the ratio of miR-221 and miR-375 has 92% sensitivity and 93% specificity to differentiate normal tissue from tumor tissue in head and neck cancer (68). However, in a study of HPV-positive HNSCC-cell line NHOK, subsisted in oropharynx, hypopharynx and oral cavity, miR-221 was reported downregulated (208).

The presentation of various evidences regarding involvement of different miRNAs in the initiation and progression of various cancers in the foregoing text clearly establishes their importance in cancer research. However, interdisciplinary studies involving larger cohort of patients are required to take the application of miRNAs in cancer therapy.

Conclusions

Ample evidences accumulated through different studies have established crucial importance of miRNAs in regulating various cellular processes implicated in tumorigenesis. Analysis of differential expression of different miRNAs in tumor cells has opened up new possibilities of developing miRNA-based biomarkers for the diagnosis and prognosis of different cancers. Since majority of the miRNAs affect more than one cancer, it is worthwhile to identify the key players operating common in different cancers. The leads from miRNA research unravel the cross talks between different molecular factors operating during tumorigenesis. Moreover, miRNA status also helps in understanding the mechanism of drug resistance in cancer treatment. All these new developments in cancer biology are likely to contribute towards development of new diagnostic and prognostic biomarkers, identification of novel drug targets, and devising effective strategies for the general and personalized management of cancer.

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