IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2021 Vol.:20, Issue:2

MicroRNAs in Leukemogenesis and their Therapeutic Applications

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Nazima Begum*[1], Mirza Imroz Baig [1]

1) *Department of Pharmaceutical Biotechnology, Deccan School of Pharmacy, Hyderabad. India.*

Submitted: 05 December 2020
Revised: 26 December 2020
Accepted: 16 January 2021

Keywords: miRNAs, Leukemia, Gene expression, Biomarkers

ABSTRACT

miRNAs regulate gene expression at post transcription level thereby mediate several pathophysiological conditions. They also act as epigenetic regulators to modulate biological processes and involve in malignant cell development or progression. miRNAs are evolving diagnostic and prognostic biomarkers in several cancers including leukemia. As the current clinical biomarkers have few limitations with respect to optimal clinical decision making, miRNAs may have potential clinical usage in d disease diagnosis.

HUMAN JOURNALS
www.ijppr.humanjournals.com

INTRODUCTION

MicroRNAs (miRNAs) are endogenous non-coding RNAs that consist of 19 to 25 nucleotides in size, involved in gene expression regulation usually at post-transcriptional level thereby mediates several biological processes such as apoptosis, cell proliferation, and differentiation (1-3). Dysregulation of specific miRNAs which are function as an oncogene or tumor suppressors have been associated with the development of several human malignancies and the specific miRNA expression pattern may use in the classification of human cancers. (4-6). MiRNAs have also been associated with the development of hematological malignancies and were correlated with chromosomal variations and clinical outcomes of leukemia subtypes. Specific cytogenetic changes and clinical outcomes of different subtypes of leukemia have been reported, demonstrating miRNAs have the potential to be used for clinical diagnosis, prognosis, and cancer therapy (7-13).

miRNA signature in leukemogenesis

Dysregulation of several miRNAs such as miR-15/16, miR-34b/c, miR-29, miR-181b, miR-17/92, miR-150, and miR-155 has been associated with disease progression and resistance to chemotherapy in CLL patients [14]. Nearly two-thirds of CLL patients have showed decreased miR-15a/16-1 expression levels. Indeed, miR-15a and miR-16- 1 are located in the same locus of 13q14.3 chromosome, a genomic region typically observed to be deleted in CLL patients. [15].

Micro RNA dysregulations have been observed by several mechanisms that are involved in AML pathogenesis. Previous studies have reported that miRNAs can promote leukemogenesis, modifying various biological processes such as survival, differentiation, proliferation, self-renewal, and epigenetic modification. These biological processes are typically mediated by interacting with deregulated tumor suppressor proteins or oncoproteins. These interactions are usually controlled at the post-transcriptional level. In table (1) we have summarized some candidate miRNAs which play an important role in AML pathogenesis. We have illustrated each miRNA's staus (up or down-regulation), their targets, and the functional effect of its dysregulation in AML pathogenesis.

Previously, it was reported that the functional effect of miRNA dysregulation might be depending on its expression levels. For instance, miRNA 155 overexpression may act as an oncogenic factor in AML-FLT3-ITD patients (16,17) whereas in other subtype AML patients

overexpression of miRNA 155 may act as a tumor suppressor (18,19). Elevated levels of miRNA 155 have resulted in decreased clonal proliferation. In contrast, low levels of miRNA 155 have functioned to be oncogenic and led to enhanced proliferation and colony-forming ability (20). Moreover, it was observed that miRNA 155 moderate levels were found to be associated with in poor prognosis indicating the potential oncogenic function of miRNA 155 in hematological malignancy.

Polycistronic miRNA like miRNA17 expression has been significantly elevated in MLL rearranged leukemia (21, 22). It was reported that the CDK inhibitor P21 was an important target gene for miR-17. Leukemia cells with increased levels of miR-17 have exhibited elevated LSC properties resulted in suppression of differentiation and increased cell proliferation. (21). Moreover, it has been reported that decreased miR-17-92 levels may promote myeloid lineage fate of CD34 positive HPCs derived from cord blood. miRNA125b plays an important role in regulation of hematopoiesis (23). It was observed that miRNA 125b have been differentially expressed in the hematopoietic sub population (24). Its downregulation was observed in committed progenitors whereas up-regulation observed in lymphoid progenitors compared to myeloid progenitors (25).

miRNAs also play an important role in the regulation of hematopoiesis. Moreover, they regulate the biological activity of LSC, their development, and self-renewal. (26,27). miRNAs have been showing differential expression patterns in LSCs. It was suggested that precise regulation of miRNA expression might be led to regulation of their target that eventually led to LSC resistance elimination by promoting cell death (28). miRNAs differential expression had been observed to be varied between LSC ($CD34^{+}$, $CD38^{-}$) and HSCs. They reported that levels of miRNA10a, miR29b, miR551b, miR125b, and miR151-5 were found to be elevated in HSCs compared to LSCs. (29). miRNA126 is a candidate molecule in leukemia development. miRNA126 levels have been elevated in HSC and LSCs compared to leukemia progenitor indicating the potential role of miRNA126 in the maintenance of stem cell nitch (29). miRNA 126 has found to be regulated several signaling pathways such as PI3K/AKT/MTOR and protein kinase B that play a crucial role in differentiation, self-renewal, and cell cycle progression of LSCs. However, miRNA126 shows the dual function in LSCs and HSC. Decreased levels of miRNA126 have led to increased HSC expression by inhibiting the apoptosis and colony formation ability of LSCs (30, 31, 29). miRNA-17 was shown to be regulated the LSC potential in vivo by targeting the CDK P21 thereby promotes leukemic cell development (21).

miRNAs as therapeutic targets

FDA has been approved several miRNAs for medical intervention. These candidate miRNAs play an important role in various diseases (54). Cancer cells sometimes exert resistance to conventional chemotherapy which is a major hurdle in cancer treatment. These therapies typically target blast cell populations and show poor effect on leukemic stem cells emphasizing the need for exploring new molecular targets to treat AML. miRNAs are becoming attractive molecular targets and provide a promising approach for cancer treatment. In this approach, miRNA expression would be manipulated to promote or suppress their activity. The manipulation strategies can be obtained by miRNA mimic agents delivered by synthetic vectors, dendrimer based vectors, lipid-based nanocarriers and inorganic nano-based polymers (32,33). Previously, several studies have been illustrated the miRNA-based therapeutic approaches in both in vitro and in vivo models. miRNA29b levels were showed to be elevated in AML blast cells when it was delivered by nanoparticle-based vectors. (34). In another study, it was shown that the replacement of miR 29 had resulted in decreased neoplastic infiltration and leukemic cell proliferation (35). Inhibition of leukemic cell proliferation has been observed with the restoration of miR-122, miR193a in childhood AML and xenograft model (36).

CONCLUSION:

miRNAs are evolving biomarkers and therapeutic targets as they regulate oncogene functions which make them an attractive drug targets. However, identifying the candidate miRNA and designing of delivery vehicle for a particular disease may improve therapeutic efficacy and reduce the toxicity. Further studies in large population will improve miRNA usage in CML clinical settings.

Table No. 1: miRNAs involved in AML pathogenesis

Up/down-regulated miRNAs	Down-regulated miRNA	Reference
miRNA9:Up regulation: in MLL-AML	Elevated proliferation and survival	37
miRNA29b:Down: in various subtypes of AML	Increased cell growth, decreased apoptosis, leukemic progression in vivo	38
miRNA99:Up: in pediatric-onset AML (M1–M5)	Increased proliferation, colony formation, cell survival	39
miRNA17-92: Up: in LSCs in MLL-AML	Increased proliferation colony-forming	40
miRNA192: Down: in various subtype	Increased proliferation and cell cycling, decreased differentiation	41
miRNA194-5p Down: in AML cell line	Decreased apoptosis, differentiation	42
miRNA182:Down: in AML withCEBPA mutation,	Decreased myeloid differentiation	43

Table2: miRNAs involved in CML pathogenesis

miRNA	Expression level	Target	Function	Reference
miR-130a	**Up regulation**	CCN3	platelet differentiation	**44**
miR-17-92 cluster	**Up regulation**	c-MYC	Elevated in primary CML $CD34^{+}$ cells	**45**
miR-21	**Downregulation**	Bcl2	Cell migration, growth, apoptosis and, invasion	**46**
miR-486-5p	**Upregulation**	PTEN	Hematopoietic cell differentiation	**47**
miR-217	**Upregulation**	AKT2, STAT5A	Leukemic cell proliferation	**48**
miR-181c	**Downregulation**	RAD21	Suppresses cell growth	**49**
miR-146	**Upregulation**	NFkB	Cell proliferation	**50**
miR-31	**Downregulation**	MAPK	Apoptosis	**51**
miR-155	**Downregulation**	MAPK	Cell proliferation	**52**
miR-203	**Downregulation**	DNMTs	Regulates promoter demethylation of miR-203	**53**

Table 3: Ongoing clinical studies for the microRNAs to use in different diseases (54)

miRNA gene	Drug name	Disease
miRNA34	MRX34	Lymphoma, Liver cancer
miR-16	MesomiR-1	Cardiac diseases
miR-155	Cobomarsen (MRG-106)	T-cell lymphoma/mycosis
miR-122	Miravirsen	Hepatitis C virus

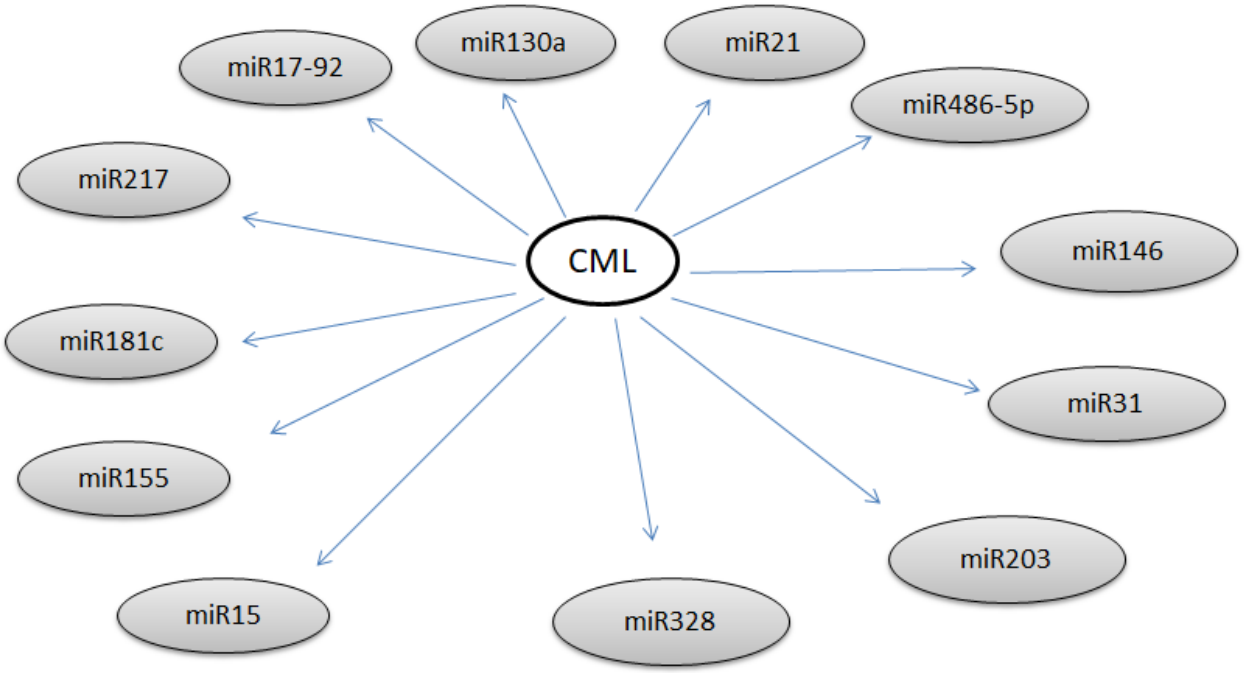

Figure No.1: miRNAs involved in Chronic Myeloid Leukemogenesis

REFERENCES:

1. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116:281–97.
2. Ambros V. The functions of animal microRNAs. Nature. 2004;431:350–5.
3. Lim LP, Lau NC, Garrett-Engele P, et al. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature. 2005;433:769–73.
4. Chen CZ. MicroRNAs as oncogenes and tumor suppressors. N Engl J Med. 2005;353:1768–71.
5. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer. 2006;6:259–69.
6. Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. Nature. 2005;435:834–8.
7. Zhang H, Luo XQ, Zhang P, et al. MicroRNA patterns associated with clinical prognostic parameters and CNS relapse prediction in pediatric acute leukemia. PLoS One. 2009;4:e7826.
8. Labbaye C, Testa U. The emerging role of MIR-146A in the control of hematopoiesis, immune function, and cancer. J Hematol Oncol. 2012;5:13.
9. Calin GA, Ferracin M, Cimmino A, et al. A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. N Engl J Med. 2005;353:1793–801.

10. Garzon R, Volinia S, Liu CG, et al. MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia. Blood. 2008;111:3183–9.
11. Gimenes-Teixeira HL, Lucena-Araujo AR, Dos Santos GA, et al. Increased expression of miR-221 is associated with shorter overall survival in T-cell acute lymphoid leukemia. Exp Hematol Oncol. 2013;2:10.
12. Jongen-Lavrencic M, Sun SM, Dijkstra MK, et al. MicroRNA expression profiling in relation to the genetic heterogeneity of acute myeloid leukemia. Blood. 2008;111:5078–85.
13. Fernando TR, Rodriguez-Malave NI, Rao DS. MicroRNAs in B cell development and malignancy. J Hematol Oncol. 2012;5:7.
14. Balatti V, Pekarky Y, Croce CM. Role of microRNA in chronic lymphocytic leukemia onset and progression. J Hematol Oncol. 2015;8:12.
15. Calin GA, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA. 2002;99(24):15524–9.
16. Zhang H, et al. Upregulation of microRNA-125b contributes to leukemogenesis and increases drug resistance in pediatric acute promyelocytic leukemia. Mol Cancer. 2011;10:108.
17. Tam W, Dahlberg JE. miR-155/BIC as an oncogenic microRNA. Genes Chromosomes Cancer. 2006;45(2):211–2.
18. Forrest AR, Kanamori-Katayama M, Tomaru Y, Lassmann T, Ninomiya N, Takahashi Y, et al. Induction of microRNAs, miR-155, miR-222, miR-424 and miR-503, promotes monocytic differentiation through combinatorial regulation. Leukemia. 2010;24:460–6.
19. Palma CA, Al Sheikha D, Lim TK, Bryant A, Vu TT, Jayaswal V, et al. MicroRNA-155 as an inducer of apoptosis and cell differentiation in acute myeloid leukaemia. Mol Cancer. 2014;13:79.
20. Narayan N, Morenos L, Phipson B, Willis SN, Brumatti G, Eggers S, et al. Functionally distinct roles for different miR-155 expression levels through contrasting effects on gene expression, in acute myeloid leukaemia. Leukemia. 2017;31:808–20.
21. Wong P, Iwasaki M, Somervaille TC, Ficara F, Carico C, Arnold C, et al. The miR-17-92 microrna polycistron regulates MLL leukemia stem cell potential by modulating p21 expression. Cancer Res. 2010;70:3833–42.
22. Mi S, Li Z, Chen P, He C, Cao D, Elkahloun A, et al. Aberrant overexpression and function of the miR-17-92 cluster in MLL-rearranged acute leukemia. Proc Natl Acad Sci USA. 2010;107:3710–5.
23. Shaham L, Binder V, Gefen N, Borkhardt A, Izraeli S. miR-125 in normal and malignant hematopoiesis. Leukemia. 2012;26:2011–8.
24. O'Connell RM, Chaudhuri AA, Rao DS, Gibson WS, Balazs AB, Baltimore D. MicroRNAs enriched in hematopoietic stem cells differentially regulate long-term hematopoietic output. Proc Natl Acad Sci USA. 2010;107:14235–40.
25. Ooi AG, Sahoo D, Adorno M, Wang Y, Weissman IL, Park CY. MicroRNA-125b expands hematopoietic stem cells and enriches for the lymphoid-balanced and lymphoid-biased subsets. Proc Natl Acad Sci USA. 2010;107:21505–10.
26. Chung SS, Hu W, Park CY. The role of microRNAs in hematopoietic stem cell and leukemic stem cell function. Ther Adv Hematol. 2011;2:317–34.
27. Liao Q, Wang B, Li X, Jiang G. miRNAs in acute myeloid leukemia. Oncotarget. 2017;8:3666–82.
28. Martianez Canales T, de Leeuw DC, Vermue E, Ossenkoppele GJ, Smit L. Specific depletion of leukemic stem cells, Can microRNAs make the difference. Cancers (Basel). 2017;9:74.
29. De Leeuw DC, Denkers F, Olthof MC, Rutten AP, Pouwels W, Schuurhuis GJ, et al. Attenuation of microRNA-126 expression that drives CD34+38− stem/progenitor cells in acute myeloid leukemia leads to tumor eradication. Cancer Res. 2014;74:2094–105.
30. Dorrance AM, Neviani P, Ferenchak GJ, Huang X, Nicolet D, Maharry KS, et al. Targeting leukemia stem cells in vivo with antagomiR-126 nanoparticles in acute myeloid leukemia. Leukemia. 2015;29:2143–53.
31. Lechman ER, Gentner B, Ng SW, Schoof EM, van Galen P, Kennedy JA, et al. miR-126 regulates distinct self-renewal outcomes in normal and malignant hematopoietic stem cells. Cancer Cell. 2016;29:214–28.
32. McDermott AM, Heneghan HM, Miller N, Kerin MJ. The therapeutic potential of microRNAs: disease modulators and drug targets. Pharm Res. 2011;28:3016–29.

33. Brown BD, Venneri MA, Zingale A, Sergi Sergi L, Naldini L. Endogenous microRNA regulation suppresses transgene expression in hematopoietic lineages and enables stable gene transfer. Nat Med. 2006;12:585–91.
34. Huang X, Schwind S, Yu B, Santhanam R, Wang H, Hoellerbauer P, et al. Targeted delivery of microRNA-29b by transferrin-conjugated anionic lipopolyplex nanoparticles: A novel therapeutic strategy in acute myeloid leukemia. Clin Cancer Res. 2013;19:2355–67.
35. Gong JN, Yu J, Lin HS, Zhang XH, Yin XL, Xiao Z, et al. The role, mechanism and potentially therapeutic application of microRNA-29 family in acute myeloid leukemia. Cell Death Differ. 2014;21:100–12.
36. Li Y, Gao L, Luo X, Wang L, Gao X, Wang W, et al. Epigenetic silencing of microRNA-193a contributes to leukemogenesis in t(8;21) acute myeloid leukemia by activating the PTEN/PI3K signal pathway. Blood. 2013;121:499–509.
37. Chen P, Price C, Li Z, Li Y, Cao D, Wiley A, et al. miR-9 is an essential oncogenic microRNA specifically overexpressed in mixed lineage leukemia-rearranged leukemia. Proc Natl Acad Sci USA. 2013;110:11511–6.
38. Garzon R, Heaphy CE, Havelange V, Fabbri M, Volinia S, Tsao T, et al. MicroRNA 29b functions in acute myeloid leukemia. Blood. 2009;114:5331–41.
39. Zhang L, Li X, Ke Z, Huang L, Liang Y, Wu J, et al. MiR-99a may serve as a potential oncogene in pediatric myeloid leukemia. Cancer Cell Int. 2013;13:110.
40. Wong P, Iwasaki M, Somervaille TC, Ficara F, Carico C, Arnold C, et al. The miR-17-92 microrna polycistron regulates MLL leukemia stem cell potential by modulating p21 expression. Cancer Res. 2010;70:3833–42.
41. Ke S, Li RC, Lu J, Meng FK, Feng YK, Fang MH. MicroRNA-192 regulates cell proliferation and cell cycle transition in acute myeloid leukemia via interaction with CCNT2. Int J Hematol. 2017;106:258–65.
42. Dell'Aversana C, Giorgio C, D'Amato L, Lania G, Matarese F, Saeed S, et al. miR-194-5p/BCLAF1 deregulation in AML tumorigenesis. Leukemia. 2017;31:2315–25.
43. Wurm AA, Zjablovskaja P, Kardosova M, Gerloff D, Brauer-Hartmann D, Katzerke C, et al. Disruption of the C/EBPα-miR-182 balance impairs granulocytic differentiation. Nat Commun. 2017;8:46.
44. Suresh S, McCallum L, Lu W, Lazar N, Perbal B, Irvine AE. MicroRNAs 130a/b are regulated by BCR-ABL and down- regulate expression of CCN3 in CML. J Cell Commun Signal. 2011;5:183–91.
45. Venturini L, Battmer K, Castoldi M, Schultheis B, Hochhaus A, Muckenthaler MU, et al. Expression of the miR-17-92 polycistron in chronic myeloid leukemia (CML) CD34+ cells. Blood. 2007;109:4399–405.
46. Seca H, Lima RT, Lopes-Rodrigues V, Guimaraes JE, Almeida GM, Vasconcelos MH. Targeting miR-21 induces autophagy and chemosensitivity of leukemia cells. Curr Drug Targets. 2013;14:1135–43.
47. Wang LS, Li L, Li L, Chu S, Shiang KD, Li M, et al. MicroRNA-486 regulates normal eryth- ropoiesis and enhances growth and modulates drug response in CML progenitors. Blood. 2015;125:1302–13.
48. Nishioka C, Ikezoe T, Yang J, Nobumoto A, Tsuda M, Yokoyama A. Downregulation of miR-217 correlates with resistance of Ph+ leukemia cells to ABL tyrosine kinase inhibitors. Cancer Sci. 2014;105:297–307.
49. Mosakhani N, Mustjoki S, Knuutila S. Down-regulation of miR-181c in imatinib-resistant chronic myeloid leukemia. Mol Cytogenet. 2013;6:27.
50. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci USA. 2006;103:12481–6.
51. Rokah OH, Granot G, Ovcharenko A, Modai S. PasmanikChor M, Toren A, Shomron N and Shpilberg O: downregulation of miR-31, miR-155, and miR-564 in chronic myeloid leukemia cells. PLoS One. 2012;7:e35501.
52. Machová Poláková K, Lopotová T, Klamová H, Burda P, Trněný M, Stopka T, et al. Expression patterns of microRNAs associated with CML phases and their disease related targets. Mol Cancer. 2011;10:41.
53. Shibuta T, Honda E, Shiotsu H, Tanaka Y, Vellasamy S, Shiratsuchi M, et al. imatinib induces demethylation of miR-203 gene: an epigenetic mechanism of anti-tumor effect of imatinib. Leuk Res. 2013;37:1278–86.
54. Johora H, Gazi SH, Jannet K. The Potential for microRNA Therapeutics and Clinical Research. Front Genet. 2019; 10: 478.