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Epigenetic modifications in cancer

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Abstract

Cancer initiation and progression is controlled by both genetic and epigenetic events. The complexity of carcinogenesis cannot be accounted for by genetic alterations alone but also involves epigenetic changes. Epigenetics refers to the study of mechanisms that alter gene expression without altering the primary DNA sequence. Epigenetic mechanisms are heritable and reversible, and include changes in DNA methylation, histone modifications and small noncoding microRNAs (miRNA). Disruption of epigenetic processes can lead to altered gene function and malignant cellular transformation. Aberrant epigenetic modifications probably occur at a very early stage in neoplastic development, and they are widely described as essential players in cancer progression. Recent advances in epigenetics offer a better understanding of the underlying mechanism(s) of carcinogenesis and provide insight into the discovery of putative cancer biomarkers for early detection, disease monitoring, prognosis, and risk assessment. In this review, we summarize the current literature on epigenetic changes causing genetic alterations that are thought to contribute to cancer, and discuss the potential impact of epigenetics future research.

Keywords

cancer; DNA methylation; epigenetics; histone modification; microRNA

Cancer, initially recognized as a genetic disease, is now known to involve epigenetic abnormalities along with genetic alterations. It is becoming clear that microenvironment-mediated epigenetic perturbations play an important roles in the development of neoplasia (1). Epigenetics refers to the study of heritable changes in gene expression that occur without a change in DNA sequence which are sufficiently powerful to regulate the dynamics of gene expression (2). The key processes responsible for epigenetic regulation are DNA methylation, histone modifications and posttran-scriptional gene regulation by noncoding RNA commonly referred as microRNAs (3). These mechanisms are critical components in the normal development and growth of cells and their modifications contribute to neoplastic phenotypes (4).

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Nothing to declare.

DNA methylation

In eukaryotes, methylation is characterized by epigenetic DNA modifications which play an important role in maintenance of genome integrity, genomic imprinting, transcriptional regulation, and developmental processes (5). DNA methylation usually takes place at the 5′ position of the cytosine ring within CpG dinucleotides, and its consequence is the silencing of genes and noncoding genomic regions. The modification at 5-methyl cytosine is catalyzed by enzyme DNA methyltransferases (DNMTs) (6). There are three main DNMTs: DNMT1, which maintains the existing methylation patterns following DNA replication, and DNMT3A and DNMT3B, *de novo* enzymes that target unmethylated CpGs to initiate methylation and are highly expressed during embryogenesis and minimally expressed in adult tissues (7). Another family member is DNMT-3L that lacks intrinsic methyltransferase activity; it interacts with DNMT3a and 3b to facilitate methylation of retrotransposons (8). Both the establishment and maintenance of DNA methylation patterns are critical for development as mice deficient in DNMT3B or DNMT1 are embryonic lethal and DNMT3A-null mice die by 4 weeks of age (9). In normal cells, DNA methylation occurs predominantly in repetitive genomic regions, including satellite DNA and parasitic elements such as long interspersed transposable elements (LINEs) and short interspersed transposable elements (SINEs), maintaining genomic integrity (10). Methylated cytosines account for approximately 1% of total nucleotides and about 75% of all CpG dinucleotides in the human genome. The CpG dinucleotides are unevenly distributed across the human genome, but are concentrated in dense pockets called CpG islands (CGIs). About 50–60% of gene promoters lie within CpG islands, and it is estimated that the human genome contains approximately 29,000 CpG sequences (11). CpG islands particularly those associated with promoters are generally unmethylated in normal cells, providing access to transcription factors and chromatin-associated proteins for the expression of most housekeeping genes and several other regulated genes although some of them (~6%) become methylated in a tissue-specific manner during early development or in differentiated tissues (4, 12). DNA methylation can inhibit gene expression directly, by inhibiting the binding of specific transcription factors, and indirectly, by recruiting methyl-CpG-binding domain (MBD) proteins. The associated MBD family members in turn recruit histone-modifying and chromatin-remodeling complexes to methylated sites (13). To date, six methyl-CpG-binding proteins, including methylcytosine binding protein 2 (MECP2), MBD1, MBD2, MBD3, MBD4 and Kaiso, have been identified in mammals. MECP2 binds methylated DNA *in vitro* and *in vivo*. It contains a MBD at its amino terminus and a transcription repression domain (TRD) in the middle (13). Furthermore, it has been shown that nucleosome remodeling complex (NuRD) can methylate DNA by interacting with DNA methylation binding protein MBD2, which directs the NuRD complex to methylate DNA (14, 15). These and other recent findings have established that DNA cytosine methylation is a critical component of epigenetic gene regulation. A list of DNA methylation genes disrupted in various human cancers is shown in Table 1.

Histone modification

Histone modifications influence chromatin structure which plays an important role in gene regulation and carcinogenesis (16). Chromatin is a highly ordered structure consisting of repeats of nucleosomes connected by linker DNA. Each nucleosome encompasses ~146 bp of DNA wrapped around an octamer of histone proteins. These octamers consist of two subunits of each of the following core histone proteins: H2A, H2B, H3 and H4 (17). Chromatin consists of DNA, histones, and non-histone proteins condensed into nucleoprotein complexes and functions as the physiological template of all eukaryotic genetic information (18). Histones are small basic proteins containing a globular domain and a flexible charged NH_2 terminus known as the histone tail, which protrudes from the

nucleosome. Regulation of gene expression occurs through posttranslational modifications of the histone tails provided by covalent modifications including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, proline isomerization, and ADP ribosylation (19–21). Posttranslational modifications to histone tails govern the structural status of chromatin and the resulting transcriptional status of genes within a particular locus. These modifications are reversible and are controlled by a group of enzymes including histone acetyltransferases (HATs) and deacetylases (HDACs), methyltransferases (HMTs) and demethylases (HDMs), kinases, phosphatases, ubiquitin ligases and deubiquitinases, SUMO ligases and proteases which add and remove such modifications (20, 22). Chromatin is divided into two distinct conformation states: heterochromatin, which is densely compacted and transcriptionally inert and euchromatin, which is decondensed and transcriptionally active (17, 23). Euchromatin is characterized by high levels of acetylation and trimethylated H3K4, H3K36 and H3K79. On the other hand, heterochromatin is characterized by low levels of acetylation and high levels of H3K9, H3K27 and H4K20 methylation (12, 24, 25). Studies have shown that histone modification levels are predictive for gene expression. Actively transcribed genes are characterized by high levels of H3K4me3, H3K27ac, H2BK5-azacytidine (H2BK5ac) and H4K20me1 in the promoter and H3K79me1 and H4K20me1 along the gene body (26). Genome-wide studies have revealed that various combinations of histone modifications in a specific genomic region can lead to a more ‘open’ or ‘closed’ chromatin structure resulting in the activation or repression of gene expression (12, 24, 25). A list of the histone-modifying genes altered during carcinogenesis is presented in Table 2.

Noncoding RNAs

MicroRNAs (miRNAs) are small ncRNAs of ~22 nucleotides and are involved in posttranslational gene silencing by controlling mRNA translation into proteins (27). miRNAs induce heritable changes in gene expression without altering DNA sequence and thus contribute to the epigenetic landscape. In addition, miR-NAs can both regulate and be regulated by other epigenetic mechanisms (28). Although miRNA are vital to normal cell physiology their mis-expression has been linked to several diseases, including cancer (4). Cancer development and miRNA profiles are now being used to classify human cancers (23, 28, 27). Approximately, 1000 miRNA genes have been computationally predicted in the human genome with each miRNA targeting multiple protein-coding transcripts. It has been predicted that miRNAs regulate the translation rate of more than 60% of protein-coding genes (7), and participate in the regulation of cellular processes. Like mRNAs, miRNAs are mainly transcribed by RNA polymerase-II although miRNA synthesis is known to occur by RNA polymerase-III in those miRNAs that reside near tRNA, Alu and mammalian-wide interspersed sequences (28). The first identified miRNAs, the products of the *Caenorhabditis elegans* genes *lin-4* and *let-7*, have important roles in controlling developmental timing and probably act by regulating mRNA translation. When *lin-4* or *let-7* is inactivated, specific epithelial cells undergo additional cell divisions instead of their normal differentiation (27). A list of miRNAs dysregulated in cancer is presented in Table 3.

Epigenetic modifications in cancer

In human cancers, aberrant epigenomics are known to contribute to various phases of neoplastic development including initiation, promotion, invasion, metastases and chemotherapy resistance. It has been proposed recently that more than 300 genes and gene products are epigenetically altered in various human cancers (4). A link between DNA methylation and cancer was first shown in 1983, when it was shown that the genomes of cancer cells are hypomethylated relative to their normal counterparts (29). In terms of DNA methylation, cancer cells show genome-wide hypomethylation and site-specific CpG island promoter hypermethylation (30, 31). Hypermethylation at specific genes typically affects

promoter CpG-islands inactivating transcription. Hypermethylation is observed at specific CpG islands. The transcriptional inactivation caused by promoter hypermethylation affects genes involved in the main cellular pathways: DNA repair [*hMLH1* (mismatch repair gene 1), *MGMT* (O6-methylguanine–DNA methyltransferase), *WRN* (Werner syndrome, RecQ helikase like), *BRCA1* (breast cancer 1)], cell cycle control ($p16^{INK4a}$, $p15^{INK4b}$, *RB*), Ras signaling {*RASSF1A* [Ras association (RalGDS/AF-6) domain family member 1], *NOREIA*}, apoptosis [*TMS1* (target of methylation-induced silencing 1), *DAPK1* (death-associated protein kinase), *WIF-1, SFRP1*], metastasis [cadherin 1 (*CDH1), CDH13, PCDH10*], detoxification [*GSTP1* (glutathione S-transferase pi 1)], hormone response (*ESR1, ESR2*), vitamin response [*RARB2* (retinoic acid receptor b2), *CRBP1*] and p53 network [$p14^{ARF}$, *p73* (also known as *TP73*), *HIC-1*] among others. This provides tumor cells with a growth advantage and increases their genetic instability and aggressiveness (22, 30). Hypomethylation in tumor cells is primarily caused by the loss of methylation from repetitive regions of the genome and the resulting genomic instability is a hallmark of tumor cells. In addition, imprinting patterns are often disturbed (32). In cancers, hypomethylation is often associated with oncogenes. c-Myc, a transcription factor that acts as an oncogene, is one of the widely reported hypomethylated genes in cancers. Hypomethylation at specific promoters can activate the aberrant expression of oncogenes and induce loss of imprinting (LOI). The most common LOI event due to hypomethy-lation is insulin-like growth factor 2 (*IGF2*), which has been reported in a wide range of tumor types, including breast, liver, lung and colon cancer (33, 34). *S100P* in pancreatic cancer, *SNCG* in breast and ovarian cancers and melanoma-associated gene (*MAGE*) and dipeptidyl peptidase 6 (*DPP6*) in melanomas are well-studied examples of hypomethylated genes in cancer (12, 35).

In addition to changes in DNA methylation, histone modification patterns are also altered in human tumors. Recent studies have shown that histone modification levels are predictive for gene expression. Actively transcribed genes are characterized by high levels of H3K4me3, H3K27ac, H2BK5ac and H4K20me1 in the promoter and H3K79me1 and H4K20me1 along the gene body (26). Loss of acetylation is mediated by HDACs that have been found to be over-expressed or mutated in different tumor types. Aberrant expression of both HMTs and HDMs are observed in various cancer types (36). A recent study has described inactivating mutations in the histone methyltransferase *SETD2* and in the histone demethylase *UTX* and *JARID1C* in renal carcinomas (36, 37). H3 acetylation and H3K9 dimethylation can discriminate between cancerous and nonmalignant prostate tissue and H3K4 trimethylation can predict occurrence of prostate-specific antigen serum level elevation after prostatectomy for cancer (28). *EZH2* (enhancer of zeste homolog 2) expression is an independent prognostic marker that is correlated with the aggressiveness of prostate, breast and endometrial cancers (38).

Because abnormal cell proliferation is a hallmark of human cancers, it seems possible that miRNA expression patterns might denote the malignant state. Indeed, altered expression of a few miRNAs has been found in some tumor types (39, 40). The first association between miRNA and cancer development was described in chronic lymphocytic leukemia with chromosome 13q14 deletion. This deletion deregulates miRNA-15 and miRNA-16 (41). Most of the targets of these two miRNAs are involved in cell growth and cell cycle. The *let-7* is one of the most widely studied miRNA families in cancer. Alterations of *let-7* function have been described in several human cancer types, including carcinomas of the head and neck region, lung, colon, rectum and ovary. It acts mainly as a tumor-suppressor miRNA (28). miRNA-145 is a well-known tumor-suppressor miRNA downregulated in many human cancers owing to aberrant DNA methylation of its promoter and/or p53 mutations (42). This miRNA is a pluripotency repressor which regulates silencing of *OCT, SOX2 and KLF4* in human embryonic stem cells; these genes are required for cell self-renewal and pluripotency maintenance (43). Interestingly, it is becoming apparent that the

expression of epigenetic regulatory enzymes such as DNMT, HATs, and HMTs can be controlled by miRNAs (44). In particular, the miRNA-29 family can directly regulate the expression of DNMTs such that downregulation of this family of miRNAs in small-cell lung cancer results in increased expression of DNMT3A and 3B causing a global genomic hypermethylation and specific methylation-induced silencing of tumor-suppressor genes such as *FHIT* and *WWOX* (45, 46).

Influence of epigenetics on cancer genetics

It is evident that discrete genetic alterations in neoplastic cells alone cannot explain multistep carcinogenesis whereby tumor cells are able to express diverse phenotypes during the complex phases of tumor development and progression. In fact, cancer cells have an altered epigenome compared to the tissues from which they arise. Deregulated epigenetic mechanisms may initiate genetic instability, resulting in the acquisition of genetic mutations in tumor-suppressor genes and activating genetic mutations in oncogenes. Moreover, epigenetic disruptions in tumors are generally of a clonal nature, indicating occurrence in early generations of cells (47). It is well known that 5-methylcytosine (m5C) residues are 'hot spots' for mutations, which can destabilize gene structure and function. One-third of germ-line point mutations leading to human genetic diseases occur at CpGs and most of these mutations are C→T transitions (48). This is because m5C is highly mutable by deamination, resulting in transitional mutations (i.e. C→T) at CpGs. In view of the symmetry of these CpG motifs, the methylcytosine on the opposite strand may also be affected, leading to (G→A) changes. As a consequence, CpGs are hot spots for mutations, in a variety of genes. (48, 49) G→A transitions are found in 44.8% cases of leukemia and myelodysplasia, and in 60% of colon cancer cases. C→T and tandem CC-TT mutations are found in basal cell and squamous cell carcinomas (50). Methylation increases the rate of hydrolytic deamination and also increases the reactivity of neighboring guanines to electrophiles (50, 51). The oxidation of m5C may contribute to the high frequency of C→T transitions at CpG sequences. Oxygen radicals can react with m5C to oxidize the 5, 6-double bond; the intermediate product, m5C glycol, then deaminates to form thymine glycol (52, 53). Oxidative stress can contribute to tumor development not only through genetic but also through epigenetic mechanisms. As noted earlier, the presence of hydroxyl radicals can cause a wide range of DNA lesions including base modifications, deletions, strand breakage and chromosomal rearrangements. Such DNA lesions have been shown to interfere with the ability of DNA to function as a substrate for the DNMTs, resulting in global hypomethylation (54). The presence of 8-OHdG in CpG dinucleotide sequences has been shown to strongly inhibit methylation of adjacent cytosine residues (55, 56). In addition, 8-OHdG may not be recognized by proof-reading enzymes and thus may persist as a mutation resulting in G→T transversions (57, 58). These studies suggest that oxidative DNA damage can affect patterns of DNA methylation leading to aberrant gene expression and possibly contributing to the development of malignancy.

Hereditary cancer genes and cancer predisposition

Studies of familial cancer have identified a group of genes whose mutational inactivation results in predisposition to a characteristic spectrum of cancers. The tumor-suppressor gene, *RB* which is mutated in retinoblastoma, was the first hereditary cancer gene to be identified. Subsequently, other tumor-suppressor genes operating through a diverse range of mechanisms were identified in other familial cancers, e.g. adenomatosis polyposis coli *(APC)* mutations were identified in cases of familial adenomatous polyposis coli and $p16^{INK4a}$ mutations were identified in cases of familial melanoma (59). DNA repair genes such as the *BRCA1*, *MLH1*, and *MSH2* are also often involved in predisposition to familial cancer (60, 61). Specific allele sequence variants such as single nucleotide polymorphisms (SNPs) affect the probability of CpG islands methylation in the *cis* region. *Cis*-acting DNA

mutations have been shown to cause constitutional epi-mutations early in cancer development (62). One example of epigenetic silencing caused by sequence alterations in *cis* is the methylation of expanded CGG repeats within the *FMR1* promoter in the fragile X mental retardation syndrome (63). Little is known about what causes variation in methylation levels and how this variation relates to future pathogenesis. Genetic factors may play key roles in maintaining a normal methylation pattern, but environmental factors also play an important role. Polymorphisms in *MTHFR*, *DNMT3b*, and *MTR* genes, involved in methyl metabolism or DNA methylation, are some of the obvious genetic candidates for variation in methylation in both normal and tumor tissues (64).

Epigenetic biomarkers

Methylated DNA sequences represent potential bio-markers for diagnosis, staging, prediction of prognosis and monitoring of response to therapy. Epigenetic markers can be evaluated in resected tumors or in body fluids (65). For example, the frequency of occurrence of hypermethylated *CDH13*, *MYOD1*, *MGMT*, *p16* ^{INK4a} and *RASSF1A* genes varies significantly among cancer types. These changes can be detected in plasma DNA and urine. Recently, combined hypermethylation assays for small number of genes such as *RASSF1A*, *RARβ2*, *APC* and *GSTP1* have been used to discriminate between benign and cancerous changes in the prostate (66, 67). Furthermore, repetitive DNA elements such as SINEs and LINEs and other repetitive sequences are often hypomethylated. Their presence has been used to characterize some human cancers, but their clinical utility remains questionable (68).

Histone modification patterns also provide prognostic and diagnostic information in cancer. Repressive chromatin structures characterized by particular histone modifications such as H3K9, H3K27 and H4K20 methylation may precipitate DNA methylation. Generalized changes in chromatin structure and histone modification, such as increased H3K4 dimethylation and H3K18 acetylation activation, are associated with poor prognosis (69). Whether the extent of these changes correlates with alteration in gene activity is a major limitation.

More recently, miRNA has been proposed as potential epigenetic biomarkers in the diagnosis of cancer. Some of the miRNA such as miR-199a, miR-200a, miR-146, miR-214, miR-221 and miR-222 have been found to be upregulated, whereas miR-100 is down-regulated in human cancers (44). The miRNA let-71 has been recently designated as a tumor-suppressor and miR-429, miR-200a and miR-200b were found to be clustered on a single primary transcript regulated by the epithelial-to-mesenchymal transition (70). Studies have shown that two other miRNAs, miR-21 and miR-181a can be used to identify the presence or absence of a malignant phenotype. A group of 27 miRNA has been shown to be significantly associated with chemotherapy response and proposed as possible prognostic and diagnostic biomarker (71, 72).

Conclusions

The epigenetic modification patterns associated with the development and progression of cancer are potentially clinically useful. The development of DNA methylation markers may prove useful for early cancer detection, establishing a diagnosis of cancer, or predicting the prognosis in cancer cases. Recent advances in epigenomic approaches allow mapping of the methylation/acetylation state and miRNA levels in the genome with high accuracy, which may help in the identification of biomarkers for various diseases. Understanding the molecular events that initiate and maintain epigenetic gene silencing could lead to the development of clinical strategies for the prevention and therapy of cancer.

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Table 1

DNA methylation gene changes in various human cancers

DNA methyltransferase	Function	Alterations	Cancer type
DNMT 1	Maintenance of methylation, repression of transcription	Upregulation, mutation	Colorectal cancer, ovarian cancer
DNMT3a	*De novo* methylation during embryogenesis, imprint establishment, repression	Upregulation	Colorectal cancer, breast cancer, ovarian cancer, esophageal squamous cell carcinoma
DNMT3b	*De novo* methylation during embryogenesis, repeat methylation repression	Upregulation	Breast cancer, hepatocellular carcinoma, colorectal cancer,
DNMT3L	Interacts with DNMT3a &b and facilitate methylation	Upregulation	
Methyl-CpG- binding proteins			
MeCP2	Transcription repression	Upregulation, Mutation	Prostate cancer, Rett syndrome,
MBD1	Transcription repression	Upregulation, Mutation	Prostate cancer, colon cancer, lung cancer
MBD2	Transcription repression	Upregulation, Mutation	Prostate cancer, colon cancer, lung cancer
MBD3	Transcription repression	Upregulation, Mutation	Colon cancer, lung cancer
MBD4	DNA repair, glycosylase domain, repair of deaminated 5-methylC	Upregulation, Mutation	Colon cancer, gastric cancer, endometrial cancer
Kaiso	Transcription repression	Upregulation	Colon, intestinal, lung cancer

DNMT, DNA methyltransferase; MBD, methyl-CpG-binding domain.

Table 2

Histone modification genes altered in various human cancers

Histone deacetylases	Alterations	Cancer type
HDAC1	Upregulation/Downregulation	Colorectal cancer, cervical dysplasias, endometrial stromal sarcomas, gastric carcinomas, colon cancer
HDAC2	Upregulation/Mutation	Multiple gastric carcinomas, colon cancer
HDAC3	Upregulation	Colon cancer
HDAC4	Upregulation/Downregulation /Mutation	Prostate, breast and colon cancer
HDAC5	Under expression	Colon cancer, AML
HDAC6	Upregulation	Breast, AML
HDAC7	Upregulation	Colon cancer
HDAC8	Upregulation	Colon cancer
SIRT1	Upregulation/Downregulation	Colon cancer
SIRT2	Downregulation, Deletion	Glioma
SIRT3	Upregulation	Breast cancer
SIRT4	Downregulation	AML
SIRT7	Upregulation	Breast, thyroid carcinoma
Histone acetyl transferases		
P300	Mutation, Translocation, Deletions	Colorectal, breast, ovarian, hepatocellular and oral carcinomas,
CBP	Mutation, Translocation, Deletions	Colon, breast, ovarian and AML
PCAF	Mutation	Colon
MOZ	Translocation	Hematologic malignancy
MORF	Translocation	Hematologic, uterine leiomyomata
Tip60	Downregulation, translocation	Colorectal, prostate cancer
GCN5	Downregulation, mutation	Prostate, breast ovary
PCAF	Rare mutation	Colon cancer
HBO1	Upregulation	Testis, breast, ovary and bladder cancer
Histone methyltransferase		
MLL1	Translocation, Amplification	Hematologic malignancies
MLL2	Amplification	Glioma, pancreatic cancer
MLL3	Mutation, Deletion	Hematologic malignancies, colon cancer
MLL4	Amplification	Solid tumor
SUV39H1-2	Mutation overexpression	Ovarian, colon
G9a	Gene Repression	Colon, gastric, breast cancer
RIZ1/ PRDM2	Underexpression, Mutations	Colorectal, gastric cancer
EVI1	Chromosomal rearrangement	Myeloid leukemia
EZH2	Amplification, Upregulation	Prostate, breast ovarian cancer
SUZ12	Upregulation	Prostate, breast ovarian cancer
BMI1	Upregulation	Prostate, breast ovarian cancer
NSD1	Translocation, Upregulation	AML
NSD2	Translocation	Multiple myeloma
NSD2	Translocation	Multiple myeloma
NSD3	Translocation, Amplification	AML, breast cancer

Histone deacetylases	Alterations	Cancer type
SYMD2	Upregulation	Breast, colon cancer
DOT1	Upregulation	AML
Histone demethylases		
LSD1/BHC110	Downregulation	Breast cancer
JARID1A-D	Upregulation /Inactivation mutation	Leukemia, prostate, breast renal carcinoma
JHDM2a, 2b	Upregulation	T-cell lymphoma
JMJD2A/JHDM3A	Upregulation	Squamous cell carcinomas, lung cancer
JMJD3	Downregulation	Lung, liver cancer
UTX	Inactivation mutation	Squamous cell carcinomas, renal cell carcinomas

CBP, CREB binding protein; Dot1, disruptor of telomeric silencing EZH2, enhancer of zest homolog2; Gcn5, general control nonderepressible; HBO1, histone acetyltransferase binding to ORC1; HDAC, histone deacetylase; JARID, Jumonji, AT-rich interactive-domain JHDM, JmjC domain-containing histone demethylase 1; JMJD, Jumonji domain containing 2; LSD1, lysine specific demethylase 1; MLL, myeloid/lymphoid or mixedlineage leukemia-associated protein; Morf, *MOZ*-related factors; MOZ, monocytic leukemia zinc finger protein; NSD1, nuclear receptor-binding SET-domain protein 1; p300, E1A binding protein p300; PCAF, p300/CBP-associated factor; PRMT, protein arginine methyltransferase 1; RIZ1, retinoblastoma protein-interacting zinc finger 1; SIRT, Sir2 histone deacetylase gene family; SMYD2, split SET/MYND domain-containing histone H3 lysine 36-specific methyltransferase; SUV39H, suppressor of variation 3–9 homolog; TIP60, human HIV-1 Tat interactive protein 60; UTX, ubiquitously transcribed tetratricopeptide repeat, X chromosome.

Table 3

MicroRNAs alteration in various human cancers

MicroRNAs	Target gene(s)	Alterations	Cancer type
miR-127	Bcl-6	Upregulation	Bladder cancer
miR-124	CDK6	Upregulation	Colon cancer
miR-223	NFI-A, MEF2C	Upregulation	Acute myeloid leukemia
miR-34b/34c	p53 network, CDK6, E2F3	Upregulation	Colon cancer
miR-17, miR-92	c-MYC	Upregulation	Lung cancer
miR-372, miR-373	RAS, p53,CD44	Upregulation	Testicular germ cell tumor and breast cancer
miR-21	PDCD4, PTEN, TPM1, REC, TIMP3, BCL2	Upregulation	Glioblastoma, breast, lung, prostate,
miR-155	RHOA	Upregulation	Burkitt's lymphoma, breast, colon, and lung cancers
miR-146	NF-κB	Upregulation	Breast, pancreas and prostate cancers
miR-92b	PRMT5	Upregulation	Brain primary tumors
miR-520	CD44	Upregulation	Breast cancer
miR-10b	HOXD10	Upregulation	Metastatic breast cancer
miR-9	CDH1	Upregulation	Breast cancer
miR-127, miR-199a	BCL6, E2F1	Upregulation	Cervical cancer
miR-421	CBX7, RBMXL1	Upregulation	Gastric cancer
miR-1228, miR-195, miR30b, miR-32, miR345	CDKN2A, NF2, and JUN	Upregulation	Malignant mesothelioma
miR-190, miR-196	HGF	Upregulation	Pancreatic cancer
miR-125	AKT, ERBB2-4, FGF, FGFR, IGF, MAPKs, MMP11, SP1, TNF, VEGF	Upregulation	Breast cancer
miR-29	DNMT3a&b	Upregulation	Lung cancer
miR-1	FoxP1	Upregulation	Hepatocarcinoma
miR-9-3	E-cadherin	Upregulation	Colorectal, melanoma, head and neck cancer
miR-34a	CD44, Notch1	Upregulation	Hematological, prostate, breast cancer
miR-181c	Notch4, K-Ras	Upregulation	Gastric, colorectal cancer
miR-200c, miR-141, miR-429	ZEB1/ZEB2	Upregulation	Colorectal, breast, lung cancer
miR-126	CRK1, PIK3R2, SPRED1, VCAM1	Downregulation	Breast and lung cancer
miR-146a, miR-146b	ROCK1, IRAK1, TRAF6	Downregulation	Prostate cancer and papillary thyroid carcinomas
miR-340, miR-421, miR-658	MYC, RB, PTEN	Downregulation	Lymph node metastasis and gastric cancer
let-7a-3	RAS, IGF-II	Downregulation	Lung and ovarian cancer
miR-221, miR-222	CDKN1C/P57 and CDKN1B/P27	Downregulation	Hepatocellular carcinoma
miR-9	NF-κB	Downregulation	Ovarian and lung cancer
miR-218, miR-145	PXN	Downregulation	Breast, lung and prostate cancer
miR-25, miR-32, miR-142	ITGAα1	Downregulation	Lung cancer and solid tumor
miR-124, miR-183	ITGBβ1	Downregulation	Lung cancer
miR-143	ERK5	Downregulation	Cervical cancer
miR-372, miR-373	LATS2	Downregulation	Testicular germ cell cancer

MicroRNAs	Target gene(s)	Alterations	Cancer type
miR-181	VGFR	Downregulation	Lung cancer
miR-370	MAP3K8	Downregulation	Cholangiocarcinoma
miR-342	ER, PR and HER2	Downregulation	Breast and colon cancer
miR-145	ER	Downregulation	Colon and breast cancer
miR-124, miR-183	ITGB1 β	Downregulation	Lung cancer
miR-101	EZH2	Downregulation	Prostate, breast , Lung
miR-143	DNMT3a	Downregulation	Colorectal cancer
miR-9-1	FGF family	Downregulation	Breast, ovarian, pancreas cancer
miR-137	CDK6, E2F6, LSD	Downregulation	Glioblastoma, oral, colorectal cancer
miR-129-2	SOX4	Downregulation	Gastric, endometrial, colorectal cancer
miR-145	OCT/SOX2/KLF	Downregulation	Prostate cancer
miR-148	TGIF2	Downregulation	Colorectal, melanoma, head and neck cancer
miR-199a	IKKB	Downregulation	Hepatocarcinoma, testicular ovarian cancer
miR-203	ABL1	Downregulation	Hematological, liver cancer
miR-205	ZEB1/ZEB2	Downregulation	Bladder, breast, prostate cancer
miR-335	SOX4/TNC	Downregulation	Breast cancer
miR-342	PDGFRA	Downregulation	Ovarian, breast cancer

BCL2, B-cell lymphoma 2 protein; CBX7, chromobox 7; CD44, cluster differentiation 44; CDH1, cadherin-1; CDK6, cyclin D kinase 6; CDNK2A, cyclin-dependent kinase inhibitor 2A; CRK1, Cdc2-related kinase1; ER, estrogen receptor; ERBB2-4 or (HER4), human epidermal growth factor receptor 4; ERK5, extracellular signal-regulated kinase 5; FGFR, fibroblast growth factor receptor; FOXP1, forkhead box protein O1; HGF, hepatocyte growth factor; HOXD10, homeobox D10; IGF-II, insulin-like growth factor 2; IRAK1, interleukin-1 receptor associated kinase-1; KLF, Kruppel-like factors; LATS2, large tumor-suppressor, homolog 2; MAPKs, mitogen-activated protein kinase; MEF2C, myocyte enhancer factor 2C; MMP11, matrix metalloproteinase11; NF2, neurofibromatosis, type 2; NFIA, nuclear factor 1 A-type; NF-kB, nuclear factor-κB; OCT4, octamer-binding transcription factor 4; P53, tumor protein 53; PDcD4, programmed cell death 4; PDGFRA, alpha-type platelet-derived growth factor receptor; PIK3R2, Phosphatidylinositol 3-kinase regulatory subunit beta; PR, progesterone receptor; PRNT5, protein arginine *N*-methyltransferase 5; PTEN, phosphatase and tensin homolog; PXN, paxilin; ITGβ1, integrin beta-1; RAS, rat sarcoma; Rb, retinoblastoma; RBMX L1, RNA binding motif protein X-linked; RECK, reversion inducing cysteine rich protein kazal Motif; ROCK1, rho-associated, coiled-coil containing protein kinase 1; ROHA, Ras homolog gene family member A; SOX4, SRY (sex determining region Y)-box 4; SPRED1, sprouty-related, EVH1 domain containing 1; TNFα, tumor necrosis factor-alpha; TPM1, tropomyosin 1; TRAF6, TNF receptor associated factor 6; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; ZEB1, zinc finger E-box-binding homeobox 1.