SnapShot: MicroRNAs in Cancer

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Cell

Human MicroRNAs	Deregulation in Cancer	Molecular Mechanisms, Targets	Diagnostic, Prognostic Marker
***let-7* family** (various)	Downregulated in lung, breast, gastric, ovary, prostate and colon cancers, CLL, leiomyomas; *miR-98* downregulated in head and neck cancer. Point mutation in *let-7e* transcript affects miRNA maturation.	Repress cell proliferation and growth. *let-7f* promotes angiogenesis. Targets: CCND1, CDC25a, CDC34, CDK6, CRD-BP, DICER, HMGA2, HOXA9, IMP-1, ITGB3, MYC, RAS, TLR4.	SNP in K-RAS 3′ UTR (*let-7a* binding site) increases NSCLC risk (cancer predisposition). Low expression of *let-7a-2* in lung and ovarian cancer and of *let-7b* in uveal melanoma (poor prognosis). *let-7i* affects chemotherapy potency. Intranasal delivery of *let-7a* reduces growth of Ras-induced mouse lung tumors.
	let-7a-3 hypomethylated in lung adenocarcinoma; overexpressed in AML	*let-7a* represses NF2 and decreases chemotherapy-induced apoptosis in vitro. Target: CASP3.	
miR-10b (2q31.1, intergenic)	Downregulated in breast cancer. Overexpressed in metastatic breast cancer (does not predict metastasis in early stages).	Activates cell migration and extracellular matrix remodeling. Target: HOXD10.	
***miR-15a, miR-16-1* cluster** (13q14.3, intron 4 noncoding RNA *DLEU2*)	Downregulated in CLL, DLBCL, multiple myeloma, pituitary adenoma, prostate and pancreatic cancer. Germline mutations in B-CLL patients and in NZB mice that develop CLL-like disorder.	Induce apoptosis in leukemia cells. *miR-16* regulates cell cycle by downregulating G0/G1 proteins. Targets: BCL2, CAPRIN1, CARD10, CCND1, CDK6, CDC27, CGI-38, CYCE, DMTF1, HMGA2, MCL1, MYB, NGN2, VEGF, WNT3A.	Low expression of *miR-15a*, *miR-16* in de novo CLL (good prognosis). *miR-16* modulates chemotherapy potency, sensitivity to vincristine in gastric cancer (predicts response).
	Upregulated in nasopharyngeal carcinoma	Target: BRCA1	
***miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-17-92* cluster** (13q31.3, intron 3 C13orf25)	Overexpression in lung and colon cancer, lymphoma, multiple myeloma, medulloblastoma	*miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1* increase tumor growth and tumor vascularization; *miR-20a* is antiapoptotic; transgenic *miR-17-92* mice develop lymphoproliferative disease and autoimmunity. Targets: AIB1, AML1, BIM1, CTGF, CDKN1A, E2F1, E2F2, E2F3, HIF-1A, PTEN, TGFBR2, TSP1, Rb2/P130.	High plasma levels of *miR-92* discriminate colorectal and gastric cancer from normal (diagnostic)
	LOH at *miR-17-92* locus in melanoma (20%), ovarian (16.5%) and breast (21.9%) cancer	*miR-17* reduces breast cancer cell proliferation. *miR-20* induces senescence via LRF. Targets: AIB1, CYCD1.	
***miR-106b-93-25* cluster** (*7q22.1*)	Overexpression in gastric, colon, and prostate cancer, neuroblastoma, multiple myeloma	Reduces apoptotic response after TGFβ stimulation via BIM. Targets: CDKN1A, E2F1, BIM.	
miR-21 (17q23.1, 3′UTR TMEM49)	Overexpression in glioblastoma, breast, lung, prostate, colon, stomach, esophageal, and cervical cancer, uterine leiomyosarcoma, DLBCL, head and neck cancer	*miR-21* knockdown induces apoptosis in glioblastoma. *miR-21* induces invasion, metastasis in colorectal cancer. Targets: BCL2, MASPIN, PDCD4, PTEN, TPM1, RECK, RASA1.	*miR-21* high expression in colon, breast, and pancreatic cancer (poor prognosis). *miR-21* high expression in de novo DLBCL (good prognosis). *miR-21* modulates chemosensitivity in NCI60 cells.
***miR-29* family** (various)	Downregulation in CLL, colon, breast, and lung cancer, and cholangiocarcinomas	Induce aberrant methylation in lung cancer via DNMT3A,B; induce apoptosis via p53 and MCL1. Targets: CDC42, DNMT3A, B, MCL1, PIK3R1, TCL1.	*miR-29c* low expression correlates with short time from diagnosis to therapy in CLL (poor prognosis)
	Upregulation in breast cancer	Induces EMT transition, metastasis. Target: TTP metallopeptidase.	
***miR-34* family** (1p36.23, 11q23.1, intergenic)	Downregulated in pancreatic cancer and Burkitt's lymphoma without MYC translocation. Hypermethylation of *miR-34b,c* in colon cancer.	*miR-34a* induces upregulation of p53, downregulation of E2F in colon cancer. Targets: BCL2, CCND1, CCNE2, CDK4,6, MYC, DLL1, E23, Notch1, MYCN, MET, HMGA2, SIRT1.	*miR-34a* low expression in CLL associated with p53 inactivation, chemotherapy-refractory disease (predicts response)
miR-101 (1p31.3, 9p24.1)	Downregulation in prostate cancer, hepatocellular carcinoma, and bladder cancer	Alterations in global chromatin structure via repression of EZH2. Targets: COX2, EZH2, MCL1.	
miR-122a (18q21.31 intergenic)	Downregulation in hepatocellular carcinoma	Targets: CAT-1, CCNG1	
***miR-124a* family** (various)	Hypermethylation in colon, breast, gastric, and lung cancer, leukemia, lymphoma	Targets: CDK6, ITGB1, FOXA2, LAMC1, MTPN, MAPK14	
miR-125a, miR-125b (various)	Downregulation in glioblastoma, breast, prostate and ovarian cancer	Targets: ERBB2, ERBB3, LIN28, LIN41, TNFSF4	
	Upregulation in myelodysplastic syndrome and AML with t(2;11)(p21;q23), urothelial carcinoma	Target: p53	
miR-127 (14q32, RTL1 exon)	Hypermethylation in tumor cell lines	Targets: BCL6, RTL1	
***miR-143, miR-145* cluster** (intergenic, 5q32)	Downregulated in colon adenoma/carcinoma, in breast, lung, and cervical cancer, in B cell malignancies	*miR-143*, *miR-145* precursor sequences abnormally processed in colon cancer. Targets: MYC, ERK5, HOXA9, KRAS, PARP8.	
miR-155 (21q21.3, exon 3 ncRNA BIC)	Overexpressed in pediatric Burkitt's lymphoma, Hodgkin's lymphoma, primary mediastinal lymphoma, DLBCL, breast, lung, colon, pancreatic cancer	Pre-B cell proliferation, lymphoblastic leukemia/high-grade lymphoma in *miR-155* transgenic mice. Targets: AGTR1, AID, IKBKE, TP53INP1.	High expression of *miR-155* in lung cancer, DLBCL, and aggressive CLL (poor prognosis)
***miR-181* family** (various)	Overexpressed in breast, pancreas, prostate cancer	MYCN regulates transcription of *miR-181* cluster. Targets: HOXA11, TCL1.	Low expression of *miR-181* in aggressive CLL with 11q deletion (poor prognosis)
***miR-221, miR-222* cluster** (Xp11.3, intergenic)	Overexpressed in CLL, thyroid papillary carcinoma, glioblastoma. Downregulated in AML.	Promotes cancer cell proliferation; *miR-221, miR-222* impair TRAIL-dependent response. Targets: c-KIT, P27, CDKN1B, P57, CDKN1C, ESR1.	
***miR-200* family** (various)	Downregulated in clear-cell carcinoma, metastatic breast cancer	Promote invasion together with *miR-205*. Downregulation of *miR-200* family (and *miR-205*) directly involved in TGFβ-mediated EMT. Targets: ZEB1, 2; TGFβ.	
***miR-372, miR-373* cluster** (19q13.41, intergenic)	Overexpression of *miR-373* in testicular cancer	Indirectly antagonize p53-mediated CDK inhibition during RAS-induced senescence. *miR-373* transactivates *CDH1* transcription by targeting the promoter region. Targets: LATS2, CD44.	High expression of *miR-372* in NSCLC (poor prognosis)

Antitumorigenic
Oncogenic

See online version for legend and references.

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MicroRNAs (miRNAs) (http://microrna.sanger.ac.uk/sequences/) are 19 to 25 nucleotide-long noncoding RNA molecules that regulate gene expression both at the level of messenger RNA degradation and translation. MicroRNAs are typically excised from a 60 to 110 nucleotide-long hairpin precursor (fold-back) RNA structure (pre-miRNA) by the RNase III enzyme Dicer and are incorporated into the RNA-induced silencing complex (RISC). The pre-miRNA sequence is transcribed from a larger Pol II primary transcript (pri-miRNA) processed by Drosha and exported from the nucleus to the cytoplasm. Strongly conserved among distantly related organisms (including invertebrates, vertebrates, and plants), miRNAs are involved in a variety of biological processes including cell cycle regulation, differentiation, development, metabolism, neuronal patterning, and aging. Alterations in miRNA expression are involved in the initiation, progression, and metastasis of human tumors. Functional germline mutations in the *miR-15a* and *miR-16-1* cluster are associated with familial chronic lymphocytic leukemia (CLL) and breast cancer, whereas a common SNP in *pre-miR-146a* decreases mature miRNA expression and predisposes to papillary thyroid carcinoma. Furthermore, *miR-155* transgenic mice show proliferation of pre-B cells and develop lymphoblastic leukemia/high-grade lymphoma. Mice overexpressing *miR-17-92* in lymphocytes develop lymphoproliferative disease and autoimmunity and die prematurely. During cancer progression, dramatic overexpression or downregulation of mature and/or precursor miRNAs occurs in most tumors. The miRNAs *miR-10b*, *miR-373*, and *miR-520c* promote tumor invasion and metastasis, whereas *miR-335*, *miR-206*, and *miR-126* are suppressors of breast cancer metastasis. The differential expression of miRNA genes in malignant compared with normal tissue can be explained by three different mechanisms: location of miRNAs in cancer-associated genomic regions, epigenetic mechanisms, and alterations in the miRNA processing or transcription machinery. The *let-7* miRNA family and the *miR-15a*/*miR-16-1* clusters are located in loci deleted in lung cancer and CLL, respectively; the *miR-17-92* genomic locus is amplified in B cell lymphoma. The miRNA *miR-127* is re-expressed after DNA demethylation and histone deacetylase inhibition in cancer cells; *miR-124a* is transcriptionally inactivated by hypermethylation of CpG islands in different tumor cell lines. Impaired miRNA processing enhances cellular transformation and tumorigenesis, as shown by the conditional deletion of Dicer1, which increases tumor development in a K-Ras-induced mouse model of lung cancer. Moreover, reduced expression of Dicer and Drosha has been observed in various human cancers. Several transcription factors regulate the expression of miRNAs, e.g., the tumor suppressor protein p53 regulates the expression of *miR-34* family members, MYC is a negative regulator of miRNA expression, STAT3 regulates *miR-21* expression at the transcriptional level, and Twist transactivates *miR-10b* transcription.

The functional consequences of altered patterns of miRNA expression are just starting to be understood. Self-sustaining growth signals can be induced by *miR-21* overexpression, which is responsible for *PTEN* repression and loss of negative regulation by AKT kinase. Insensitivity to antigrowth signals is achieved by inhibition of E2F transcription factors caused by overexpression of the *miR-17-92* cluster on chromosome 13q31.1 and by overexpression of the *miR-106b-25* cluster on chromosome 7q22.1. Specifically, *miR-20a* inhibits expression of *E2F2* and *E2F3*, whereas *miR-17-5p*, *miR-20a*, *miR-106b*, and *miR-92* inhibit expression of *E2F1*. Modulation of apoptosis may occur by direct regulation of miRNAs by proapoptotic (p53 and *miR-34* family) or antiapoptotic (IL6/STAT3 and *miR-21*) pathways, or by direct targeting of antiapoptotic (BCL2, MCL1 proteins and the *miR-15/16* cluster) or proapoptotic (TP53BP1 and *miR-155*) proteins. Deregulation of telomerase activity can be achieved in tumors through reduced expression of *miR-138*, which represses translation of *TERT* mRNA and induces unrestricted proliferation. Blood vessel formation (angiogenesis) is regulated by miRNAs, and hypoxia is a proven regulator of miRNA expression. The oncomi*R-17-92* cluster that is regulated by MYC participates in the creation of a more aggressive, richly perfused tumor phenotype, whereas hypoxia contributes to the modulation of miRNA expression (including *miR-210*) partly by direct transcriptional activation of HIF-1 by specific miRNAs. Due to the specificity of targets and regulatory mechanisms, an miRNA may be an oncogene in one tumor type but a tumor suppressor in another.

MicroRNA expression profiling of human tumors has identified signatures that are associated with diagnosis, prognosis, and treatment efficacy. Distinct miRNA fingerprints characterize highly aggressive cancers, e.g., overexpression of *miR-155* and downregulation of *let-7* miRNAs in lung cancer cells indicates a poor prognosis. Furthermore, miRNA profiling can be used to successfully classify poorly differentiated tumors, including those with an unknown primary site. For example, high expression of *miR-21* is associated with poor survival and a poor therapeutic response to chemotherapy in colon cancer patients. The development of agents that block or mimic the expression and functions of miRNAs may represent a new therapeutic option for treating cancer patients.

Abbreviations

AID, activated induced cytidine deaminase; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; EMT, epithelial-mesenchymal transition; LOH, loss of heterozygosity; LRF, leukemia/lymphoma-related factor; NSCLC, non-small cell lung cancer; NZB, New Zealand Black; TTP, ADAM metallopeptidase with thrombospondin type I motif.

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