Research Journal of Recent Sciences _____ ISSN 2277-2502
Vol. **1(11),** 70-76, November **(2012)** *Res.J.Recent Sci.*

Review Paper

OncmiRs: Small Noncoding RNA with Multifaceted Role in Cancer

Joseph Baby and Nair Vrundha M.
Interdisciplinary Research Centre, Department of Biotechnology, Malankara Catholic College, Mariagiri, Kaliakkavilai, TN, INDIA

Available online at: www.isca.in
Received 24th August 2012, revised 11th October 2012, accepted 15th October 2012

Abstract

Several advancements in cancer research occur till date and the involvement of miRNAs in cancer threw new hope to cancer therapy. OncomiRs are miRNAs which plays significant role in cancer. It serves as a double edged sword in cancer because up- regulation and down- regulation of miRNAs are observed in cancerous cells and hence acts as oncogenes and tumor suppressors respectively. Since, cancer is a disease affecting multiple cell types and with different stages, treatment of it remains as a biggest challenge. miRNA turns to be a promising therapeutic tool in cancer due to its regulatory role. This review briefs the multiple role of miRNA in cancer with special emphasis on tumor microenvironment, cell proliferation, angiogenesis, metastasis and apoptosis. Moreover the tumor suppressor and oncogenenic role of miRNAs are also discussed.

Key words: MicroRNA, cancer, oncogenes, tumor suppressors, gene regulation, angiogenesis, apoptosis.

Introduction

MicroRNAs are small ~22 nucleotides (nt) long, non protein coding, single standed RNAs found in both plants and animals[1]. In 1993, Lee *et al*., in the victor ambros lab first discovered miRNA, lin- 4 in *Caenorhabditis elegans* through a genetic screen for defects in the temporal control of post-embryonic development[2] and the term microRNA was coined in 2001. Unlike siRNA, they are found endogenous. Many miRNAs are found to be highly conserved molecules. The complete mature miRNA sequence of let-7, isolated primarily in *Caenorhabditis elegans*, has been evolutionarily conserved from worms to humans. Currently, thousands of miRNAs have been identified in nematodes, amphibians, fishes, plants, mammals and viruses using different approaches including experimental methods, computational approaches, EST and genomic survey sequence analysis[3]. Out of hundreds of miRNAs that have recently been identified, only about 200-300 miRNAs have been currently identified in humans. Studies prove that miRNAs could also cause gene silencing[4]. Recent evidence indicates that miRNAs exhibit important regulatory roles in development, cell proliferation, cell survival and apoptosis and thus play a central role in gene regulation in health and disease. In this review, we brief gene regulation of miRNA, its association with cancer, furthermore with instances to prove it as tumor suppressors and oncogenes.

OncmiR: All rounder in Cancer

Cancer a deadly enemy up on which the human race battles over centuries. Researchers are focusing to understand it from the molecular level. Cancer is a complex genetic disease in which oncogene amplification and/or tumor suppressor gene mutation leads to step-wise deregulation of cell proliferation and apoptosis. OncmiRs are those miRNAs which is believed to be involved in cancer. A number of studies reported that specific microRNA signature had been found in each cancer tissue and microRNA based cancer classification is a very effective and potential tool[5]. The involvement of miRNAs in cancers was confirmed through the observation that miRNAs are frequently located in cancer-associated genomic regions, which include minimal regions of amplification, loss of heterozygosity, fragile sites and common breakpoint regions in or near oncogenes or tumor suppressor genes[6]. The first report linking miRNAs and cancer involves CLL (B cell lymphocytic leukemia). MiRNAs show globally lower expression in cancer tissues than in normal tissues. Abnormalities in miRNA expression have been implicated in several forms of solid tumors such as cervical, breast, colorectal, lung and also in at least two forms of leukemia. Figure- 1 details the function of miRNA in normal tissues as well as oncogenes and tumor suppressors. This instance shows the role of miRNA in cancer. The few different processes in cancer like cell proliferation, modulate tumor microenvironment, angiogenesis, metastasis, apoptosis where miRNA plays crucial role are discussed.

Cell Proliferation: It is well known that unlike the normal cells, in tumor cells the proliferation and survival pathways are disturbed. It was found that Let-7 is a key regulator of multiple genes for cell proliferation either directly or indirectly. Let -7 directly regulates few proto-oncogenes: RAS, CDC25a, CDK6, and cyclin D thus controlling cell proliferation. Hence cancer cells with poor or deleted let-7 expression causes activation of oncogenes and results in a cascade of events like stimulating cell cycle, DNA synthesis and cell division. Another study in cervical cancer cell line HeLa, shows that miR-21 is highly expressed and it was already found overexpressed in many cancers. But its function in cervical cancer is a question hence Yao and co-workers inhibited its expression in HeLa. Interestingly they found increased expression of tumor

suppressor genes PDCD4 and a huge suppression in cell proliferation[7]. In lung and colon cancer cells miR-192 inhibits cell proliferation and induces cell apoptosis but in colon cancer cell inhibiting cell proliferation by miR-192 is dependent on p53 status[8]. A study[9] shows that transfection of miR-34a in uveal melanoma cells leads to significant inhibition of cell proliferation. They found that miR-34a down regulates the expression of c-Met proteins and hence acts as tumor suppressor. Significant increase in miR-95 was found in colorectal cancer through microarray analysis and moreover RNAi based knock down of miR- 95 decreased the ratio of cell growth. Over expression of a reporter gene SNX1 blocked miR-95 induced colorectal cancer cell proliferation hence showing the oncogenic role of miR- 95[10]. These instances highlight the role of oncmiRs in cell proliferation.

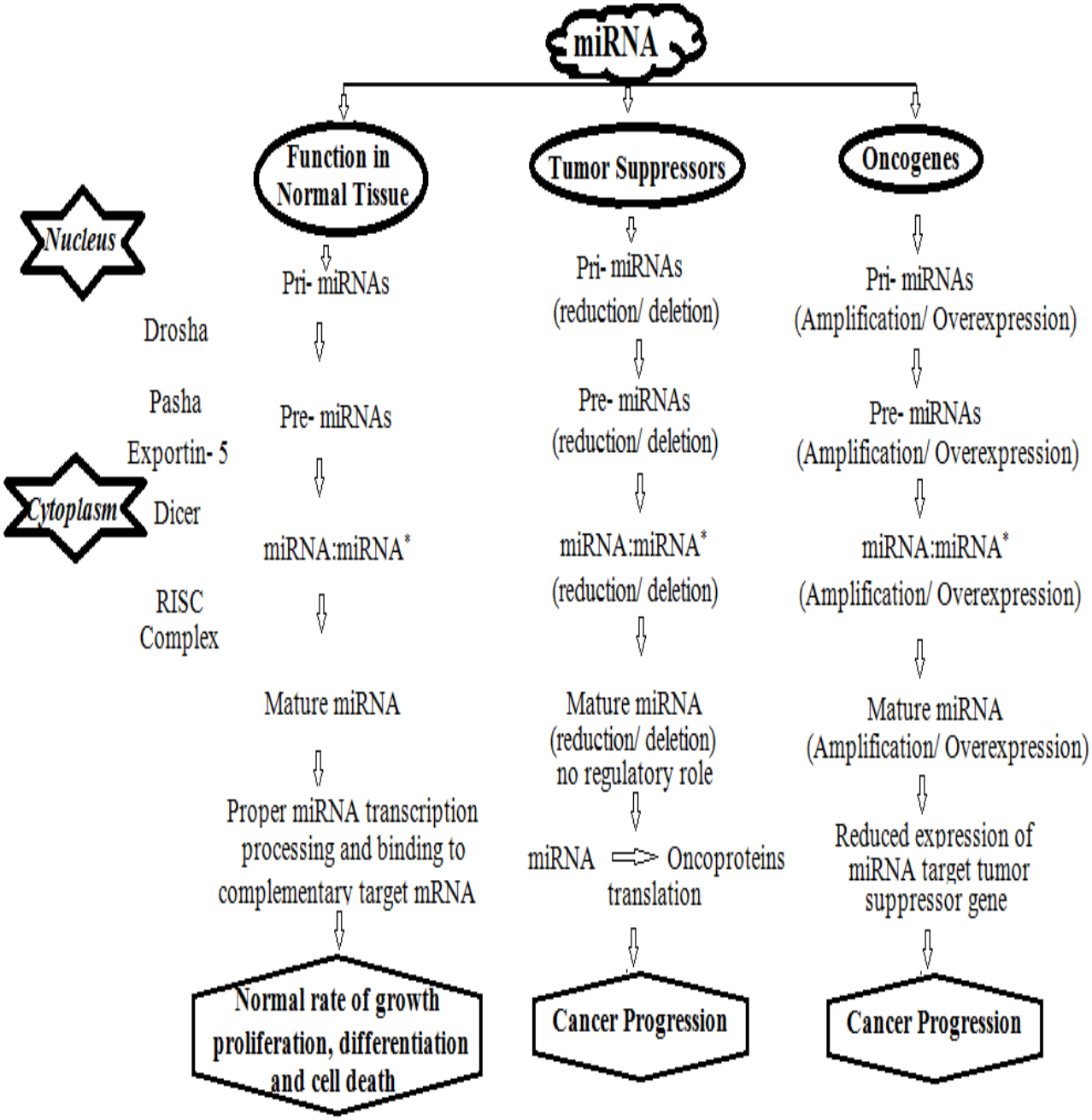

Figure-1
Pipeline Comparing Function of OncmiR

Modulate tumor microenvironment: Tumor microenvironment is being considered to play crucial role in the development of tumor as in cell growth, progression, and development of life threatening metastasis. It is believed that these environments transfer necessary signals which stimulate the transcription factors. Hence through transcription factors non- malignant stromal cell induces the developing cancer cells to invade distant tissues. It can transfer both positive and negative signals. The various therapeutics in clinical trials like interferon- alpha, neovastat, avastin, vitaxin, VEGF trap and all to target molecules in the tumor microenvironment. Monitoring changes of this intrinsic part of tumor *i.e*., tumor microenvironment, will help to identify cell or proteins targets that had undergone modifications while tumor progression. In the microenvironment of prostate cancer cells the epithelial cells interact with the inflammatory and mesenchymal cells in the presence of extra cellular matrix. Significance of miRNA in tumor microenvironment is an unexplored area since Musumeci and his co- workers[11] shown its importance in prostate cancer. They showed the down regulation of miR-15 and miR-16 in fibroblasts surrounding the prostate tumor. It was already established that miR15a and miR-16-1 down regulation causes progression of prostate tumors. Oncogene such as *Bcl-2, Ccnd1, Ccne1, Bmi-1 and Wnt* family members which cause cell proliferation and invasion are targeted by miR-15 and miR-16[12]. More over two new targets *Fgf-2 and Fgfr1* of miR-15 and miR-16 has been found which further the molecular mechanism through tumor and stromal cells influence each other and promote tumor both *in vivo* and *in vitro.* Hence it was considered that these miRNAs could be targeted for therapeutics in prostate cancer. The miRNAs such as mir-17/20, miR-21, miR-29b, miR-29c, miR-31, miR-143, miR-145, miR-146a, miR-146-b, miR-320, miR- 503 has been found in the tumor microenvironment of variety of cancers showing its significance in cancer.

Angiogenesis: Vascular endothelium is the barrier between circulating blood and tissue, typical loss of this endothelial quiescence leads to unfavorable conditions including tumor progression. The growth of blood vessels up on angiogenic activation is a complex process which involves epithelial cell proliferation, degradation of extra cellular matrix, change of their adhesive properties, migration, inhibition of apoptosis, formation of tube like-structures and at last matured into new blood vessels. There are some *in vivo* and *in vivo* reports on dicer independent miRNAs in angiogenesis[13]. Through subcutaneous delivery of Dicer knockdown HUVEC in to nude mice was the first study in vivo to prove the role of endothelial miRNA in angiogenesis. Epithelial cell miRNAs: let-7f and miR-27b has been shown to prove pro- angiogenic effects and it was revealed with 2′-O-methyl oligonucleotides inhibitors. A study shows that over expression of miR-221 and miR-222 increases the tumor induced angiogenesis[14]. Transfection of miR-155 into human primary lung fibroblasts reduced angiotensin II-induced ERK1/2 activation[15]. The role of *GAX* gene, a homeobox gene in vascular endothelial cells inhibits angiogenesis. It was found that miR-130a inhibits *GAX* and promotes angiogenesis. Another report indicates that miR-17~ 92 clusters are highly expressed in endothelial cells. One of the components of this cluster is miR- 92a which controls the growth of new blood vessels and hence it is a candidate for therapy[16]. EGFL7 an epidermal growth factor- like domain 7, a protein was an endothelial cell derived factor involved in spatial arrangement of cells during vascular tube assembly. miR-126 was found to be located within the *egfl7* gene, found to have major role in vessel development through VEGF signaling and angiogenesis[17]. In considering its regulatory role in angiogenesis, miRNAs definitely serves as a potential therapeutic targets.

Metastasis: Metastasis, a process of spreading tumor to distant organs from the primary neoplasm site is a complex and multi step process. It was found that in addition to the alterations in the protein coding genes, small non coding RNA alterations could also support metastasis in tumors such as breast, liver, prostate and colorectal cancers. MiRNA expression in metastatic human breast carcinoma cell line (MDA-MB-231) identified six miRNAs with a relatively low expression in metastatic cells. Among that miR-335 and miR-206 suppressed metastasis *in vivo* and the miR-335 targets were SOX4, PTPRN2, MERTK and TNC. Another study in breast cancer cell lines show MIR-146a/b as tumor suppressors by evaluating its role in metastasis. It was already known that miR-146- a and b inhibit invasion and migration of cancer by down regulating NFκB in breast cancer cells by targeting IRAK1 and TRAF6[18]. These ideas were used in *in vivo* experiments and found its targets were EGF receptor and ROCK1 both of which are involved in promoting metastasis. It was found that miR-31 found to be inhibiting multiple steps of metastasis resulting in powerful inhibition of the metastatic process. A study found that miR-10b was highly expressed in metastatic breast cancer cell lines but not in primary human mammary epithelial or spontaneously immortalized cells. A pathway was identified in which prometastatic gene TWIST1 up-regulates miR-10b which increases through RHOC through HOXD10[19]. Study on miR-373 and miR -520c was found to be promoting migration and metastasis[20] in breast cancer cells and interestingly their metastatic rate was higher in lymph node. miR-182 is a part of the cluster miR-183-96-182, promote hepatocellular carcinoma. Another miRNA promoted hepatocellular carcinoma is miR-143 and it is up-regulated by NFκB and decreases adhesion. More understanding on the regulatory genes and the gene products will unravel the complexity of cancer metastasis.

Apoptosis: Programmed cell death termed as apoptosis, maintains homeostasis in multicellular organisms and hence failure to undergo it leads to tumerogenesis. Role of miRNA in apoptosis was first found by Xu and colleagues[21] in *Drosophila*. miR- 14 was one of the enhancer found in eye-specific expression of the Drosophila cell death activator Reaper and its effect on apoptosis is highly dosage sensitive. Drice was considered as the possible target for miR-14 which controls it

directly or indirectly. *Bantam,* a gene known to express in developmental stages, codes for a miRNA. Expression of bantam could significantly reduce E2Fand DP-induced apoptosis, resulting in even stronger tissue overgrowth. Inhibition of miR-24 in A549cell s resulted in the significant reduction of cell growth. It is considered as an anti- apoptotic factor in human glioblastoma cells[22]. It was suggested that miR-15 and miR- 16 antagonize tumor development by promoting apoptosis. The role of various miRNA in apoptosis yet remains to be determined.

miRNAs As Tumor Suppressor

Tumor suppressor genes like p53 protect cell from various cellular stresses and protect the cell from entering in to a state of malignancy. A variety of miRNAs have been identified that appear to have tumor suppressor functions. A recent study has shown that there is a global down-regulation of miRNA expression in various tumor tissues. B Cell Lymphocytic Leukemia (CLL) is characterized by the deletion of miR-15a and miR-16-1, two clustered miRNAs, within the 13q14.3 locus[23]. Deletions at this region also occur in approximately 50% of mantle cell lymphoma, in 16-40% of multiple myeloma and in 60% of prostate cancers, suggesting the location of one or more tumor suppressor genes at this locus. Northern analysis suggested that both miRNAs were downregulated in the 70% of cases. A predicted target of these miRNAs is B cell lymphoma 2 (Bcl2), an anti-apoptotic protein. The down-regulation of miR-15 and miR-16 leads to an in increase in Bcl2 expression[24]. miR-15a and miR-16-1 were also expressed at lower levels in pituitary adenomas as compared to normal pituitary tissue and their expression inversely correlated with tumor size. Let-7 miRNAs are considered as classical tumor suppressors due to their frequent downregulation in cancers like lung or colon[25]. Ras oncogenes were the first target described to be regulated by the let-7 miRNA family. In both *C. elegans* and human lung cancer cell lines Let-7 negatively regulated RAS and it was not expressed in human lung cancer tissues. Furthermore, overexpression of let-7 in A549 lung adenocarcinoma cell line inhibited lung cancer cell growth. Recent studies reported that another target of let-7 miRNA family is high mobility group A2 (Hmga2) protein, oncogenic in a variety of tumors, including benign mesenchymal tumors and lung cancers.

Chromosomal translocations disrupt the repression of Hmga2 by let-7 miRNA which promotes anchorage-independent growth, a characteristic of oncogenic transformation. In lung cancer cell line restoration of the steady state levels of let-7 inhibited cell replication. Studies in human colon cancer tumors and cell lines show that in addition to Ras, c-Myc might also be a target of let-7 as its expression reduces levels of RAS and c-MYC proteins. miR-143 and miR-145 has been found to be downregulated in colorectal cancers, B-cell lymphomas and in cervical cancers. A recent report showed that TCL1, an oncogene that is overexpressed in CLL cells and Mcl-1, an anti-apoptotic Bcl-2 family member are targets of miR-29 genes. Ciafre *et al.* identified a group of miRNAs: miR-128, miR-181a, miR-181b and miR-181c were downregulated in glioblastoma[26]. In primary neuroblastoma tumors, miR-34a on chromosome 1p36.23 was generally expressed at lower levels and it directly targeted the mRNA encoding E2F3 and significantly reduced E2F3 protein levels. This result suggested that miR-34a acted as a tumor suppressor of neuroblastoma tumorigenesis. miR-34a was frequently absent in pancreatic cancer cells and its responsive genes were highly enriched for those that regulated cell-cycle progression, apoptosis, DNA repair and angiogenesis.

Slack's research group demonstrates that let-7 miRNA inhibits the growth of lung cancer cells in culture and in lung tumors in mice. They also showed that let-7 can be applied as an intranasal drug to reduce tumor formation in a RAS mouse model lung cancer[27]. Bhattacharya *et al.*,[28] identified two miRNAs, miR-15a and miR-16, that are underexpressed in ovarian cell lines and in primary ovarian tissues. Oncogenic activation of Bmi-1 is found in a wide variety of epithelial malignancies including ovarian cancer. Bmi-1 protein levels are downregulated in response to miR-15a or miR-16 expression and lead to significant reduction in ovarian cancer cell proliferation and clonal growth, suggesting the development of therapeutic strategies by restoring miR-15a and miR-16 expression in ovarian cancer and in other cancers. Apart from the above mentioned miR18-a, miR-203, miR-30-c, miR-218, miR-375[29, 30, 31] were also found as tumor suppressors.

miRNA As Oncogenes

Oncogenes, which induce cells to be cancerous, are always upregulated in cells for instance α-Syn and leads to cancer progression[32]. He *et al.*, [33] found the over expression of the miR-17-92 polycistron at 13q31.3 in B-cell lymphomas. It is also found to be over expressed in several other cancers such as solid cancers, lung cancer and malignant lymphoma cell lines proving it as potential oncogenes. Recent studies in mouse B-cell lymphoma model reveals miR-19 is a key oncogenic componenet of mir-17-92 cluster[34]. In breast tumors miR-21 was found to be over expressed when compared to normal breast tissues[35]. Zhu *et al.*, identified down regulation of tumor suppressor, tropomyosin 1 in breast cancer by miR-21 could result in tumor growth supporting the notion that tropomyosin 1 as a potential miR-21 target[36]. It was found to be over expressed in head and neck cancer cell lines, brain tumor and glioblastoma proving it as an oncogene. The glioblastoma tissues and glioblastoma cell lines analysis shows strong upregulation of miR-221. In cervical cancer tissues, increased expression of miR-15b, miR-16, miR-146a, miR-155 and miR-223 has been observed. Cimmino and colleagues[24] reported that miR-15 and miR-16 regulate apoptosis by targeting BCL2. miR-155 was found over expressed in lung cancer, lymphoblastic leukemia/high-grade lymphoma, B-cell lymphomas, Hodgkin's lymphomas, Burkitt lymphomas and in human breast cancer cells suggesting that it may act as oncogene[35]. Studies proved that miRNA expression can be regulated by DNA methylation

and it has been suggested that altered miRNA gene methylation might contribute to human tumorigenesis. Let-7a-3 was found to be methylated by the DNA methyltransferases DNMT1 and DNMT3B. The gene was heavily methylated in normal human tissues but hypomethylated in some lung adenocarcinomas. Brueckner *et al*.,[37] identified let-7a-3 as an epigenetically regulated miRNA gene with oncogenic function and suggest that aberrant miRNA gene methylation might contribute to the human cancer epigenome. Analysis of human breast tumors by Wang *et al*., [38] revealed that miR-27b expression increases during cancer progression, paralleling a decrease in ST14 (suppressor of tumorigenicity 14) expression. The 3′-untranslated region of ST14 contains a regulatory element for miR-27b and luciferase experiments indicate that antisense miR-27b enhances ST14 expression in cancer cells which reduces cell proliferation as well as cell migration and invasion. Knockdown or over expression of a specific miRNA allows studying the specific roles of the miRNA in cancer development. Studies also shows miR- 421, miR- 506-514 clusters, miR-197, miR-9, miR-675 as oncogenes[39, 40]. Table-1 briefs the examples for miRNA involved in tumor progression or suppression and the type of cancer which they cause.

Conclusion

All non coding RNAs are not miRNAs, hence identifying a common sequence signature or biochemical action of miRNA helps to overcome this challenge. Little is known about how miRNAs are regulated; much less what polymerase transcribes them. Furthermore, nothing is known about what signals conveys the temporal and/or spatial expression of miRNAs. This can be predicted to become an active area of research that will be highly important in the study of development and disease. Moreover predicting the impact of miRNAs on target proteins is challenging because of their different regulatory effects at the transcriptional and translational levels. Using chromatin modifying drugs to activate tumor suppressor miRNAs can regulate target oncogenes and it may lead to novel cancer therapies in the future. miRNAs can complement other genomic and proteomic biomarkers for cancer diagnosis and prognosis. While hundreds of human microRNAs are known, relatively little is known about their roles and targets. Effective delivery of microRNA in to targeted tissues and maintaining their continuous activity still remains as an obstacle. New technologies such as next generation sequencing techniques are proved to be much promising in miRNA research. Once overcoming all these difficulties miRNA remains as a promising cancer therapeutic tool.

Table-1
Oncogenic and tumor suppressor miRNAs and its occurrence in cancer

miRNA	oncogene/tumor suppressor	Cancer Type	Reference
miR-15a	tumor suppressor/ oncogene	Non-small cell lung cancer, prostate cancer	26, 80
miR-155	oncogene	B-cell malignancy	9, 77
miR-21	oncogene	glioblastoma, cholangiocarcinomas	49, 64, 81
miR-372	oncogene	testicular germ-cell tumors	82
miR-29	tumor suppressor	B-cell chronic lymphocytic leukemia	83
mir-26 a	oncogene	glioma	84
miR- 31	oncogene	Oral cancer	85
miR- 184	oncogene	squamous cell carcinoma of tongue	86
miR-143	tumor suppressor	colorectal cancer	87
hsa-miR-17–5p	oncogene	neuroblastoma	88
miR-34-a-b-c	tumor suppressor	pancreatic, colon and breast cancer	66, 89, 90
Let-7	tumor suppressor	lung cancer, breast cancer, Burkitt lymphoma and colon Cancer	15, 54, 56, 57, 75, 91
miR-222	Oncogene	prostate, glioblastoma	92
miR- 346	Oncogene	Breast Cancer	93
miR-200b	Oncogene	tongue squamous cell carcinoma	94
miR- 10a	Oncogene	myeloid leukemia	95
miR-218	tumor suppressor	oral cancer	96
miR- 30c	tumor suppressor	Breast Cancer	97
miR-506-514 cluster	Oncogene	malignant melanoma	98
miR-22	tumor suppressor	Breast Cancer	93
miR-7	tumor suppressor	Schwannoma tumors	99
miR-203	tumor suppressor	melanoma cells	100
miR-18a	tumor suppressor	bladder cancer	101
miR-421	oncogene	biliary tract cancer	102

Acknowledgements

The authors deeply thank the management of Malankara Catholic College for their kind support in research activities.

References

1. Bartel D.P., MicroRNAs: Genomics, biogenesis, mechanism and function, *Cell*, **116,** 281-97 **(2004)**

2. Lee C., Rosalind Feinbaum, L. Rhonda Ambros, Victor, The *C. elegans* Heterochronic Gene lin-4 Encodes Small RNAs with Anitsense Complementary to lin-14, *Cell*, **75,** 843-854 **(1993)**

3. Lee R.C. and V. Ambros, An extensive class of small RNAs in *Caenorhabditis elegans, Science*, **294,** 862-864 **(2001)**

4. Pasquinelli A.E., Reinhart B.J., Slack F., Martindale M.Q. and Kuroda M.I. *et al*., Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA, *Nature*, **408,** 86-89 **(2000)**

5. Lu J., Getz G., Miska E.A., Alvarez-Saavedra E. and Lamb J., *et al*., Microrna expression profiles classify human cancers, *Nature***, 435,** 834-8 **(2005)**

6. Calin G.A., Sevignani C. and Dumitru C., *et al*., Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers, *PNAS*, **101,** 2999-3004 **(2004)**

7. Yao Q., Xu H., Zhang Q.Q., Zhou H. and Qu L.H., MicroRNA-21 promotes cell proliferation and down-regulates the expression of programmed cell death 4 (PDCD4) in HeLa cervical carcinoma cells, *Biochem Biophys Res Commun,* **388(3),** 539-42 **(2009)**

8. Feng S., Cong S., Zhang X., Bao X., Wang W., Li H., Wang Z., Wang G., Xu J., Du B., Qu D., Xiong W., Yin M., Ren X., Wang F., He J. and Zhang B., MicroRNA-192 targeting retinoblastoma 1 inhibits cell proliferation and induces cell apoptosis in lung cancer cells, *Nucleic Acids Res*., **39(15)**, 6669-78 **(2011)**

9. Yan D., Zhou X., Chen X., Hu D.N., Dong X.D., Wang J., Lu F., Tu L. and Qu J., MicroRNA-34a inhibits uveal melanoma cell proliferation and migration through downregulation of c-Met, *Invest Ophthalmol Vis Sci*, **50(4),** 1559-65 **(2009)**

10. Huang Z., Huang S., Wang Q., Liang L., Ni S., Wang L., Sheng W., He X. and Du X., MicroRNA-95 promotes cell proliferation and targets sorting Nexin 1 in human colorectal carcinoma, *Cancer Res*., **71(7),** 2582-9 **(2011)**

11. Musumeci M., Coppola V., Addario A., Patrizii M., Maugeri-Saccà M., Memeo L., Colarossi C., Francescangeli F., Biffoni M., Collura D., Giacobbe A., D'Urso L., Falchi M., Venneri M.A., Muto G., De Maria R. and Bonci D., Control of tumor and microenvironment cross-talk by miR-15a and miR-16 in prostate cancer, *Oncogene,* **30(41),** 4231-42 **(2011)**

12. Mbeunkui F. and Johann D.J., Jr. Cancer and the tumor microenvironment: a review of an essential relationship, *Cancer Chemother Pharmacol*., **63(4),** 571–582 **(2009)**

13. Suarez Y., Fernandez-Hernando C., Yu J., Gerber S.A., Harrison K.D., Pober J.S., Iruela-Arispe M.L., Merkenschlager M. and Sessa W.C., Dicer-dependent endothelial microRNAs are necessary for postnatal angiogenesis, *Proc Natl Acad Sci U S A,* **105,** 14082–14087 **(2008)**

14. le Sage C., Nagel R., Egan D.A., Schrier M., Mesman E., Mangiola A., Anile C., Maira G., Mercatelli N., Ciafrè S.A., Farace M.G. and Agami R., Regulation of the p27(Kip1) tumor suppressor by miR-221 and miR-222 promotes cancer cell proliferation, *EMBO J*., **26(15),** 3699-708 **(2007)**

15. Martin M.M., Lee E.J., Buckenberger J.A., Schmittgen T.D. and Elton T.S., MicroRNA-155 regulates human angiotensin II type 1 receptor expression in fibroblasts, *J Biol Chem*., **281(27),** 18277-84 **(2006)**

16. Bonauer A., Carmona G., Iwasaki M., Mione M., Koyanagi M., Fischer A., Burchfield J., Fox H., Doebele C., Ohtani K., Chavakis E., Potente M., Tjwa M., Urbich C., Zeiher A.M. and Dimmeler S., MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice, *Science,* **324(5935),** 1710-3 **(2009)**

17. Nikolic I., Plate K.H. and Schmidt M.H., EGFL7 meets miRNA-126: an angiogenesis alliance, *J Angiogenes Res*., **2(1),** 9 **(2010)**

18. Bhaumik D., Scott G.K., Schokrpur S., Patil C.K., Campisi J. and Benz C.C., Expression of microRNA-146 suppresses NF-nB activity with reduction of metastatic potential in breast cancer cells, *Oncogene,* **27,** 5643–7 **(2008)**

19. Ma L., Teruya-Feldstein J. and Weinberg R.A., Tumour invasion and metastasis initiated by microRNA-10b in breast cancer, *Nature*, **449,** 682–8 **(2007)**

20. Huang Q., Gumireddy K. and Schrier M., et al. The microRNAs miR-373 and miR-520c promote tumour invasion and metastasis, *Nat Cell Biol*, **10,** 202–10 **(2008)**

21. Xu P., Vernooy S.Y., Guo M. and Hay B.A., The Drosophila microRNA Mir-14 suppresses cell death and is required for normal fat metabolism, *Curr Biol,* **13,** 790–795 **(2003)**

22. Chan J.A., Krichevsky A.M. and Kosik K.S., MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells, *Cancer Res.,* **65,** 6029-6033 **(2005)**

23. Calin G.A., C.D. Dumitru M. Shimizu R. Bichi and S. Zupo *et al*., Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic

lymphocytic leukaemia, *Proc. Natl. Acad. Sci. USA*., **99,** 15524-15529 **(2002)**

24. Cimmino A., Calin G.A., Fabbri M. and Ferracin M. *et al*., MiR15 and miR-16 induce apoptosis by targeting BCL2. *PNAS*, **102,** 13944-13949 **(2005)**

25. Volinia S., Calin G.A. and Liu C.G. *et al*., A microRNA expression signature of human solid tumors defines cancer gene targets, *Proc. Natl Acad. Sci. USA*., **103,** 2257-2261 **(2006)**

26. Ciafre S.A., Galardi S., Mangiola A., Ferracin M. and Liu C.G. *et al*., Extensive modulation of a set of microRNAs in primary glioblastoma, *Biochem. Biophys. Res. Commun*., **334,** 1351-1358 **(2005)**

27. Esquela-Kerscher A., Trang P., Cheng A., Ford L. and Weidhaas J. *et al*., The let-7 microRNA reduces tumor growth in mouse models of lung cancer, *Cell Cyc.*, **7,** 759-64 **(2008)**

28. Bhattacharya R., Nicoloso M., Arvizo R., Wang E. and Cortez A. *et al*., Mir-15a and MiR-16 control Bmi-1 expression in Ovarian Cancer, *Cancer Res.*, **69,** 9090-9095 **(2009)**

29. Tanic M., Yanowsky K., Rodriguez-Antona C., Andrés R., Márquez-Rodas I., Osorio A., Benitez J. and Martinez-Delgado B., Deregulated miRNAs in Hereditary Breast Cancer Revealed a Role for miR-30c in Regulating KRAS Oncogene, *PLoS One*. **7(6),** e38847 **(2012)**

30. Noguchi S., Mori T., Otsuka Y., Yamada N., Yasui Y., Iwasaki J., Kumazaki M., Maruo K. and Akao Y., Anti-oncogenic microRNA-203 induces senescence by targeting E2F3 protein in human melanoma cells, *J Biol Chem*., **287(15),** 11769-77 **(2012)**

31. Tao J., Wu D., Li P., Xu B., Lu Q., Zhang W., microRNA-18a, a member of the oncogenic miR-17-92 cluster, targets Dicer and suppresses cell proliferation in bladder cancer T24 cells, *Mol Med Report,* **5(1),** 167-72 **(2012)**

32. Choong C. and Say Y., Knockdown of α-Synuclein Enhances Susceptibility to Staurosporine Induced Apoptosis in Human Melanoma SK-MEL28 Cells, *Journal of Biological Sciences*, **11,** 135-145 **(2011)**

33. He L., Thomson J.M., Hemann M.T., Hernando-Monge E. and Mu D. *et al*., A microRNA polycistron as a potential human oncogene, *Nature*, **435,** 828-833 **(2005)**

34. Virginie O., Bennett M.J., Walker J.C. and Ma C. *et al*., Mir-19 is a key oncogenic component of mir-17-92, *Genes Dev*., **23,** 2839-2849 **(2009)**

35. Iorio M.V., Ferracin M., Liu C.G., Veronese A. and Spizzo R. *et al*., MicroRNA gene expression deregulation in human breast cancer, *Cancer Res*., **65,** 7065-7070 **(2005)**

36. Zhu S., Si M.L., Wu H. and Mo Y.Y., MicroRNA-21 Targets the tumor suppressor gene Tropomyosin 1 (TPM1), *J.Biol.Chem*., **282,** 14328-14336 **(2007)**

37. Brueckner B., Stresemann C., Kuner R., Mund C. and Musch T. *et al*., The human let-7a-3 locus contains an epigenetically regulated microRNA gene with oncogenic function, *Cancer Res*., **67,** 1419-1423 **(2007)**

38. Wang Y., Rathinam R., Walch A. and Alahari S.K., ST14 (suppression of tumorigenicity 14) gene is a Target for miR-27b and the inhibitory effect of ST14 on cell growth is independent of miR-27b regulation, *J. Biol. Chem*., **284,** 23094-23106 **(2009)**

39. Streicher K.L., Zhu W., Lehmann K.P., Georgantas R.W., Morehouse C.A., Brohawn P., Carrasco R.A., Xiao Z., Tice D.A., Higgs B.W., Richman L., Jallal B., Ranade K. and Yao Y.A, Novel oncogenic role for the miRNA-506-514 cluster in initiating melanocyte transformation and promoting melanoma growth, *Oncogene,* **31(12),**1558-70 **(2012)**

40. Zhong X.Y., Yu J.H., Zhang W.G., Wang Z.D., Dong Q., Tai S., Cui Y.F. and Li H., MicroRNA-421 functions as an oncogenic miRNA in biliary tract cancer through down-regulating farnesoid X receptor expression, *Gene*., **493(1)**, 44-51 **(2012)**