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MicroRNA's in cancer as biomarkers and therapeutic keys

Sindhuja Sreedharam, Vinayaga Moorthi Puthamohan* and Sona Valiya Parambil

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. elegance* 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 isoforms 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 multcistronic RNA transcript. In animals, it constitute a gene regulatory molecule and had impact on gene expression 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

* Correspondence: vinayputhu@gmail.com
Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India

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 leathal 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 *HOXD*10 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 *HOXD*10 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

Table 1 microRNA expressions in different cancer cell/tumor

S. NO.	miRNA	REGULATION	CANCER	ROLE	AUTHOR	
1	miR-10b	Up-regulated	Metastatic - Breast Cancer cells	Cell migration and Invasion nin Murine Xenograft	[23]	Breast Cancer
2	miR-21	Up-regulated	Human Glioblastoma Tumor Tissue	Aggressive disease status: High tumor grade, negative hormone receptor status and ductal carcinoma	[24]	
3	miR-17-5p	Up-regulated	MDA-MB-231 Breast Cancer Cells	–	[25]	
4	miR-205	Up-regulated	Breast Cancer cells	Prevents invasion, Proliferation and anchorage independent growth	[26]	
5	miR-17-5p	Down-regulated	MDA-MB-231 Breast Cancer Cells	Migration and Invasion	[25]	
6	miR-200	Down-regulated	Invasive Breast cancer cells lines with mesenchymal phenotype	Drug resistance in Human Breast cancer	[27]	
7	miR-145	Down Regulated	Breast Cancer Cells	Marker for early cancer diagnosis	[28]	
	miR-21	Up-regulated	Esophageal Squamous Cell Carcinoma (ESCC)	–	[29]	
8	miR-25	Up-regulated	ESCC	Cell migration and Invasion directly	[30]	
9	miR-17-92	Up-regulated	75% of ESCC	Promote Cell Growth in vitro and In vivo	[31]	
10	miR-10b	Up-regulated	ESCC	Cell motility and Invasiveness	[32]	Esophageal Squamous Cell Carcinoma
11	miR-196a	Up-regulated	ESCC	Cell Proliferation and Anchorage independent growth and Suppress apoptosis	[33]	
12	miR-145	FSCN1, novel target gene for miR-145, Upregulated	ESCC	Extensive tumor and Lymphnode metastasis and Poor prognosis	[34]	
13	miR-19a	Down Regulated	ESCC	Induce apoptosis in vitro and Impaired Tumor Growth in vivo	[31]	
14	miR-375	Down-regulated	ESCC	Downregulates IGF1R	[35]	
15	miR-205	Down regulated	ESCC	Increased Zinc Finger E-box binding homeobox 2	[36]	
16	miR-21	Up-regulated	GC	Oncomer in GC by inhibiting the tumor-suppressor genes PDCD4 and PTEN	[37–39]	Gastric Cancer
17	miR-106a	Up-regulated	GC	down regulate IL10 expression	[40]	
18	miR-101	Down Regulation	GC	Induce COX2 expression which activates activates the arachidonic acid/prostaglandin E2 pathway following cell proliferation	[41]	

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-106-25

It is a polycistronic and found in chromosome 7q22.1. It encodes miR-25, 93 and miR-106b. It is found upregulaed 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.

miR-17-92

miR-17-92, the oncomir-1, is a oncogenic miRNA [55, 56] found located in 13q31.3 and codes for miR-17, 18a, 19a, 20a, 19b-1 and miR-92-1. Its cluster found expressed about 75% in tumors of ESCC [31] and its expression enhances the cell growth in both in vitro and in vivo.

miR-10b

Its over expression was noticed in different cancer types [57–60] such as ESCC [32]. Its role in ESCC as inducing factor of invasiveness and motility of cell was noticed by Tian et al. [32]. A gene that suppress the migration of cell and invasiveness of the esophageal cancer was identified as KLF4, which is an miR-10b target.

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 *SP1* 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 hypermethylating 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

Table 2 Circulating microRNA expressions in different cancer cell/tumor

S. NO.	miRNA	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 l ymphnode, lymph invasion and low prognosis level	[115]
5	mir-21	Over expression in Tongue Sqamous 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 Tumorogensis	[118]

Table 3 Exosomal microRNA expressions in different cancer cell/tumor

S. NO.	miRNA	Cancer	Role	Author
1	miR-200b	Colorectal Cancer	Increase proliferation	[119]
2	miRNA-146b	Papillary Thyroid Cancer	Negative Proliferation	[120]
3	miRNA-222	Papillary Thyroid Cancer	Negative Proliferation	[120]
4	miRNA-106b	Pancreatic Cancer	Promotes Gemcitabine Resistance	[121]

AChe 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 oncogenes 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 sqamous cell carcinoma and caused resistance to radiotherapy [114]. In, Eosphoageal 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 tumorogenisis [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; mRNAs: Messanger RNAs; ncRNA: Non-coding RNA; UTR: Untranslated region; miRBase: miRNA database; DGCR8: DiGeorge critical region 8; Alu: Alanine; ssRNA: Single stranded RNA; Hox: Homeobox; HOXD10: Homeobox D10 gene; ER+: Estrogen receptor-positive; PR^{+}: Progesterone Receptor; MCF7: Michigan cancer foundation-7; *HBP1*: HMG box-containing protein 1; *let-7*: lethal 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; TPM1: Tropomyosin-1; PTEN: Phosphatase and tensin; PCD4: Programmed cell death 4; NSE: Neuron specific enolase levels; CDH: Cadherin; KLF4: Krüppel-like factor 4; ANXA1: Annexin A1; PDK1: 3-phosphoinositidedependent protein kinase-1; IGF1R: insulin-like growth factor 1 (IGF-1) receptor; FSCN1: Actin-binding protein, fascin homolog 1; IL: Interleukin; SP 1: Schwangerschafts-Protein; EGR1: Early growth response gene 1; EZH2: Enhancer of zeste homolog 2; COX: Cyclooxygenase; RAS: Reticular activating system; HRAS: Harvey rat sarcoma viral oncogene; KRAS: Kirsten rat sarcoma; NRAS: Neuroblastoma RAS Viral Oncogene; ROCK1: Rho-associated protein kinase 1; ERK: Extracellular signal-regulated kinase; AChE: Acetylcholinesterase; CGH: Comparative genomic hybridization; CpG: Cytosine (C)-phosphate-guanine (G) in the DNA sequence.; HNSCC: Head and neck squamous cell carcinoma

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