MicroRNA’s in cancer as biomarkers and therapeutic keys

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Abstract
MicroRNA (miRNA), the noncoding RNAs, are short length with 22 nucleotides. It involved in various biological process. Its expression is found varied in cancer and hence used as a marker. miRNAs are become important entity that changes the expression of genes in disease particularly cancer. In this review, different types of miRNAs were addressed with its relationship in different types of cancer. The level of expression miRNA is depends upon the different stages and could be used as a marker for early diagnosis. The circulating as well as exosome miRNA in cancer was also discussed. This review could facilitates us to study the miRNA as biomarker and it additionally paves way for therapeutic approaches.

Background
A couple of decades ago, provenances of microRNA (miRNA) discovery lead to the new arena in molecular biology. In humans, more than 2000 miRNAs were discovered and it regulate more than 25% of the genes. It’s often well connected with various diseases and hence they are useful for diagnosis [1]. miRNAs, the noncoding RNAs, are short length with nearly twenty two nucleotides. It is found in eukaryotes and they are part of all pathways in our biological system [2]. It controls the cellular process such as cell cycle, inflammation, cell differentiation and cell death, through inhibition of mRNAs stability and translation. Hence, this miRNAs are inevitable in all biological process and signaling in a cell. Its dysregulation is often leads to genesis of cancer [3].

The first miRNA was discovered in the year 1993 and was outcome of the two different studies reported Lin-4 as small non coding RNA from Ceanorhabditis elegans heterochronic gene lin-4 [4]. At that time, this small non coding RNA was considered as a specific tool used by the worms to manage their heterochronic gene expressions. After 7 years, Reinhart et al. [5] other small ncRNAs in C. elegans represented Let-7, the heterochronic gene. They together with lin-4 RNA were initiating the cascades of heterochronic genes regulation via RNA-RNA interaction at 3’ untrasnlated region of the gene target [5]. It lead to trace the other small ncRNA and it unveiled the existence of ncRNAs in different organisms in which it plays as potential regulatory control and then named as microRNAs [6–8]. Later it was identified that they are all inhabitant of plants, animals and now miRNA database revealed a total of 2042 and 1281 mature RNAs in human and mouse respectively [9]. In mammals, miRNAs genes have paralogue, i.e., different isofoms while it is well conserved in animals. There were 8 isoforms were existing in 11 genomic loci. Interestingly, in C. elegans almost 55% of the miRNAs were found similar to humans. The majority of miRNA gene occupy regions away from annotated gene often due to one transcriptional unit. Over 50% of the miRNA genes are clustered and normally transcribed as multicistronic RNA transcript. In animals, it constitute a gene regulatory molecule and had impact on gene expres- sion and thus in cancer it exert unique role in phenotype of the disease [3]. In cancer, miRNA play a role in disease initiation, movement of cell from site of origin, disease prognosis and response during treatment [10].

Main text
Biogenesis
The biogenesis of miRNA starts with the formation of pri-miRNA, the long transcript. The RNA polymerase II...
transcribe the pri-miRNA and keep the mRNA with all its features (5′ Cap and 3′ Poly(A) tail) [11, 12]. Similarly, genomic repeats also generate set of miRNAs through other pathways i.e., In Alu repeats, the RNA polymerase III transcribe the miRNA [13]. Pri-miRNA to pre-miRNA formation occurs in nucleus with the help of RNase III (Drosha) and DGCR8, its partner [14–16]. DGCR8 generate the pre-miRNA, hairpin shaped, by cutting the stem from stem-ssRNA junction [17, 18].

**Biological roles Of miRNAs**

The Dicer and DGCR8 deficient mouse model are the first initiative to explore the significance of miRNAs in developmental stages of mammals since biogenesis of miRNA associated with DGCR8. Break in any of the step in biogenesis of miRNA is found lethal to embryo [19, 20]. Its, any of the genes, loss of function in tissues also causes developmental dysfunction in associated tissues [21]. Mouse models with miRNA knockout already demonstrated its, the genes, role in all tissue type and its associated developmental defects [21, 22].

**Dysregulation of miRNAs**

Literatures portray the existence of miRNA role either in up-regulation or down regulation in diseases experienced by human. MiRNA dysregulation often thought to be linked with one of the factor in progression of disease. In cancers, its altered expressions were highly reported [1]. The list of miRNA’s expressed in breast, esophageal and gastric caner are listed in Table 1.

**Cancer**

**Breast cancer**

**Oncogenic miRNA** In cancer, upregulation of oncogenic miRNA was frequently noticed and they deliver its action through suppressing the tumor suppressor gene that regulates the normal cell regulatory and cleaning process such as apoptosis etc. [42]. The following are the some of the miRNAs recorded in breast cancers.

**miR-10 family** miR-10a, 10b are the members of miR-10 family resides in Hox cluster. In murine xenograft breast cancers model, miR-10b is, found over expressed, inducing metastasis and invasion through HOXD10 gene [23]. Its expression level was found positively associated with all clinical features such as size of the tumor, proliferation, stages, metastasis while it is negatively associated with PR+, ER+ and level of E-cadherin. Its, miR-10b, transcription factor enhances invasion and metastatic ability through HOXD10 in cell lines and animal models [23, 43, 44].

**miR - 21** It is also involved in breast cancer cell migration and invasion [45, 46]. Chan et al. recorded higher miR-21 level in tumor tissue of human glioblastoma and generated cell line out of it. It helped them to compare it with brain tissues of fetal and adult non neoplastic tissues [24]. Besides miR-21, miR-125b, 145, 155 expressions were also noticed aberrantly in breast cancer [47]. Its, miR-21, upregulation is found correlated with increasing in grade of the tumor, status of the receptors of hormones and ductal carcinoma.

**miR-17-92** A polycistron, comprising mature miR-18b, 19b, 20a, 92, 93, 106 [48]. miR-17-5p is found elevated in invasive breast cancer cells (MDA-MB-231) while not expressed in MCF-7 (non invasive) cells. miR-17-5p target the HBP1-beta catenin pathway in MCF-7 cell to perform as highly invasive and migratory when ectopically expressed while this miRNA, in in vitro, is suppressing the MDA-MB-231 cell and inhibit the cell migration and invasion [25].

**Tumor suppressor** In C. elegans embryogenesis importance of let-7 family in determination of cell type was noticed by Reinhart et al. [49]. It consists of let-7a-g, miR-98 and miR-202. It involved in various physiological such as development, cell adhesion, muscle formation and gene expression regulation. Let-7 family is found lost during early disease progression stage in breast cancer [28].

**miR-200 family** It consists of miR-200a, 200b, 200c, 141 and miR-429. These are EMT suppressors [50–52]. They were found lost in mesenchymal phenotypic cell lines of invasive breast cancer. The drug resistances found in human breast cancers were found linked to miR-200 down regulation [27].

**miR-205** It is found down regulated in triple negative breast cancer cell [26, 52]. Its expression prevents the growth and development of the breast cancer cell. Triple negative breast cancer cell can be protected by miR-205 as tumor suppressor. Its expression supports the inhibition of different physiological mechanisms of the cell in in vitro and in vivo.

**miR-145** It is found down regulated in breast cancer tissues compared to normal breast tissue in a study by Iorio et al. [47]. It is often used as early diagnostic biomarker due to its expression pattern in breast cancer [28, 53].

**Esophageal cancer**

**Oncogenic miRNA**

**miR-21** It, used for the ESCC prognosis, has strong relationship with development of EAC and ESCC. In many
human cancers, it is highly expressed. It has strong control over PTEN, tropomysin-1, programmed cell death 4 and maspin that are regulators of survival, invasive and apoptosis [29].

**miR-10b**

It is a polycistronic and found in chromosome 7q22.1. It encodes miR-25, 93 and miR-106b. It is found upregulated in NSE and from which to BE and EAC. It is also shows potential cell development, anti-apoptotic as well as enhance the cell cycle in in vitro and in vivo tumorigenic activity [54]. miR-25 targets the E-cadherin gene at 3’UTR and enhances migration and cell invasion in ESCC. This miR-25 showed the oncogenic activity by inhibiting CDH1.

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miR-196a
In premalignant esophageal cancers tissues, its expression was found high as well as in different cancer types [33, 61–66]. In EC, Annexin A1 was targeted by this miRNA to suppress its function [65–67]. It function as factor of cell proliferating and factor of anchorage independent growth and thus inhibit the apoptosis.

Tumor suppressor miR-375
In EC, it function as PDK1 regulator (negative) and its promoter regions is hypermethylated adequately [68]. In mice, its role as inhibitors of motility of cell, proliferation of cell, formation of tumor, clonogenicity and metastasis was noticed. Its interaction with IGFIR 3′ UTR often down regulates it and both are negatively correlated [35].

miR-145
It is induced by p53, the tumor suppressor and it targets the c-Myc [69]. Another gene called FSCN1, which was expressed highly in ESCC (tumors) while not in normal epithelium, was also found recorded as target gene for this miRNA. The reduction in the prognosis and metastasis in lymphnode was found correlated with FSCN1 expression [34].

Gastric cancer
Oncogenic miRNA
miR-21
Its expression, compared to normal tissue, was found upregulated in GC [37–39] while it is inversely correlated with expression of PDCD4 [70–72]. It also targets the PTEN and hence perform as oncomer since it suppresses PDCD4 and PTEN in GC [73].

miR-106a
In GC, compared to normal tissues, it is found upregulated in various human tumors [74]. It reflect as G1-S transition positive regulator [74] and its binding with 3′UTR down regulates the cytokine such as IL10 in hematopoietic stem cells [40]. It was also regulated by SPI and EGR1 for down regulating IL10 [40].

Tumor suppressor miR-101
In most of the cancers, the progression of cancer was due to epigenetic pathway dysregulation by inhibiting miR-101 and inducing EZHR over expression [75, 76]. Since, in GC, this miRNA targeting the COX2, its down regulation causes expression of COX2 [41] which controls the activation of prostaglandin E2 and arachidonic acid pathways.

Let-7
Its expression controls (reduce) the expression of RAS genes such as H, K and NRAS. Its expression, compared to normal lung tissue, was found noticed low in lung tumor while inversely higher expression of RAS protein was noticed in lung tumor [77]. In gastric tumorigenesis RAB40C, which is a let-7a target, role was well recorded [78].

miR-148
It is found inactivated in GC by hypermethylation its promoter region [79] and this causes upregulation of DNA methyltransferase [79]. It act on the ROCK1 to down regulate it and tumor cell invasion [80].

Lung cancer
Oncogenic miRNA miR-21
It support the cell growth, invasiveness of tumor and metastasis [81] by suppressing the tumor suppressor genes. Its expression was found noticed high in mouse lung cancer (K-ras ) dependent and controls the Spry1, Spry2, Btg2 and Pdcd4 by targeting the regulators of ERK/MEK/Ras [81–83]. It also act on the Apaf1, Fas1g, Pdcd4 and RhoB, the pro-apoptotic gene products, to apoptosis inhibition while PDCD4 directly associated with metastasis and invasion [83].

miR-197
Its knockdown results in induction of apoptosis and involved in p53 pathway which causes uncontrolled cell proliferation [84].

miR-212

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Table 2: Circulating microRNA expressions in different cancer cell/tumor

| S. NO. | microRNA | Cancer                          | Role                                              | Author |
|-------|----------|---------------------------------|---------------------------------------------------|--------|
| 1     | mir-375  | Low in OSCC patient plasma      | Sensitive to Radiotherapy                         | [112]  |
| 2     | mir-125b | Low in OSCC patient plasma      | Proliferation inhibition and migration            | [113]  |
| 3     | mir-196  | Over expressed in Head and neck squamous cell carcinoma (HNSCC) | Resistance to Radiotherapy | [114]  |
| 4     | mir-150  | Low expression in Esophageal Squamous Cell Carcinoma | Involved in tumor malignancy – metastasis in Lymphnode, lymph invasion and low prognosis level | [115]  |
| 5     | mir-21   | Over expression in Tongue Squamous Cell Carcinoma | Late stage marker and metastasis in Lymph node | [116]  |
| 6     | mir-134  | HNSCC                           | Metastasis                                        | [117]  |
| 7     | mir-146a | High Concentration in OSCC       | Increase in metastasis and Tumorogenesis         | [118]  |
ACh level was found associated with rapid development of tumor and lower survival rate [85] since it was altered by this miRNA by acting at 3′ UTR.

miR-17-5p and miR-20a
In lung cancers, its different types of miR-17-92 clusters were found highly expressed [86]. In lung cancer, that over express miR17–92, miR-17-5p and miR-20a is targeted for inducing the apoptosis [87].

Tumor suppressor B-Cell Lymphocyte 2 (BCL2)
It is known for its apoptosis regulation. Its over expression was found associated with cancer development and it also act as resistance exerting member against anticancer drugs or agents [88–90].

miR-608
Its upregulation was found recorded in mostly tissues [91] and its higher expression cause apoptosis [92]. It was proposed to have higher interaction with signaling pathways [93].

Mechanism for miRNA dysregulation
The mechanisms by which over expression of miRNA were recorded in different cancer through following types,

Genomic abnormality Chromosomal aberration is associated with tumorigenesis. In humans [94] and mouse [95] occurrence of miRNA was recorded in regions or fragile sites associated with cancer. Different analytical tools revealed the existence of association between miRNA expression level and copy number variations [96–102].

Epigenetic factors In different cancer types, silence of tumor suppressor gene was due to CpG hypermethylation which also includes histone modifications [103].

Transcriptional regulation miRNA expression often associated with transcription factors also. In many cases, during differentiation, switching on of tissue specific miRNAs were activated by transcription factors which includes oncopgenes and tumor suppressor gene. Its association was well documented in cancer.

Regulation at miRNA processing steps Processing efficiency and stability of precursors often help to maintain the level miRNA (mature) while its variation was noticed in mature miRNA and its precursor [104–111].

Circulating miRNA in Cancer
Circulating miRNA play an important role in different cancer as prognostic as well as therapeutic markers (Table 2). Low level mir-375 and mir-125b expression were noticed in OSCC patients that are involved in radiotherapy and proliferation [112, 113]. Similarly, mir-196 was found highly expressed in Head and Neck squamous cell carcinoma and caused resistance to radiotherapy [114]. In, Esophageal squamous cell carcinoma (SCC), miR-150 was found in low level which are involved in tumor malignancy such as metastasis and lymph node invasion [115]. Similarly, Tongue squamous cell carcinoma, mir-21 was found in high expression and was used as marker for late stage as well as metastasis in lymph node [116]. Mir-134 found involved in metastasis in HNSCC [117]. Higher expression level of mir-146a was noticed in OSCC that caused increased metastasis and tumorogenesis [118].

Exosomal miRNA in Cancer
Exosomal miRNA are often involved in exchange of RNA (Table 3). miRNA-200b was involved in increased proliferation in colorectal cancer [119]. Similarly, in Papillary thyroid cancer, negative proliferation was exerted by miRNA-146b and miRNA222 [120]. Chemotherapeutic drug, gemcitabine resistance to pancreatic cancer was induced by miRNA-106b [121]. Thus, the exosomal miRNA involved in regulating cancer proliferation and conferring resistance to the cancer cells.

Conclusion
miRNA are the key biomarker in the field of cancer research. Its regulation describes the exact status like nature, development and its metastatic condition of the cancer. This review have discussed many such miRNA and emphasized the importance in the developmental cancer research. It could facilitate the early diagnosis and the therapeutic targets simultaneously for the greater reduction in cancer mortality. miRNA controlled signalling pathways portrays the precise key paths need to be focused for the treatment of cancer in efficient way.
Abbreviations
miRNAs: MicroRNAs; miRNAs: Messenger RNAs; ncRNA: Non-coding RNA; UTR: Untranslated region; miRBase: miRNA database; DGC8R: DiGeorge critical region 8; Alu: Aluine; ssRNA: Single stranded RNA; Hox: Homeobox; HOXD10: Homeobox D10 gene; ERα: Estrogen receptor-positive; PP: Progesterone Receptor; MCF7: Michigan cancer foundation-7; HBPI: HMG box-containing protein 1; let-7: let-7 gene; BT-IC: Breast tumor initiating cells; EMT: Epithelial–mesenchymal transition; ZEB1: Zinc finger E-box-binding homeobox 1; ZEB2: Zinc finger E-box-binding protein 2; EAC: Ehrlich ascites carcinoma; ESCC: Esophageal squamous cell carcinoma; 3′ UTR: 3′ untranslated regions; TP1M: Tpmy1-mopinosin-1; FEN1: Phosphatase and tensin; PCDA4: Programmed cell death 4; NSE: Neuron specific enolase.

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References
1. Hammond SM. An overview of microRNAs. Adv Drug Deliv Rev. 2015;87:3–14. https://doi.org/10.1016/j.addr.2015.05.001.
2. Mario A, Croce CM. MicroRNA in Cancer and cachexia-a mini-review. J Infect Dis. 2015;212(suppl 1):S74–7 https://doi.org/10.1093/infdis/jiv197.
3. Gianpiero OL, Garofalo M, Croce CM. MicroRNAs in cancer. Annu Rev Pathol Mech Dis. 2014;9(1):287–314 https://doi.org/10.1146/annurev-pathol-012513-104715.
4. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75: 843–54 PubMed: 8252621.
5. Peinhardt BJ, Slack FJ, Varju B, Pasquinelli AE, Bettinger J, et al. The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. Nature. 2000;403:901–6 PubMed: 10706289.
6. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science. 2001;294:853–8 PubMed: 11679670.
7. Lau NC, Lim LP, Weinstein EG, Bartel DP. An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. Science. 2001;294: 858–62 PubMed: 11679671.
8. Lee RC, Ambros V. An extensive class of small RNAs in Caenorhabditis elegans. Science. 2001;294:862–4 PubMed: 11679672.
9. Kozomara A, Griffiths-Jones S. miRBase: integrating microRNA annotation and deep-sequencing data. Nucleic Acids Res. 2013;39:D152–7 PubMed: 21037258.
10. Brock H, Wang Z, Yang C. The role of microRNAs in metal carcinogen-induced cell malignant transformation and tumorigenesis. Food Chem Toxicol. 2016;98:858–65 https://doi.org/10.1016/j.fct.2016.02.012.
11. Lee Y, Kim M, Han J, Yeom KH, Lee S, et al. MicroRNA Genes Are Transcribed by RNA Polymerase II. EMBO J. 2004;23:4057–60 PubMed: 15372022.
12. Borchert GM, Lanier W, Davidson BL. RNA Polymerase III Transcribes Human microRNAs. Nat Struct Mol Biol. 2006;13:1097–101 PubMed: 17009701.
13. Lee Y, Ahn C, Han J, Choi H, Kim J, et al. The Nuclear RNA III Drosha Initiates microRNA Processing. Nature. 2003;425:415–9 PubMed: 14508493.
14. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of Primary microRNAs by the Microprocessor Complex. Nature. 2004;422:231–5 PubMed: 15313879.
15. Gregory RI, Yan KP, Amuthan G, Chandrima D, Torosajd B, et al. The Microprocessor Complex Mediates the Genesis of microRNAs. Nature. 2004;428:235–40 PubMed: 15531878.
16. Sun LY, Dutta A. MicroRNAs in cancer. Annu Rev Pathol. 2009;4(1):199–227 https://doi.org/10.1146/annurev.pathol.4.110807.092222.
17. Cai R, Hagedorn CH, Cullen BR. Human microRNAs Are Processed From Capped, Polyadenylated Transcripts That Can Also Function as mRNAs. Rna. 2004;10:1957–66 PubMed: 15525708.
18. Han J, Lee Y, Yeom KH, Nam JW, Heo I, et al. Molecular Basis for the Recognition of Primary microRNAs by the Drosha-DGCR8 Complex. Cell. 2006;125:887–901 PubMed: 16751099.
19. Bernstein E, Kim SY, Carmell MA, Murchison EP, Alcorn H, Li MZ, Mills AA, Elledge SJ, Anderson KV, Hannon GJ, Dicer is essential for mouse development. Nat Genet. 2005;35:215–7 PubMed: 14528307.
20. Wang Y, Medvid R, Melton C, Jaensch R, Bliloch R, DGCR8 is essential for microRNA biogenesis and silencing of embryonic stem cell self-renewal. Nat Genet. 2007;39:380–5 PubMed: 17259983.
21. Park CY, Choi YS, McManus MT. Analysis of microRNA knockouts in mice. Hum Mol Genet. 2010;19:R169–75 PubMed: 20805106.
22. Vidalga JA, Ventura A. The biological functions of microRNAs: lessons from in vivo studies. Trends Cell Biol. 2015;25(3):137–47.
23. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature. 2007;449:682–688. PMID: 17898713; https://dx.doi.org/10.1038/nature06174.
24. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antipapoptotic factor in human glioblastoma cells. Cancer Res. 2005;65:6029–6033. PMID:16024602; https://doi.org/10.1158/0008-5472.CAN-05-0137.
25. Li H, Bian C, Liao L, Li J, Zhao RC. mir-17-5p promotes human breast cancer cell migration and invasion through suppression of HBPI. Breast Cancer Res Treat. 2011;121:565–575. PMID:2050989; https://dx.doi.org/10.1007/s12032-011-0059-4.
26. Jelena R, Apostolos Z, Thomas V, Maria K, Demetrios AS, Efstratiou NS. MicroRNA expression analysis in triple-negative (ER, PR and Her2/neu) breast cancer. Cell Cycle. 2011;10:1957–62. PMID:21919182.
27. Chen J, Tian W, Cai H, He H, Deng Y. Downregulation of microRNA-200c is associated with drug resistance in human breast cancer. Med Oncol. 2011; 28:2527–34. PMID: 22107191; https://doi.org/10.1007/s12032-011-0177-4.
28. Semperre LF, Christsensen M, Silhavoy AG, Bak M, Heath CV, Schwartz G, et al. Altered MicroRNA expression confined to specific epithelial cell subpopulations in breast cancer. Cancer Res. 2007;67:11612–11620. PMID:18089790; https://dx.doi.org/10.1158/0008-5472.CAN-07-5019.
29. Selcuklu SD, Donoghue MT, Spillane C. miR-21 as a keyregulator of oncogenic processes. Biochem Soc Trans. 2005;33:98–25. PMID:16024602; https://doi.org/10.1158/0008-5472.CAN-05-0137.
30. Xu X, Chen Z, Zhao X, et al. MicroRNA-25 promotes cell migration and invasion in esophageal squamous cell carcinoma. Biochem Biophys Res Commun. 2012;414(4):640–5. https://doi.org/10.1016/j.bbrc.2012.01.067.
31. Liu M, Wang Z, Yang S, et al. TNF-alpha is a novel target of mir-19a. Int J Oncol. 2011;38(4):1013–22.
32. Tian Y, Luo A, Cai Y, Su Q, Ding F, Chen H, Liu Z. MicroRNA-10b promotes migration and invasion through KLF4 in human esophageal Cancer lines. J Biol Chem. 2010;285(11):7986–94.
33. Luthra R, Singh RR, Luthra MG, et al. MicroRNA-196a targets annexin A1: a microRNA-mediated mechanism of annexin A1 downregulation in cancers. Oncogene. 2008;27(52):6667–78.

34. Hashimoto T, Ito T, Inoue H, et al. Prognostic significance of fascin overexpression in human esophageal squamous cell carcinoma. Clin Cancer Res. 2005;11(17):6057–60.

35. Kong KL, Kwong DL, Chan TH, et al. MicroRNA-375 inhibits tumour growth and metastasis in oesophageal squamous cell carcinoma through repressing insulin-like growth factor 1 receptor. Gut. 2012;61(1):33–42.

36. Matsuhashi K, Iomoto H, Yamaguchi N, et al. MiRNA-205 modulates cellular invasion and migration via regulating zinc finger E-box binding homeobox 2 expression in esophageal squamous cell carcinoma cells. J Transl Med. 2013;11:30.

37. Li X, Zhang Y, Zhang H, Liu X, Gong T, Li M, Sun L, Ji G, Shi Y, Han S, Nye V, Chen Z, Zhao Q, Ding J, Wu K, Daiming F. microRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. Mol Cancer Res. 2011;9:824–33 PMID. 21628394. https://doi.org/10.1158/1541-7786.MCR-10-0529.

38. Inoue T, Iinuma H, Ogawa E, et al. Clinical and pathological significance of microRNA-205 in human esophageal squamous cell carcinoma. J Gastrointest Surg. 2012;16(9):1717–24 microRNA cluster: a novel diagnostic tool in large B-cell malignancies. J Clin Oncol. 2005;23(9):1197–202.

39. Li X, Zhang Y, Zhang H, Liu X, Gong T, Li M, Sun L, Ji G, Shi Y, Han S, Nye V, Chen Z, Zhao Q, Ding J, Wu K, Daiming F. microRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. Mol Cancer Res. 2011;9:824–33 PMID. 21628394. https://doi.org/10.1158/1541-7786.MCR-10-0529.

40. Sharma A, Kumar A, Achj J, Haniharman M, Brahmachaki SK, Agraval A, Ghosh B. Posttranscriptional regulation of inter-10k expression by hsa-miR-106a. Proc Natl Acad Sci U S A. 2009;106:5561–6 PMID. 19307576. https://doi.org/10.1073/pnas.0807431106.

41. He XP, Shao Y, Li XL, Wu X, Chen GS, Sun HH, Xu W, Chen GS, Sun HH, Xu X, Tang D, Zheng XF, Xue YP, Huang GC, Sun WH. Downregulation of miR-101 in gastric cancer correlates with cyclooxygenase-2 overexpression and tumor invasion. FEBS J. 2012;279:4201–12 PMID. 23013439. https://doi.org/10.1111/febs.12013.

42. Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. Dev Biol. 2007;307:2012–19 PMID. 17698803; https://doi.org/10.1016/j.ydbio.2006.08.028.

43. Moriarty CH, Pursell B, Mercurio AM. miR-10b targets Tiam1: implications for cancer progression. J Pathol. 2008;214:228–33 PMID. 18059215. https://doi.org/10.1002/path.22407.

44. Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. Dev Biol. 2007;307:2012–19 PMID. 17698803; https://doi.org/10.1016/j.ydbio.2006.08.028.

45. Han M, Liu M, Wang Y, Mo Z, Bi X, Liu Z, et al. Re-expression of miR-21 reverses epithelial-mesenchymal transition and cancer stem cell characteristics in MCF-7 cells. Mol Cancer. 2012;11(18 Pt 1):6013–20 PMID. 22187223; https://doi.org/10.1186/s11011-011-1195-5.

46. Han M, Liu M, Wang Y, Chen X, Xu J, Sun Y, et al. Antagonism of miR-21 reverses epithelial-mesenchymal transition and cancer stem cell phenotype through AKT/ERK1/2 inactivation by targeting PTEN. PLoS One. 2012;7:e39520 PMID. 22671812. https://doi.org/10.1371/journal.pone.0039520.

47. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Res. 2005;65:7065–7068. PMID: 16103053; https://doi.org/10.1158/0008-5472.CAN-05-1783.

48. Fassina A, Marino F, Srii M, Zambello R, Venturina L, Fassan M, et al. The miR-17-92 microRNA cluster: a novel diagnostic tool in large B-cell malignancies. Lab Invest. 2012;92(2):1574–1582 PMID. 22964854; https://doi.org/10.1038/lab.2012.129.

49. Reinhart BJ, Slack FJ, Bussmann M, Pasquinelli AE, Temin BC, Rougvie AE, et al. The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. Nature. 2000;404:301–96. PMID: 10706289; https://doi.org/10.1038/nr.2002.607.

50. Park SM, Gaur AA, Segal E, Peter ME. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. Genes Dev. 2008;22:894–907. PMID: 18381893; https://doi.org/10.1101/gad.146060.4.
Zhu A, Cao Q, Mani RS, Shankar S, Wang X, Ateeq B, Laxman B, Cao X, Jing X, Ramnayanan K, Brenner JC, Yu J, Kim JH, Han B, Tan P, Kumar-Sinha C, Lonigro RJ, Palanisamy N, Maher CA, Chinnayyan AM. Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. Science. 2008;322:1695–P MDID: 19008416. https://doi.org/10.1126/science.1156395.

Carvalho J, van Grieken NC, Pereira PM, Sousa S, Tijssen M, Buffart TE, Diodato B, Grabsch H, Santos MA, Meijer G, Seruca R, Carvalho B, Oliveira C. Lack of microRNA-101 causes E-cadherin functional deregulation through EZH2 up-regulation in gastrointestinal cancer. J Pathol. 2012;228:31–P MDID: 22450701. https://doi.org/10.1002/path.4032.

Johnson SM, Grothaus H, Shigara I, Byrom M, Janis R, Cheng A,Labourier E, Reinert KI, Brown D, Slack FJ. RAS is regulated by the let-7 microRNA family. Cell. 2005;120:45–P MDID: 15766522. https://doi.org/10.1016/j.cell.2005.01.014.

Yang Q, Jie Z, Cao H, Greenlee AR, Yang C, Zou F, Jiang Y. Low-level expression of let-7a in gastric cancer and its involvement in tumorigenesis by targeting RAB40C. Carcinogenesis. 2011;32:713–P MDID: 21349817. https://doi.org/10.1093/carcin/bgr035.

Zhu A, Xia L, Zuo J, Jin S, Zhou H, Yao L, Huang H, Han Z. MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in gastric cancer. Med Oncol. 2012;29:2701–P MDID: 22167392. https://doi.org/10.1007/s12032-011-0134-3.

Zhang B, Liang L, Wang C, Huang S, Cao X, Zha R, Liu J, Diao J, Tian Q, Wu J, Ye Y, Wang Q, Long Z, Zhou Y, Dui C, He X, Shi Y. MicroRNA-148a suppresses tumor cell invasion and metastasis by downregulating ROCK1 in gastric cancer. Clin Cancer Res. 2011;17:7574–83 MDID: 21944419. https://doi.org/10.1158/1078-0432.CCR-11-1714.

Zhu S, Wu H, Wu F, Nie D, Sheng S, Mo Y. MicroRNA-21 targets tumor suppressor genes in invasion and metastasis. Cell Res. 2008;18:1380–P MDID: 18207205.

Hatley ME, Patrick DM, Garcia MR, et al. Modulation of K-Ras-dependent lung tumorigenesis by microRNA-21. Cancer Cell. 2010;18:282–P MDID: 20832705.

Liu Z, Liu M, Srinivasini V, et al. MicroRNA-21 promotes cell transformation by targeting the programmed cell death 4 gene. Oncogene. 2008;27:4737–9 MDID: 18537209.

Fiori ME, Barbini C, Haas TL, et al. Antitumor effect of miR-197 targeting in SK-LU1 human lung adenocarcinoma cells. PLoS ONE. 2013;8(12):e81735.

Mott JL, Kobayashi S, Bronik SF, Gores GJ. mir-29 Regulates Mcl-1 Protein Expression and Apoptosis. Oncogene. 2007;26:133–P MDID: 17404574.

Klaver J, van den Berg A, de Jong D, Blokjl J, Tamrs G, et al. Regulation of pri-microRNA BIC Transcription and Processing in Burkitt Lymphoma. Mol Cell Biol. 2007;27:4238–P MDID: 17438130.

Lee EJ, Baek M, Gusev Y, Brackett DJ, Nuovo GJ, Schmittgen TD. Systematic Evaluation of microRNA Processing Patterns in Tissues, Cell Lines, and Tumors. RNA. 2007:14:42–P MDID: 18025253.

Obemester G, Leuschner PJ, Aikenius M, Martinez J. Post-transcriptional Regulation of microRNA Expression. RNA. 2006;12:161–P MDID: 16738609.

Michael MZ, OC SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced Accumulation of Specific microRNAs in Colorectal Neoplasia. Mol Cancer Res. 2003;1:882–P MDID: 14573789.

Lu Y, Thomson JM, Wong HY, Hammond SM, Bogol BL. Transgenic Over-expression of the microRNA mir-17-92 Cluster Promotes Proliferation and Inhibits Differentiation of Lung Epithelial Progenitor Cells. Dev Biol. 2007;310:442–P MDID: 17765889.

Mineno J, Okamoto S, Ando T, Sato M, Chono H, et al. The Expression Profile of microRNAs in Mouse Embryos. Nucleic Acids Res. 2006;34:1765–71 MDID: 16582102.

Yan Y, et al. Circulating miRNAs as biomarkers for oral squamous cell carcinoma recurrence in operated patients. Oncotarget. 2017;8(5):6206–P MDID: 28408169.

Shiba M, et al. MicroRNA-125b regulates proliferation and radioresistance of oral squamous cell carcinoma. Br J Cancer. 2013;108(9):1817–21 MDID: 24014384.

Suh YE, et al. MicroRNA-196a promotes an oncogenic effect in head and neck cancer. Leuk Lymphoma. 2007;48:410–2 MDID: 17325905.

Welch C, Chen Y, Stallings RL. MicroRNA-34a Functions as a Potential Tumor Suppressor by Inducing Apoptosis in Neuroblastoma Cells. Oncogene. 2007;26:5017–P MDID: 17297439.

Tagawa S, Han M, Tanaka Y, Seto S, et al. Polycistronic microRNA cluster, miR-17-92, is overexpressed in Human Lung Cancers and Enhances Cell Proliferation. Cancer Res. 2005;65:9628–P MDID: 16170601.
120. Lee JC, Gundara J, Serpell J, Bach LA. Papillary thyroid cancer-derived exosomes contain miRNA-146b and miRNA-222. J Surg Res. 2015; 196(1):39–48.

121. Fang Y, Zhou W, Rong Y, Kuang T, Xu X, Wu W, Wang D, Lou W. Exosomal miRNA-106b from cancer-associated fibroblast promotes gemcitabine resistance in pancreatic cancer. Exp Cell Res. 2019;383:111543.

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