Role of microRNAs in solid tumors

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Abstract

Accumulating experimental evidence indicates that microRNAs play important roles in various biological processes, such as cell differentiation, proliferation, metabolism and apoptosis. In addition, several reports concluded that altered expression of specific microRNA genes contributes to the initiation and progression of cancer. Here, we summarize the current knowledge about aberrant expression of various microRNAs in human solid cancers (e.g., lung, breast, and gastric cancers), their target proteins, and the relationship between their expression and response to chemotherapies. We also review the potential for using microRNAs as biomarkers for the diagnosis and cancer therapy. The development of treatment strategies against human solid cancers based on the profile and/or certain features of microRNAs is promising.

What is microRNA?

MicroRNAs are noncoding, single-stranded RNAs, 18-25 nucleotides long, and were first reported in *Caenorhabditis elegans* in 1993.[1] Subsequent studies led to the identification of microRNAs in human RNA,[2] as well as to the understanding of their mechanisms of action. Most human miRNAs are found within introns of either protein-coding or noncoding mRNA transcripts,[3] and they do not code for any protein although they are RNA sequences.

MicroRNA genes are generally transcribed by RNA polymerase II in the nucleus to form pri-miRNA transcripts. These are processed into pre-miRNAs by a microprocessor complex, which contains the Rnase III enzyme Drosha[4] and DGCR8.[5] Exportin5 and a RanGTP[6] transport the pre-miRNAs from the nucleus to the cytoplasm, where they are further processed by the RNAase III enzyme Dicer.[7] The mature miRNA is retained in RISC (RNA-induced silencing complex)[8] and it is currently understood that microRNAs mainly bind to the 3' untranslated region (UTR) of their target mRNAs. However, recent studies have reported that microRNAs do not only bind to 3'UTR but also to 5'UTR[9,10] or open reading frame (ORF)[11,12] of the target mRNA. By binding to the 3'UTRs, 5'UTR or ORF of target mRNAs, microRNAs regulate the translation of proteins from mRNA or degrade the mRNA itself.[13] While microRNAs are thought to repress the translation of target mRNAs, recent results demonstrated that microRNAs can activate the expression of the target genes.[14] In the same study, microRNA was reported to be essential for translation activation under growth arrest conditions. Regulation of translation by microRNAs might change from repression to activation depending on the cell cycle.

In addition, because microRNA can bind even to mRNA that is not partially complementary,[15] microRNA and mRNA do not correspond one-to-one,[16] such that one microRNA may regulate several mRNAs or one mRNA may be regulated by several microRNAs. For example, in human gliomas, miR-34a inhibits the expression of multiple oncogenes (e.g., c-Met, Notch-1/Notch-2 and CDK6) by binding to their 3'-UTR and suppressing tumor growth.[17] Thus, these microRNAs potentially regulate approximately 30% of all genes encoding human proteins[18] and appear to achieve a wide range of cell functions, such as cell generation, differentiation, and proliferation.

Aberrant expression of microRNAs in solid cancers

With regard to the relationship between microRNA and cancer, the initial studies reported that B-cell chronic lymphocytic leukemia is associated with downregulation or deletion of miR-15 and miR-16 genes.[19] Other studies subsequently showed that more than half of the microRNAs were located near the unstable DNA region, where chromosomal deletions or amplifications associated with cancer in large the majority of cancer cells.[20] Thus, in cancer tissues, detailed profiling of microRNA should be informative and useful for evaluation of the cancer properties. In fact, it is reported that the expression levels of microRNAs vary widely depending on the cancer type and degree of differentiation[9] and that cancers can be even classified according to the microRNA profile, but not the mRNA profile.[21]

MicroRNAs include both microRNAs that act to inhibit cancer and microRNAs that conversely target tumor suppressor genes and act like oncogenes. To date, numerous reports have examined the aberrant expression of microRNAs and the association between the level of microRNA expression and prognosis in a number of human carcinomas. Table 1 lists the major microRNAs with reported aberrant expression in solid cancers. To study the relationship between microRNAs and cancer, it is important to examine not only aberrant expressions of microRNAs in carcinomas but also the gene targeted by these microRNAs and to understand their overall roles in cancer. For example, miR-21 is a typical oncogene microRNA whose aberrant expression has been confirmed in various cancers such as breast cancer,[22] lung cancer,[23] esophageal cancer,[24] colorectal cancer,[25] pancreatic cancer,[26] and hepatocellular carcinoma.[27] Interestingly, the Bcl-2[22] and PTEN[27] genes are target genes of miR-21, and the oncogene-like function of miR-21 is mediated through the suppression of such tumor suppressor genes.

Lung cancer

One major microRNA, the let-7 family, was first reported to alter the prognosis of patients with lung cancer.[28] Oncogenes such as RAS 29) and HMGA2[30] are already known as target genes of the let-7 family. In 2008, the first microRNA-knockout mouse was reported, the miR-17-92 knockout mouse, which exhibited hypoplasia of the lungs and B lymphocytes.[31] MiR-17-92 may also be involved in the process of lung carcinogenesis, and further studies are desirable. In fact, several reports have described the relationship between the expression of miR-17-92 and lung cancer.[32-35] On the other hand, the expression of microRNA was recently reported to correlate with smoking.[36] Based on the relationship between smoking and lung cancer, further studies are needed to determine the relationship between smoking and microRNA expression. It is anticipated that such studies will allow the design of new approaches for cancer treatment.

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Breast cancer

Breast cancer is a major cause of cancer mortality in women,[37] and one of the cancers most studied in relation to microRNA. The aberrant expression of many microRNAs has been reported (Table 1). Several studies reported the association between stem cells or cancer stem cells and microRNAs, such as the let-7 family,[38] miR-200c,[39] and miR-30,[40] in breast cancer. Furthermore, it is interesting that the number of studies conducted using a murine breast cancer model has been increasing relative to studies on other cancers. One study showed that miR-31 can impede local invasion and suppress metastasis from primary breast tumor *in vivo* and that the expression level of miR-31 correlates inversely with metastasis in human breast cancer.[41] Another study found low expression levels for miR-126 and miR-335 in primary human breast tumors and restoration of the expression of these microRNAs significantly reduced bone metastases *in vivo*.[42]

Esophageal cancer

Enzymes that contribute to the biogenesis of microRNA in esophageal cancer were first reported in 2006.[43] However, there are few reports that have described the relationship between esophageal cancer and aberrant expression of microRNA, compared with other solid tumors (Table 1). This may be due to the difficulty in collecting tissue samples from patients with esophageal cancer because esophagectomy is mostly performed in limited number of institutions. In this regard, a recent study using 70 tissue samples of esophageal cancer collected from several centers in three countries found that up-regulation of miR-21 expression and down-regulation of miR-375 expression correlated significantly with poor prognosis.[44] Further studies are needed to explore the potential therapeutic effects of microRNAs, such as improvement in sensitivity to radio- and chemo-therapy.

Gastric cancer

The expression of microRNA in gastric cancer was first reported in 2006 in a study that used microarray analysis;[45] the results showed aberrant expression of 28 microRNAs (22 up-regulated and 6 down-regulated). Gastric cancer includes various histopathological subtypes, such as three degrees of differentiation, mucinous, papillary and signet ring cell, and microRNAs are expressed differentially in this cancer according to histopathological subtype.[45] Thus, detailed analysis based on classification of histopathological types is necessary for proper analysis of aberrant expression of microRNA in gastric cancer. Although the number of studies on microRNA in gastric cancer is smaller than colorectal cancer and breast cancer, reports published in 2010 indicate increased interest in the aberrant expression of microRNA in this type of cancer (Table 1).

Colorectal cancer

Similar to breast cancer, the expression of microRNA, including aberrant expression, in colorectal cancer has been the topic of several studies (Table 1). For example, among patients with stage II colorectal cancer, those with high expression of miR-320 and miR-498 are considered to have better relapse-free survival than patients with low expression.[46] The same report indicated that analysis of the expression of a combination of several microRNAs can predict relapse with 81% accuracy rate, suggesting the potential of microRNA as a biomarker of recurrence. Another feature of colorectal cancer is the association between the expression of microRNAs and the p53 pathway [47-51]

Hepatocellular carcinoma

Several reports have described the aberrant expression of microRNAs in hepatocellular carcinoma (HCC) (Table 1). The expression of microRNA is also reported to be associated with HBV and HCV infections[52,53] which are closely related to HCC, and the association with hepatocarcinogenesis has been indicated.[54] Reduced expression of miR-122 in a chimpanzee model of HCV hepatitis/HCC was reported to result in successful control of HCC,55 and the clinical application to humans is greatly anticipated.

Pancreatic cancer

Pancreatic cancer is one of the most malignant cancers, and ranks eighth among the causes of death worldwide.[37] In addition to searching for aberrant expression of microRNA in pancreatic cancer (Table 1), analysis of the clinical significance of microRNA on early detection of cancer and the therapeutic outcome would be desirable. In this regard, it has been reported that profile analysis of microRNA expression can differentiate pancreatic cancer from chronic pancreatitis,[56] which is sometimes difficult to distinguish from pancreatic cancer. In fact, the expression of miR-196a-2 has already been used as a marker for differentiating pancreatic cancer from pancreatitis.[57] MiR-155 is also reportedly useful for early detection of intraductal papillary mucinous neoplasm (IPMN).[58]

Ovarian cancer

Although there are numerous reports on the aberrant expression of various microRNAs in ovarian cancer (Table 1), interestingly, there are almost no reports on miR-21, which is a typical proto-oncogene. Several studies examined the relationship between microRNA and sensitivity to cisplatin or paclitaxel chemotherapy, which is often used in clinical settings. For example, among patients with ovarian cancer undergoing cisplatin-based chemotherapy, the complete responders to chemotherapy showed significantly higher expression of let-7i in their tumors compared with the other patients that did not respond completely, and ovarian cancer cells with overexpression of let-7i were more sensitive to cisplatin than those with low expression.[59]

Glioblastoma

Glioblastoma is one of the highest-grade tumor among human intracranial tumors, and aberrant microRNA expression in glioblastoma has been reported in many studies (Table 1). To improve the prognosis of patients with glioblastoma, the development of biomarkers for early detection of glioblastoma, for example circulating microRNAs, is needed. This is particularly important since glioblastoma respond well to treatment with temozolomide, an oral alkylating agent often used for the treatment of intracranial tumors (Table 2).

Anti-cancer therapy and microRNA

In addition to the aforementioned studies that identified aberrant expression of microRNAs in various cancers, it is anticipated that novel anticancer therapeutic strategies will be designed in the future that are based on microRNAs, including chemotherapeutic agents, anti-hormone receptor agents and radiotherapy that target specific microRNAs. Furthermore, changes in the expression levels of microRNAs during any such therapy, relative to the baseline (using microarray analysis), could be also used to predict the sensitivity/resistance of tumors to the anti-tumor agents as well as monitor the response to such treatment.

Table 2-1 shows the relationship between certain microRNAs and the response to chemotherapy. For example, previous studies using microRNA microarray analysis showed down-regulation of 10 microRNAs and up-regulation of two microRNAs in chemoresistant gastric cancer cells compared with parent cells[60] and down-regulation of two microRNAs and up-regulation of 13 microRNAs in chemoresistant glioblastoma cells compared with parent cells.[61] Another study found significantly low levels of let-7i expression in chemotherapy-resistant patients.[59] These studies highlight the potential application of microRNAs to the prediction of the tumor response to chemotherapy.

Table 2-2 also lists few microRNAs that were

Table 1. Aberrant expression of microRNA in solid cancers.

MicroRNA	Target	Expression in tumor	Function	ref
Lung				
let-7	NS	Down	Tumor suppressor	89
let-7	HMGA2, K-RAS	Down	Tumor suppressor	90
let-7	CDK6, N-RAS	Down	Tumor suppressor	91
miR-15a,16	CyclinD1, D2, E1	Down	cell cycle arrest is induced	92
miR-17-92	HIF1α	NS	miR-17-92 regulates HIF1α expression under normoxia	34
miR-17-92	NS	Up	miR-17-92 is relation to development of B cell and lung	31
miR-21	NS	Up	oncogene, EGFR signaling regulates miR-21 expression	93
miR-21	NS	Up	miR-21 knock-out mice suppresses Tumor development	94
miR-29	DNMT3A, 3B	Down	Tumor suppressor	95
miR-128b	EGFR	NS	miR-128b LOH is positive prognostic factor	96
miR-145	Mucin1	Down	Tumor suppressor	97
miR-221, 222	PTEN, TIMP3	Up	Oncogene	98
miR-488, 503, 647	NS	NS	miR expression pattern to predict recurrence	99
Breast				
let-7	HRAS, HMGA2	Down	Tumor suppressor	38
miR-9	CDH1	Up	Oncogene	100
miR-10b	RHOC	Up	Oncogene	101
miR-10b	HOXD10	Up	Oncogene	102
miR-17/20	IL-8, CK8, CXCL1	Down	Tumor suppressor	103
miR-21	PDCD4	Up	Oncogene	104
miR-29a	TTP	Up	Oncogene	105
miR-30	Ubc9, ITGB3	Down	Tumor suppressor	40
miR-31	F2d3, ITGA5, MMP6 etc.	Down	Tumor suppressor	41
miR-126, 335	SOX4, Tenascin	Down	Tumor suppressor	42
miR-146a,b	IRAK1, TRAF6	Down	Tumor suppressor	106
miR-193b	uPA	Down	Tumor suppressor	107
miR-200family, 205	ZEB1, SIPI	NS	miR-200 family regulate ZEB1 and SIP1	108
miR-200c	BMI1	Down	Tumor suppressor	39
miR-373, 520c	CD44	Up	Oncogene	109
miR-661	Nectin-1, StarD10	Up	Oncogene regulated by SNAI1	110
Esophagus				
miR-10b	KLF4	Up	Oncogene	111
miR-16, 30e, 200a	NS	Up	Oncogene	112
miR-21	PDCD4	Up	Oncogene	24
miR-21, 375	NS	miR-21: up, -375: Down	miR-21: oncogene, miR-375: Tumor suppressor	44
miR-106b	p21	Up	Oncogene	113
miR-133a,b,145	FSCN1	Down	Tumor suppressor	114
miR-196a	ANXA1	Up	Oncogene	115
miR-373	LATS2	Up	Oncogene	116
Stomach				
let-7g,miR-214, 433	NS	miR-422: Down	let-7, miR-422: Tumor suppressor; miR-214: oncogene	117
miR-9	NF-κβ	Down	Tumor suppressor	118
miR-9, 433	RAB34, GRB2	Down	Down-regulated in gastric cancer	119
miR-23a	IL-6R	Up	Oncogene	120
miR-31	NS	Down	Down-regulated in gastric cancer	121
miR-101	EZH2, Cox2, Mcl-1, Fos	Down	Tumor suppressor	122
miR-126	Crk	Down	Tumor suppressor	123
miR-129	CDK6	Down	Tumor suppressor	124
miR-129-2	SOX4	Down	Tumor suppressor	125
miR-130b	RUNX3	Down	Tumor suppressor	126
miR-141	NS	Down	Tumor suppressor	127
miR-181c	NOTCH, KRAS	Down	Tumor suppressor	128
miR-212	MeCP2	Down	Tumor suppressor	129
miR-218	Robo1	Down	Tumor suppressor	130
miR-218	ECOP	Down	Tumor suppressor	131
miR-372	LATS2	Up	Oncogene	132
miR-375	PDK2, 14-3-3	Down	Tumor suppressor	133
miR-421	CBX7, RBMXL	Up	Up-regulated in gastric cancer	134

Continued next page.

Table 1. Continued from previous page.

Colon				
miR-16	Wip1	Down	Down-regulated in colon cancer	47
miR-18*	KRAS	Down	Tumor suppressor	135
miR-21	CDC25A	Up	Oncogene	136
miR-34a	E2F	Down	Tumor suppressor	137
miR-106a	E2F1	Down	Tumor suppressor	138
miR-107	HIF1β	Down	Tumor suppressor	48
miR-143	DNMT3A	Down	Tumor suppressor	139
miR-145	IRS1	Down	Tumor suppressor	140
miR-155	MSH1, MSH2	Up	Oncogene	141
miR-192	NS	NS	Proliferative effect of miR-192 depends on p53	50
miR-196a	NS	Up	Oncogene	142
miR-320, 498	NS	Down	Tumor suppressor	46
miR-675	RB	Up	Oncogene	143
Liver				
miR-18a	ERα	Up	Oncogene	144
miR-21	PTEN	Up	Oncogene	27
miR-26a	NS	Down	Tumor suppressor	145
miR-101	Mcl-1	Down	Tumor suppressor	68
miR-122	CyclinG1	Down	Tumor suppressor	146
miR-122	NS	Down	Tumor suppressor	147
miR-151	PhoGD1A	Up	Oncogene	148
miR-181b	TIMP3	Up	Oncogene	149
miR-193b	Mcl-1	NS	HCV proteins alter miR expressions	53
miR-196	Bach1	NS	miR-196 inhibits HCV expression	54
miR-221	CDKN1C/p57, CDKN1B/p27	Up	Oncogene	150
miR-221	Bmf	Up	Oncogene	151
miR-222	PPP2R2A	Up	Oncogene	152
miR-223	STMN1	Down	Tumor suppressor	153
Pancreas				
miR-21	NS	Up	Oncogene	154
miR-27a	Sprouty2	Up	Oncogene	155
miR-96	KRAS	Down	Tumor suppressor	156
miR-107	CDK6	Down	Tumor suppressor	157
miR-146a	EGFR, IRAK1, NFκβ, MTA2	Down	Tumor suppressor	158
miR-155	TP53INP1	Up	Oncogene	159
miR-196a-2	NS	Up	Oncogene	57
miR-210	EFNA3	Up	Oncogene	160
Ovary				
let-7i	NS		Tumor suppressor	59
miR-9, 223	NS	miR-9: down, miR-223: down	miR-9: Down-regulated, miR-223: up-regulated in recurrent ovarian cancer	161
miR-15a, 16	Bmi-1	Down	Tumor suppressor	162
miR-20a	APP	Up	Oncogene	163
miR-27a	NS	Up	Oncogene	164
miR-31	CEBPA, STK40, E2F2	Down	Tumor suppressor	165
miR-34b, 34c	NS	Down	Tumor suppressor	166
miR-125a	ARID3B	Up	Oncogene	167
miR-185	Six1	Down	Tumor suppressor	168
miR-199a	IKKβ	Down	Tumor suppressor	169
miR-199a, 214	NS	Up and down	Twist1 regulates miRs	170
miR-200a, 200b	ZEB1,2	Up	up-regulated in ovarian cancer	171
miR-210	E2F3	NS	miR-210 is a key regulator of hypoxia	172
miR-221, 222	CDKN1C	Down	Tumor suppressor	173
Glioblastoma				
miR-7	EGFR	Down	Tumor suppressor	174
miR-10b	RhoC, uPAR	Up	Oncogene	175
miR-17-92	Smad, etc.	Up	Oncogene	176
miR-17-92	CTGF	Up	Oncogene	177
miR-21	NS	Up	Oncogene	178
miR-26a	PTEN, RB1, MEKK2	Up	Oncogene	179
miR-34a	NC	Down	Tumor suppressor	17
miR-128	Bmi1	Down	Tumor suppressor	180
miR-153	Bcl-2, Mcl-1	Down	Tumor suppressor	181
miR-196	NC	Up	High expression shows poorer survival.	182
miR-221, 222	p27, p57	Down	Tumor suppressor	183
miR-222, 339	ICAM1	Up	MiRs correlate with CTL-mediated cytolysis	184
miR-296	HGS	Up	miR-296 contributes to angiogenesis	185

NS; not stated

reported to show changes in their expression during cancer treatment. For example, significant reductions in let-7a and let-7b expression levels, relative to the baseline levels, were noted at 8 h after irradiation in lung cance,[62] where a significant increase in miR-34 expression was monitored following irradiation-induced DNA damage[63] in breast cancer tissue. The development of resistance to chemotherapy is also a problem during cancer treatment. In the cancer stem cell theory, the pluripotent and self-replication properties of the stem cells affect resistance to chemotherapy 38,[64] while microRNAs are known to regulate stem cell functions.[65-67] Thus, microRNAs seem to affect the stability of resistance to antitumor therapies in cancerous tissues. In fact, several recent studies described the correlation between resistance to anticancer drugs and expression of microRNAs known to be involved in stem cell functions (Table 2-2). Furthermore, many of microRNAs are known to enhance sensitivity or reduce the resistance to anti tumor therapy. For example, the hematomas in which miR-101 had been introduced showed higher sensitivity to anticancer agents[68] and the expression of miR-206 correlated inversely with that of estrogen receptor-α.[69] Table 2-3 lists some MicroRNAs known to influence the sensitivity to anti-cancer therapy.

Regulation of microRNA

Because microRNA regulate the expression of many mRNAs and microRNAs do not correspond one-to-one to mRNA, a comprehensive analysis is required to understand the regulation of such expression. To gain a better understanding of the overall picture of carcinogenesis, including the function of microRNAs, one should understand the mechanisms involved in the regulation of microRNA expression itself. Previous studies proposed that epigenetic mechanisms and other proteins regu-

Table 2. microRNAs related to sensitivity of anti-cancer therapy.

MicroRNA	Treatment	Target	Function	Year	Ref
2-1. MicroRNAs that are associated with response prediction					
Stomach					
miR15a,16	ADR, VCR, VP16, CDDP	NS	Increase sensitivity	2008	60
Ovary					
let-7i	CDDP	NS	Increase sensitivity	2008	59
Glioblastoma					
miR-195	Temozolomide	NS	Increase sensitivity	2010	61
2-2. MicorRNAs those expressions altered during a therapy					
Lung					
let-7b,g	Radiation	NS	Increase sensitivity	2007	62
Several miRs	Radiation	Int J oncol	22 miRs expression were changed	2009	186
Breast					
miR-34	Radiation	NS	Decrease sensitivity	2009	63
Pancreas					
miR-22	Curcumin	ESR1, SP1	NS	2008	187
2-3. MicroRNA that influences the sensitivity to anti-cancer therapy					
Lung					
miR-181a, 630	CDDP	NS	Increase sensitivity	2010	188
miR-181b	CDDP	Bcl2	Increase sensitivity	2010	189
Breast					
let-7	Epi-ADM	H-RAS, HMGA2	Related to tumor initiating cells	2007	38
Esophagus					
miR-27a	ADR, VCR, 5-FU, CDDP	Bcl2, MRP1	Decrease sensitivity	2010	190
miR-296	As above	Bax	Decrease sensitivity	2010	191
Stomach					
miR-221, 222	Radiation	NS	Decrease sensitivity	2010	192
miR-451	Radiation	MIF	Increase sensitivity	2009	193
Colon					
miR-140	5-FU	HDAC4	Decrease sensitivity	2009	194
miR-143	5-FU	NS	Increase sensitivity	2009	195
miR-215	MTX, TDX	NS	Decrease sensitivity	2010	196
Liver					
miR-26a	IFNα	NS	Decrease sensitivity	2009	197
miR-199a-3p	ADR	mTOR, c-Met	Increase sensitivity	2010	198
Pancreas					
miR-21	GEM	NS	Decrease sensitivity	2010	199
miR-21	5-FU	NS	Decrease sensitivity	2010	200
miR-21	GEM	NS	Decrease sensitivity	2009	201
Ovary					
miR-27a	TXL	MDR1	Decrease sensitivity	2010	202
miR-100	everolimus	MTOR	Increase sensitivity	2010	203
miR-200c	TXL	TUBB3	Increase sensitivity	2009	204
Glioblastoma					
miR-21	Temozolomide	Bax, Bcl-2	Decrease sensitivity	2010	205
miR-21	VM-26	LRRFIP1	Decrease sensitivity	2009	206

CDDP, cisplatin; ADR, doxorubicin; VCR, vincristine; VP16, etoposide; MTX, methotrexate; TDX, thymidylate synthase inhibitor Tomudex; GEM, gemcitabine; TXL, taxol; VM-26, Teniposide; NS. not stated.

late the expression of microRNAs as described below.

Epigenetic mechanisms

Epigenetic modification means aberrant gene expression due to DNA methylation or histone deacetylation. DNA methylation occurs in specific genomic areas called CpG-islands, which are commonly present in the promoter area of the gene.[70] Methylation of CpG-island is triggered by DNA methyltransferases (DNMTs) and histone modifications are catalyzed by histone deacetylases (HDACs) and histone methyltransferases (HMTs). Tumor genes are globally hypomethylated compared with those of normal tissues,[71] and methylation of CpG islands in the gene promoter area results in inactivation of tumor suppressor genes.[70] Thus, epigenetic modifications could be involved in carcinogenesis, in addition to other well-defined genetic mechanisms, such as gene mutations and loss of deficiency of heterozygosity.

It was demonstrated recently that certain genes, in particular those with hypermethylated promoters, require Dicer to maintain the epigenetic status.[72] As mentioned above, Dicer is a key enzyme in microRNA biogenesis. That is a first report that shows the correlation between epigenetic changes of DNA and microRNAs.

Then, Several other studies have reported that epigenetic mechanisms regulate the expression levels of microRNAs. For example, the first report in 2006[73] showed that abnormal methylation correlates with miR-127 expression in several cancer cells. Although miR-127 is not expressed in cancer cells, strong upregulation of this microRNA was noted after treatment with chromatin-modifying drugs (which are also DNA demethylating agents and HDAC inhibitors). Another study showed that the oncoprotein AML1/ETO, an acute myeloid leukemia-associated fusion protein, induced heterochromatic silencing of miR-223 by recruiting DNMTs and HDAC1 activities.[74] These results point to a complex epigenetic regulation of microRNAs. Table 3-1 lists a group of microRNAs known to be regulated by epigenetic mechanism.

On the other hand, new evidence suggests that microRNAs can control the expression levels of DNMTs and HDACs. For example, microRNA members of the miR-29 family directly target DNMT3A and DNMT3B. Enforced expression of the miR-29 family induced reexpression of methylation-silenced tumor suppressor genes in lung cancer cells, which resulted in inhibition of cancer growth in xenograft models.[75] Other studies showed that miR-1 directly targeted HDAC-4 in murine myoblasts[76] while miR449a regulated cell growth by repressing HDAC-1 expression in human prostate cancer cells.[77] Table 3-2 lists few microRNAs known to control epigenetic mechanisms.

The above studies enhance our understanding of aberrant epigenetic mechanisms in cancers and may prove useful in identifying new targets for cancer therapy.

Regulation by other factors

Among the various families of microRNAs, the let-7 family, which is known to have tumor suppressor function, is under the control of LIN28, which is overexpressed in germ cells by RNA-binding proteins, at the stage of Drosha enzyme processing.[78] The latter study indicated the specificity of the regulatory mechanism of LIN28 to the let-7 family by demonstrating the lack of any inhibitory effects on other microRNA. Dicer, another enzyme involved in the processing of microRNAs, also inhibits the let-7 family and forms a negative feedback loop with let-7 family.[79] Other studies reported the regulation of microRNAs by other transcription factors, such as p53[80] and c-myc,[81] suggesting that many factors are intricately involved in the mechanisms that regulate microRNAs in cancers. The number of microRNA-related regulatory factors reported to date is not very large, but it is expected to expand exponentially in the future.

MicroRNAs as biomarkers for cancer

Although many aspects of microRNA formation in the cell remain unclear, it is becoming evident that microRNAs are more stable in the cells than mRNA. Accordingly, it is anticipated that microRNAs may serve as biomarkers of cancer better than mRNA. Historically, intrinsic microRNA levels in the circulation were

Table 3. microRNAs that are regulated by epigenetic gene silencing.

MicroRNA	Cancer type	Target	Detail	Year	Ref
3-1. Some microRNAs of which expression controlled by epigenetic mechanism					
let-7a-3	Ovary	NS	let-7a-3 methylation is associated with survival	2007	207
miR-1	Liver	FoxP1, MET, HDAC4	Overexpression in cells treated with 5- AZA	2008	208
miR-9-1	Breast	NS	Overexpression in cells treated with 5-AZA	2008	209
miR-9, 34b/c, 148a	Various types	oncogenes	Overexpression in cells treated with 5-AZA	2008	210
miR-9, 129, 137	Colon	NS	Overexpression in cells treated with 5- AZA	2009	211
miR-34b, -34c	Colon	BTG4	miR-34b/c methylation is frequently observed in cancer cells	2008	212
miR-124a	Colon	CDK6	Overexpression in cells treated with 5-AZA	2007	213
miR-127	Bladder	BCL6	Overexpression in cells treated with 5-AZA	2006	73
miR-129-2	Ovary	SOX2	Overexpression in cells treated with epigenetic drugs	2009	214
miR-137a	Colon	LSD1	miR-137 methylation is specific for cancer	2010	215
miR-223	Leukemia	NS	AML1/ETO induced heterochromatic silencing of miR-223	2007	74
miR-370	Biliary duct	MAP3K8	Overexpression in cells treated with 5-AZA	2008	216
miR-512-5p	Stomach	Mcl-1	Overexpression in cells treated with 5- AZA	2009	217
3-2. Some microRNAs that controlls epigenetic mechanism					
miR-1	Myoblast (not malignant)	HDAC-4	MiR-1 represses HDAC-4	2006	76
miR-29 family	Lung	DNMT3a, 3b	Enforced expression restores normal patterns of DNA methylation	2007	75
miR-29b	Leukemia	DNMT3a, 3b	Enforced expression restores normal patterns of DNA methylation	2009	218
miR-148a, b	Various types	DNMT3b	MiR-148 represses DNMT3b	2008	219
MiR-449	Prostate	HDAC-1	MiR-449 directly targets HDAC-1	2009	77

5-AZA, 5-Aza-20-deoxycytidine; NS, not stated.

found to be relatively stable against endogeneous RNAase.[82] Subsequent studies reported higher blood miR-195 and let-7 expression levels in patients with breast cancer compared with healthy subjects and that these expression levels fell after surgical excision of the tumor.[83] Furthermore, the expression levels of miR-29a and miR-92a were also found to increase with the stage of colorectal cancer,[84] suggesting their potential suitability as a cancer screening tool.

Recent studies have reported measurement of microRNAs in other body fluids in addition to blood, such as feces[85] and sputum.[86] For example, significantly higher expression levels of miR-21 were found in the sputum of patients with lung cancer compared with healthy subjects, indicating high sensitivity and specificity.[87] On the other hand, the expression levels of miR-125a and miR-200a in the saliva were significantly lower in patients with oral cancer than healthy subjects.[88] Further studies are needed to design simple and noninvasive assays that accurately measure microRNAs collected from human tissues. Such methods will be helpful for screening of cancer or assessment of the therapeutic effects of anti-cancer treatment.

Future perspective of microRNA

As noted earlier, microRNA are expected to play a major role in the future as biomarkers for screening cancer, predicting response to therapies, and assessing the effect of treatment.

Progress is also anticipated in the development of new microRNA-based anti-cancer therapies. Such therapies could be designed to restrict cancer growth by applying the mRNA regulatory function of microRNA to inhibit oncogenes or activate tumor suppressor genes. Alternatively, new therapies could be designed based on the finding of increased potency of standard chemotherapies when combined with microRNAs.

We are only just beginning to understand microRNAs and their hidden potential. Worldwide research on microRNAs, including clinical application, is currently underway. Treatment strategies against solid cancers based on profile or features of microRNAs are expected to be developed in the near future.

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