REVIEW ARTICLE

Role of MicroRNA in Acute Myeloid Leukaemia: A Review

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SUMMARY

Expression of MicroRNAs (miRNAs), key regulators of normal haematopoiesis, is reportedly dysregulated in acute myeloid leukaemia (AML). Aberrant microRNA expression has been associated with different subtypes of AML, where they exert tumor suppressive or oncogenic functions. Deregulated microRNA expression has been shown to be of prognostic significance. Furthermore, it has been demonstrated that repression and ectopic expression of microRNAs affect response to treatment in AML. Consequently, microRNAs may act as potential biomarkers in AML hence production of new anti-AML drugs directed towards increasing and/or silencing miRNA expression may suffice.

Keywords:
microRNA, AML, Tumour suppressor gene

INTRODUCTION

MicroRNAs (miRNAs) are short non-coding 19-25 nucleotide RNAs that control gene expression by cleaving their target messenger RNA (mRNA) thus inhibiting protein translation. These miRNAs are produced in the nucleus and cytoplasm (Figure 1.1), where they undergo successive enzymatic cleavage by RNA polymerase II, DROSHA and DICER1 from primary transcripts (pri-miRNA) through hairpin precursors miRNA (pre-miRNA) to mature miRNA before integration into the RNA-inducing silencing complex (RISC) [1,2].

MicroRNAs play significant roles in haematopoiesis; regulating it by targeting various factors involved in cell proliferation, differentiation and apoptosis. However, aberrant microRNA expression has been linked to pathogenesis of varied diseases, including cancer. Recently, aberrant microRNA signature was recognized as one of the hallmarks of cancer [2]. Linkage between microRNA and cancer was first reported in chronic

lymphocytic leukaemia (CLL) [3]. Several methods, including quantitative reverse transcription polymerase chain reaction (qRT-PCR), have enabled validation of individual microRNA expression to clarify the linkage of aberrant microRNA expression to cancer, whereby microRNAs may act as oncogenes or tumor suppressors [2]. Upregulation of oncogene microRNA (oncomiRs) and downregulation of tumor suppressor microRNA support leukemogenesis.

Acute myeloid leukaemia (AML), a heterogeneous haematological malignancy, travels fast predominantly resulting in poor outcome. Cytogenetic abnormalities, age, chemotherapy and secondary haematological disease affect prognosis of AML. Distinct microRNA expression signatures in subtypes of AML suggest great potential to use these miRNAs as biomarkers.

Figure 1.1 MicroRNA biosynthesis pathway. Primary miRNA (pri-mRNA) is transcribed by RNA polymerase II (RNA pol II) in the nucleus. Pri-miRNA are cleaved by DROSHA and its cofactor DGCR8 (DROSHA-DGCR 8 complex) producing precursor miRNA (pre-miRNA). Pre-miRNA is transported by Exportin-5 protein into the cytoplasm, where they are cleaved by DICER1 before incorporation into the RNA-induced silencing complex (RISC). Mature miRNA binds to 3'-untranslated region (3'-UTR) of a target mRNA to induce mRNA cleavage, translational repression and/or mRNA deadenylation [2].

Biomarkers are biochemical/genetic/molecular features that indicate physiological state of an individual and also offer prognostic, diagnostic and/or therapeutic information in diseases. Distinct microRNA expression may offer information on diagnosis and prognosis of AML to better the clinical outcome of patients [1,4]. The prospective use of miRNAs as biomarkers may further provide novel therapeutic targets in AML. This review focuses on the potential role of specific miRNAs as biomarkers in AML with reference to recent findings.

MICRORNAS

These are single-stranded RNA molecules that regulate various physiologic processes in the body. There are about 2042 microRNAs in microRNA registry [5]. Biosynthesis of miRNAs is illustrated in Figure 1.1.

ACUTE MYELOID LEUKAEMIA

AML is a malignant disease caused by increased proliferation and differentiation block in myeloid blasts. Its incidence increases with age; the median age of AML is 68 years. Cytogenetic abnormalities and dysregulated gene expression contribute to the heterogeneity of AML pathogenesis. The major prognostic factor in AML is leukaemic karyotype. Based on French-American-British and World Health Organization classifications, AML is grouped into various subtypes and associated risk depending on cytogenetics (Table 3.1).

Figure 1.1 MicroRNA biosynthesis pathway.

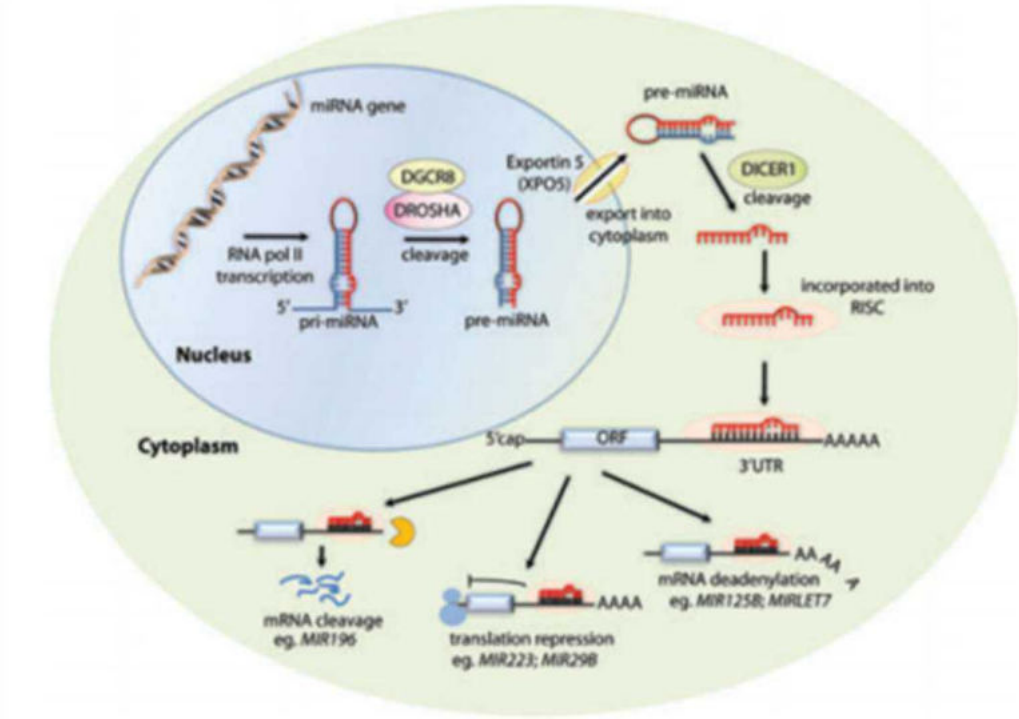


Table 3.1: Cytogenetic classification of various subtypes of AML based on prognosis

Cytogenetic abnormality	Subtype of AML	Associated risk/prognosis	Reference (s)
RUNXI/RUNXITI t(8;21)	Core binding factor leukaemia (CBFL)	Favourable	6, 7
RUNXI/MECOM (EVI1) t(3;21)	Core binding factor leukaemia (CBFL)	Favourable	7
CBFB-MYH11 inv(16) or t(16;16)	Core binding factor leukaemia (CBFL)	Favourable	6, 7
PML-RARA t(15;17)	Acute promyelocytic leukaemia	Favourable	2, 6, 7
Trisomy 8	AML not otherwise specified	Intermediate	7, 8
Translocation t(9; 11)	Acute monocytic leukaemia	Intermediate	7

Brain and acute leukaemia cytoplasmic (BAALC) expression	Cytogenetic-normal AML (CN-AML)	Poor	2
Nucleophosmin (NPM1)	Cytogenetic-normal AML (CN-AML)	Poor	9, 10
Internal tandem duplication of fms-related tyrosine kinase gene (FLT3/ITD)	Cytogenetic-normal AML (CN-AML)	Poor	10
CCAT/enhancer binding protein alpha (C/EBPA)	**Cytogenetic-normal AML (CN-AML)**	**Poor**	**1, 2**
IDH1/IDH2	Cytogenetic-normal AML (CN-AML)	Poor	4, 9
c-Kit	Core binding factor leukaemia (CBFL)	Poor	3
Deletion -7q	AML not otherwise specified	Poor	7
Deletion -7	AML not otherwise specified	Poor	6, 7
Translocation t(6;9)	Acute myeloblastic leukaemia	Poor	7
ERG expression	Cytogenetic-normal AML (CN-AML)	Poor	2

Translocation t(9;22)	**Philadelphia Chromosome positive-AML**	**Poor**	**7**
MN1 expression	Cytogenetic-normal AML (CN-AML)	Poor	2
Deletion -5	Therapy-related AML	Poor	7
Trisomy 21	.....	Poor	5
Cyclic-AMP responsive element binding protein (CREBBP)	Therapy-related AML	Poor	2
Trisomy 13 (Patau syndrome)	AML, minimally differentiated (M0)	Poor	5
Translocation t(1; 22)	Acute megakaryocytic leukaemia (M7)	Poor	2
Deletion -5q	Therapy-related AML	Poor	7
11q23 abnormalities	Acute monocytic leukaemia (M5)	Poor	7, 8, 11
Wilms tumor 1 (WT1)	Cytogenetic-normal AML (CN-AML)	Poor	9

This is a combination of FAB and WHO classifications of AML.

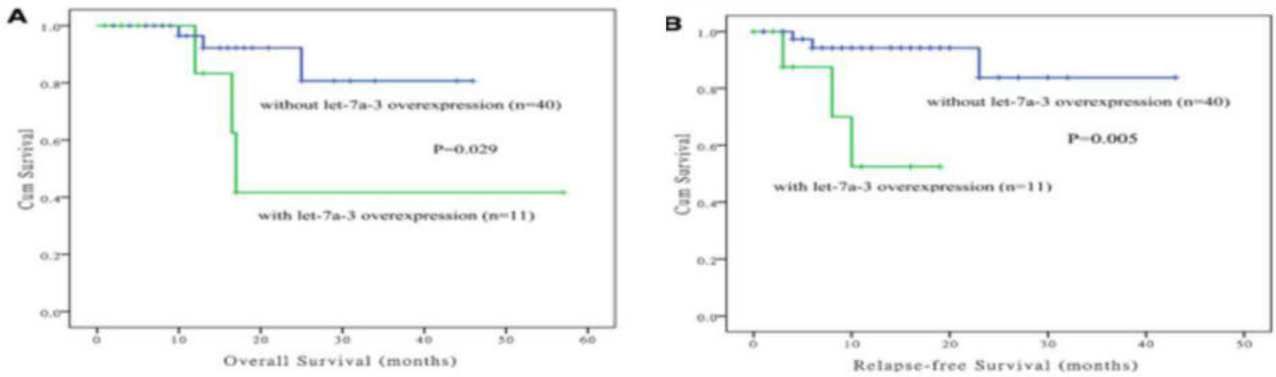
AML Subtype	MicroRNA(s) involved	Comments	Reference (s)
FLT3		Promotes apoptosis by targeting anti-apoptotic protein Pim-1	2, 3, 4, 6, 10, 12, 13, 14.
		Promotes differentiation by targeting HOXA10/MEIS	
		Blocks nuclear transcription factor NF-1A to promote apoptosis and inhibit proliferation	
		Inhibits differentiation of myeloid cells by targeting CEPBB, NFkB, JUN, PU.1, SHIP1	
Inv (3) RPN - MECOM (EVI1)	miR-449A↓	Promotes apoptosis through negative regulation of NOTCH1 and BCL2	2
KIT overexpression	miR-29b↓	Forms a network with SP1/NFkB1/HDAC resulting in KIT expression	2
ERG expression	miR-196a↑	Both miRNAs regulate ERG	2
	miR-196b↑		
BAALC overexpression	miR-148a↓	Negatively regulates BAALC expression	1, 2
	miR-3151↑	Targets USP40 and FBXL20 genes and is associated with poor overall survival (OS)	
CREBBP overexpression	miR-34b↓	Targets CREBBP regulating its expression	2
Erythroleukemia	miR-17↑	Targets pro-survival proteins BCL2, STAT5, JAK2	2, 8
	miR-92a↑		
		Regulates p53 through involvement of erythroid transcription factor GATA-1	
Acute megakaryobkastic leukemia	miR-125-2↑	Reduces expression of ST18 and DICER1	2, 15
	miR-29a↓	Associated with poor prognosis	

NPM1 mutation		Targets SERBINB9, SPARC	1, 2, 3, 14
		Targets IRF2 and KIT	
		Targets MN1,CLCN3, CRKL	
		Anti-apoptotic; targets KLF4 and RB1CC1	
CEBPA mutation	miR-181a↑	Erythroid differentiation of leukemic blasts	1, 2
	miiR-34a↓		
		Causes E2F3 overexpression and cell proliferation	
	miR-223↓	Reduces expression of CEBPA suppressor NF1-A and transcription factorE2F1	
MN1	miR-16↓	Promotes apoptosis by targeting BCL2	1
	miR-17-92↓	Involved in malignant transformation	
	miR-126↑	Promotes angiogenesis	
	miR424↑	Promotes macrophage/monocyte differentiation	
t(8;21) AML1/ETO	miR-223↑	Regulates myeloid differentiation; epigenetically regulated by RUNX1/RUNX1T1	2, 3, 16, 17
	miR-126↑	Regulates tumour suppressor PLK2 and inhibits apoptosis	
	miR-9↓	Promotes myelopoiesis and apoptosis	
	miR-221↓	Inhibits erythropoiesis through KIT downregulation	
t(15;17)	miR-125b↑	Enhances proliferation and subdues apoptosis through regulation of pro-apoptotic protein, BAK1	2
	miR-210↓	Targeted by PML-RARA	
	miR-23a↓	Targeted by PML-RARA	
t(8;16) (p11;p13) and KAT6A - reaarangement	miR-218↑	Targets proto-oncogene RET that encodes tyrosine-kinase receptor	2, 6

t(11q23) MLL - rearranged AML	miR-146a↓	Associated with poor prognosis in both ALL/AML	2, 4, 8, 10, 13, 14, 15, 17, 18
	miR-150↓	Enhances myeloid differentiation through MYB gene	
	miR-223↑	Regulates E2F2, NF1A, PU .1 Involved in myeloid differentiation	
	miR-196b↑	Regulated by MLL fusion protein	
	miR-155↓	Described as a lymphoid -specific microRNA	
	miR29a↓	Targets TCL-1, MCL-1	
	miR-17-92↑	Disrupts cell cycle by targeting CDK inhibitor	
	miR21↑	Targets tumor suppressor PTEN	
	miR-26↑	Targets TGFβ1 -regulator SMAD1	
	miR-181b↓	Targets homebox genes, HOXA7, HOXA9, HOXA11, PBX3	
	miR-495↓	Represses HOXA9 cofactors , MES1 and PBX3	

↑, upregulated - oncomiR; ↓, downregulated – tumor suppressor.

Figure 4.1: Overall (A) and relapse-free survival (B) of AML patients with and without miR-let-7a-3 expression [20].



TUMOR SUPPRESSOR MICRORNAS IN AML

Tumor suppressor microRNAs are microRNAs that repress the action of oncogenes that enhance leukemogenesis. These microRNAs promote differentiation and apoptosis of myeloid cells hence they are epigenetically silenced by oncogenes in AML. Several studies have illustrated a negative correlation between these miRNAs and aggressiveness of AML [8, 15].

MICRORNA-181

This family consists of miR-181a and miR-181b. MiR-181a was the first microRNA to be independently linked to prognosis in AML. In 2010, Schwind et al. [9] revealed an association between miR-181a overexpression and favourable outcome in 187 de novo CN-AML patients, especially in patients with FLT3-ITD and/or NPM1wild-type mutations. The prognostic significance of miR-181a overexpression in AML has been validated by two other studies. Recently, miR-181a overexpression was reportedly linked to the favourable prognosis group [15] whilst Li et al., [20] reported that upregulation of miR-181a and miR-181b in two sets of cytogenetically abnormal (CA)-AML patients was associated with better prognosis and longer overall survival (OS). Furthermore, miR-181a upregulation in AML cell line enhanced sensitivity to AML drug, Ara-C by inducing apoptosis of drug-resistant leukemic cells [19]. This correlates with Li et al. [20] findings of increased apoptosis and decreased proliferation in AML cells and mouse models following miR-181a and miR-181b overexpression.

Genes involved in development processes and innate immunity have been inversely linked to miR-181 expression. These genes include, toll like receptors (TLR2/TLR4), interleukin pathway (CASP1, Il1, IL1RN), transcription co-regulator ID1, FL1 gene, transcription factor TCF4, anti-apoptotic protein BCL2, homebox genes (HOXA/HOXB) andHOX cofactors, MEIS1 and PBX3 [8, 9, 19]. These genes promote leukemogenesis and are adverse prognosticators in AML.

However, miR-181 overexpression is directly associated with haematopoietic differentiation promoter TCF3 gene expression, decreased NF-kB expression, decreased miR-155 (oncomiR) expression, high haemoglobin level, white blood cell (WBC) count, percentage of circulating blasts and absence of extramedullary infiltration [9, 13, 15].These findings suggest miR-181 regulate immune response, differentiation and apoptosis hence highlighting a possible role of miR-181 as biomarkers in AML.

MICRORNA-LET-7

The lethal-7 (let-7) family consists of ten isoforms. Let-7a is the most studied member of this family. Conflicting reports suggest let-7a may act as a tumor suppressor or oncomiR in leukemogenesis.
Recently, Li et al. [20], reported that let-7a-3 overexpression in 102 newly diagnosed AML patients compared to normal patients is associated with a poor outcome, in contrast to what their results reveal (Figure 4.1). However, let-7a expression was repressed by stromal derived factor (SDF)-1–mediated CXCR4 activation in primary AML cells whereas transfection of let-7a induced inhibition of CXCR4and increased sensitivity of AML cells to Ara-C both in vitro and in vivo [24]. Further ChIP assay showed that transcription factor, Yin Yang 1 (YY1) binds to let-7a following SDF-1/CXCR4 signalling to thwart its suppressive actions. Genes involved in the regulation of apoptosis and immune responses, such as BCL-XL, CDK5, MYC, CASP3, RAS and interleukin-16 are possible targets of let-7a [24].

Other let-7 family members have also been associated with pathogenesis of AML. Several let-7 family members were upregulated in AML patients with NPM1 mutation and 3q26 abnormalities respectively [3,14]. Also, circulating levels of let-7b and let-7d were upregulated and downregulated respectively in plasma of 20 AML patients when compared to plasma of normal controls [5].

Upregulated let-7b expression can also distinguish acute leukemic types in mixed-lineage leukemia (MLL) which has poor prognosis [15]. These data suggest let-7 may be of prognostic and diagnostic significance in AML, however, the role of let-7a has to be elucidated with a large-cohort study.

MICRORNA-29

The miR-29 family includes three members often seen in 2 clusters: miR-29b-1/miR-29a and miR-29b-2/miR-29c [1]. MiR-29a may be overexpressed or under expressed in AML, depending on the molecular abnormalities. MiR-29a is overexpressed in patients with NPM1 and/or without FLT3/ITD mutations [6, 12] whereas Wang et al. [17] reported miR-29a under expression in 10 newly diagnosed AML patients.

Recently, diagnostic significance of miR-29a downregulation was revealed. Wang et al. [21] reported combined downregulation of miR-29a and miR-142-3p in peripheral blood mononuclear cells (PBMC) in 52 AML patients offered a better diagnostic outcome.

MiR-29b, on the other hand, is downregulated in AML, especially MLL due to its regulatory function in MLLT11 expression [17, 21]. Inverse correlation between miR-29b and MLLT11 expression was reported in primary AML cells in vivo and in vitro [25]. The authors further associated miR-29b downregulation with poor OS in MLL, in connection to Wang et al. [17] report that overexpression of 3-miRNA-outcome (miR-29b, miR-26a, miR-146a) signature in 40 AML patients conferred good prognosis.

Proto-oncogenes involved in haematopoietic development have been expressed as direct targets of miR-29. These genes include, MCL1, TCL1, DNTM3A/B, CDK6, JAK2, IGFR, SALL4 and HOXA9 [6, 21, 25]. These data reveal miR-29 offer some prognostic information due to their role in differentiation and apoptosis.

MICRORNA-150

MiR-150 is mainly expressed in secondary lymphoid organs and is over expressed during lymphoid development. It also promotes myeloid differentiation and is down regulated in AML [18]. Discordant miR-150 expression in different cells enables it distinguishes between acute leukemic types in MLL [11, 17]. Furthermore, combined plasma levels of miR-150 and miR-342 were found to be similar in AML patients that achieved complete remission (CR) and healthy controls [5].

The differentiate effect of miR-150 means it impairs proliferation of myeloid cells in AML. Therefore, miR-150 directly targets oncogene MYB that promotes self-renewal of cells [18]. These findings suggest miR-150 may have diagnostic and prognostic effect in AML.

ONCOMIRS IN AML

Oncogene miRNAs (oncomiRs) are miRNAs that promote leukemogenesis by suppressing tumor suppressor genes. In AML, oncomiRs expression is upregulated by leukemic stem cells thus affecting clinical outcome of patients. Several oncomiRs associated with AML have been identified (Table 3.1).

MICRORNA-155

MiR-155 is often overexpressed in acute leukemia. MiR-155 is regarded as a lymphoid-specific microRNA that targets PU.1, JUN and C/EBP□ genes thus inhibiting differentiation of myeloid cells [3, 17]. However, miR-155 overexpression is often associated with FLT3/ITD mutation in AML [3, 6, 7, 10, 13, 14, 15]. This association may be clinically relevant due to the prognostic value of FLT3/ITD and classification of miR-155 as an oncomiR. These findings were supported by miR-155 repression by anti-leukemic activity of silvesterol in AML cell lines carrying FLT3/ITD mutation [22].

Interestingly, miR-155 is also downregulated in FLT3/ITD-expressing AML cells. MiR-155 expression was low in FLT3/ITD-expressing

murine myeloid FDC-P1 cells [12]. This may due to independence of miR-155 expression on FLT3/ITD signaling [14]. These data suggest miR-155 overexpression is not specifically linked to FLT3/ITD mutation, therefore therapeutic targeting of miR-155 in FLT3/ITD-AML may offer no solution. New studies should be done to determine the prognostic and/or diagnostic significance of aberrant miR-155 expression in AML.

MICRORNA-9

MiR-9 has three isoforms, namely miR-9-1, miR-9-2 and miR-9-3. Its role in haematopoiesis is unknown due to contrasting reports. MiR-9 overexpression is synonymous with AML and may affect prognosis in AML. A recent study revealed miR-9 overexpression in a heterogeneous cohort of 101 newly formed AML patients had a negative impact on OS and RFS [23]. Similarly, ectopic expression of miR-9 promoted MLL-AF9/HOXA9-mediated transformation in normal mouse BM progenitor cells and in vitro [24]. Further ChIP assay in AML cell line showed that MLL-AF9 fusion protein binds to promoter regions of miR-9 to enhance its overexpression.

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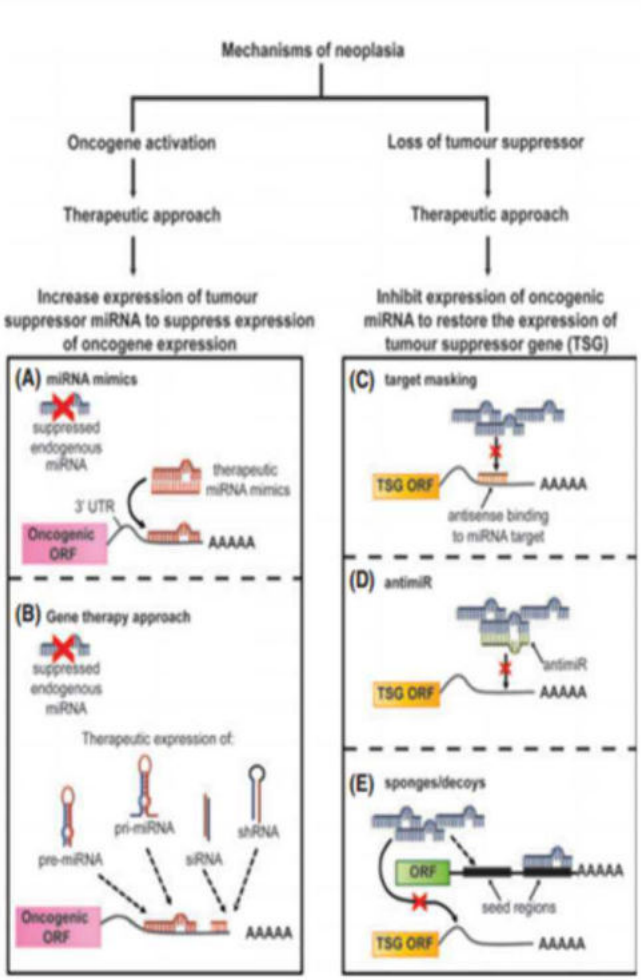
However, ectopic expression of miR-9 in ectopic viral integration site I (EVI1)-induced AML promoted myeloid differentiation and apoptosis in a murine model whilst EVI1 repressed miR-9 expression by binding to miR-9-3 promoter [16]. Furthermore, miR-9 is also downregulated in AML1/ETO rearrangement [3].

These findings suggest role of miR-9 in AML depends on the subtype involved. This disparity could be attributed to its isoforms. Gene-expression profiling revealed miR-9 targets separate genes in both context. When downregulated, miR-9 targets inhibitors of myeloid differentiation, Fox01 and Fox03, but targets RHOH and RYBP when upregulated [13, 24].



FUTURE DIRECTIONS

Figure 5.1 MicroRNA-based therapeutic strategies.AMiRNA mimics can reverse the expression and action of endogenous tumor suppressor miRNA. BGene therapy can either silence or increase expression of tumor suppressor miRNA through vector-driven expression of pre-miRNA/pri-miRNA and shRNA/siRNA respectively.C MicroRNA-masks compete with oncomiRs for antisense binding to mRNA target without inducing mRNA degradation. DAntimiR silence oncomiRs and inhibit repression of tumor suppressor gene expression by binding to oncomiRs. ESponges or decoys contain miRNA binding sites that block binding of overexpressed oncomiRs to their target sites. ORF, open reading frame. TSG, tumor suppressor gene [2].

Noting the abundance of the aforementioned information, it is evident microRNA may act as biomarkers and provide a novel insight into AML therapy. The fact that miRNAs can differentiate acute leukaemic types and enhance drug sensitivity suggest their potentials as therapeutic targets in AML. The development of microRNA-based therapy (Figure 5.1) is aimed at increasing the level of tumour suppressor microRNAs and/or silencing oncomiRs expression.

CONCLUSION

AML travels a very fast course hence accurate diagnosis and prognosis is fundamental to give the clinician a timeframe in the treatment of AML patients. Despite the success of stem cell transplantation, high relapse rates and early death are associated with the AML phenotype due to its heterogeneity. The linkage of aberrant microRNA expression to pathogenesis, diagnosis and prognosis of AML suggests a possible role for microRNAs as biomarkers as clinicians seek a solution to this problem. MicroRNAs are involved in regulation of distinct physiological processes, such as gene expression and haematopoiesis. These microRNAs offer novel therapeutic targets and suggest the development of new microRNA-based leukaemic therapies with minimal side effects. However, large-scale randomized controlled trials should be conducted to validate the efficacy and bioavailability of potential microRNA-based drugs in AML

REFERENCES

1. Marcucci, G., Mr□zek, K., Radmacher, M.D., Garzon, R. and Bloomfield, C.D. The prognostic and functional role of microRNAs in acute myeloid leukemia. Blood. 2011; 117 (4): 1121-9.
2. Gordon, J.E., Wong, J.J. and Rasko, J.E. MicroRNAs in myeloid malignancies. British Journal of Haematology. 2013; 162 (2): 162-176.
3. Cammarata, G., Augugliaro, L., Salemi, D., Agueli C., La Rosa, M., Dagnino, L., Civiletto, G., Messana, F., Marfia, A., Bica, M.G., Cascio, L., Florida, P.M., Mineo, A.M., Russo, M., Fabbiano, F. and Santoro, A. Differential expression of specific microRNA and their targets in acute myeloid leukemia. American Journal of Haematology. 2010; 85 (5): 331-339.
4. Chen, Y., Jacamo, R., Konopleva, M., Garzon, R., Croce, C. and Andreeff, M. CXCR4 downregulation of let-7a drives chemoresistance in acute myeloid leukemia. Journal of Clinical Investigation. 2013; 123 (6): 2395-2407.
5. Fayyad-Kazan, H., Bitar, N., Najar, M., Lewalle, P., Fayyad-Kazan, M., Badran, R., Hamade, E., Daher, A., Hussein, N., ElDirani, R., Berri, F., Vanhamme, L., Burny, A., Martiat, p., Rouas, R. and Badran, B. Circulating miR-150 and miR-342 in plasma are novel potential biomarkers in acute myeloid leukemia. Journal of Translational Medicine. 2013; 11: (31).
6. Danen-van Oorschot, A.A., Kuipers, J.E., Arentsen-Peters, S., Schotte, D., de Haas, V., Trka, J., Baruchel, A., Reinhardt, D., Pieters, R., Zwaan, C.M. and van den Heuvel-Eibrink, M. Differentially expressed miRNAs in cytogenetic and molecular subtypes of pediatric acute myeloid leukemia. Pediatric Blood and Cancer. 2012; 58(5): 715-721.
7. Zhi, F., Cao, X., Xie, X., Wang, B., Dong, W., Gu, W., Ling, Y., Wang, R., Yang, Y. and Liu, Y. Identification of circulating microRNAs as potential biomarkers for detecting acute myeloid leukemia. PLoS One. 2013; 8 (2): e56718.
8. Li, Z., Huang, H., Li, Y., Jiang,

X., Chen, P., Arnovitz, S., Radmacher, M.D., Maharry, K., Elkahloun, A., Yang, X., He, C., He, M., Zhang, Z., Dohner, K., Neilly, M.B., price, C., Luisser, Y.A., Zhang, Y., Larson, R.A., Le Beau, M.M., Caliguiri, M.A., Bullinger, L., Valk, P.J., Delwel, R., Lowenberg, B., Liu, P.P., Marcucci, G., Bloomfield, C.D., Rowley, J.D. and Chen, J. Upregulation of a HOXA-PBX3 homeobox-gene signature following down-regulation of miR-181 is associated with adverse prognosis in patients with cytogenetically abnormal AML. Blood. 2012; 119 (10): 2314-2324.

9. Schwind, S., Maharry, K., Radmacher, M.K., Mro'zek, K., Holland, K.B., Margeson, D., Whitman,S.P., Hickey, C., Becker, H., Metzeler, K.H., Paschka, P., Baldus, C.D., Liu, S., Garzon, R., Powell, B.L., Kolitz, J.E., Caroll, A.J., Caliguiri, M.A., Larson, R.A., Marcucci, G. and Bloomfield, C.D. Prognostic Signi□cance of Expression of a single MicroRNA, miR-181a, in Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study. Journal of Clinical Oncology. 2010; 28 (36): 5257-5264.
10. Faraoni, I., Laterza, S., Ardiri, D., Ciardi, C., Fazi, F. and Lo-Coco, F. MiR-424 and miR-155 deregulated expression in cytogenetically normal acute myeloid leukemia: correlation with NPM1 and FLT3 mutation status. Journal of Haematology and Oncology. 2012; 5: 26.
11. De Leeuw, D.C., van den Ancker, W., Denkers, F., de Menezes, R.X., Westers, T.M., Ossenkoppele, G.J., van den Loosdrecht, A.A and Smit, L. MicroRNA profiling can classify acute leukemias of ambiguous lineage as either acute myeloid leukemia or acute lymphoid leukemia. Clinical Cancer Research. 2013; 19 (8): 2187-2196.
12. Kim, K.T., Caroll, A.P., Mashkani, B., Cairns, M.J., Small, D., and Scott, R.J. MicroRNA-16 Is Down-Regulated in Mutated FLT3 Expressing Murine Myeloid FDC-P1 Cells and Interacts with Pim-1. PLoS One. 2012: 7 (9): e44546.
13. Garzon, R., Volinia, S., Liu, C.G., Fernandez-Cymering, C., Palumbo, T., Pichiorri, F., Fabbri, M., Coombes, K., Alder, H., Nakamura, T., Flomenberg, N., Marcucci, G., Calin, G.A., Kornblau, S.M., Kantarjian, H., Bloomfield, C.D., Andreeff, M. and Croce, C.M. MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia. Blood. 2008a; 111(6): 3183-3189.
14. Garzon, R., Garofalo, M., Martelli, M.P., Briesewitz, R., Wang, L., Fernandez-Cymering,C., Volinia, S., Liu, C.G., Schnittger, S., Haferlach, T., Liso, A., Diverio, D., Mancini, M., Meloni, G., Foa, R., Martelli, M.F., Mecucci, C., Croce, C.M. and Falini, B. Distinctive microRNA signature of acute myeloid leukemia bearing cytoplasmic mutated nucelophosmin. PNAS. 2008b; 105 (10): 3945-3950.
15. Zhu, Y.D., Wang, L., Sun, C., Fan, L., Zhu, D.X., Fang, C., Wang, Y.H., Zou, Z.J., Zhang, S.J., Li, J.Y. and Xu, W. Distinctive microRNA signature is associated with the diagnosis and prognosis of acute leukemia. Medical Oncology. 2012; 29 (4): 2323-2331.
16. Senyuk, V., Zhang, Y., Lui, Y., Ming, M., Premanand, K., Zhou, L., Chen, P., Chen, J., Rowley, J.D., Nucifora, G. and Qian, Z. Critical role of miR-9 in myelopoiesis and EVI1-induced leukemogenesis. PNAS. 2013; 110 (14): 5594-5599.
17. Wang, Y., Li, Z., He, C., Wang, D., Yuan, X., Chen, J. and Jie, J. MicroRNA expression signatures are associated with lineage and survival in acute leukemia. Blood Cells, Molecules and Diseases. 2010; 44 (3): 191-197.
18. Morris, V.A., Zhang, A., Yang, T., Stirewalt, D.L., Ramamurthy, R., Meshinchi, S. and Oehler, V.G. MicroRNA-150 expression induces myeloid differentiation of human acute leukemia cells and normal haematopoietic progenitors. PLoS One. 2013; 8(9): e75815.
19. Bai, H., Cao, Z., Deng, C., Zhou, L., and Wang, C. miR-181a sensitizes resistant leukemia HL-60/Ara-C cells to Ara-C by inducing apoptosis. Journal of Cancer Research and Clinical

Oncology. 2012; 138 (4): 595-602.
20. Li, Y., Lin, J., Qian, J., Qian, W., Yao, D.M., Deng, Z.Q., Liu, Q., Chen, X.X., Xie, D., An, C. and Tang, C.Y. Overexpressed let-7a-3 is associated with poor outcome in acute myeloid leukemia. Leukemia Research. 2013; 37 (12): 1642-1647.
21. Wang, F., Wang, X.S., Yang, G.H., Zhai, P.F., Xiao, Z., Xia, L.Y., Chen, L.R., Wang, Y., Wang, X.Z., Bi, L.X., Liu, N., Yu, Y., Gao, D., Huang, B.T., Wang, J., Zhou, D.B., Gong, J.N., Zhao, D.B., Gong, J.N., Zhao, H.L., Bi, X.H., Yu, J and Zhang, J.W. MiR-29a and miR-142-3p downregulation and diagnostic implication in human acute myeloid leukemia. Molecular Biology Reports. 2012; 39(3): 2713-2722.
22. Alachkar, H., Santhanam, R., Harb, J.G., Lucas, D.M., Oaks, J.J., Hickey, C.J., Pan, L., Kinghorn, A.D., Caliguiri, M.A., Perrotti, D., Byrd, J.C., Garzon, R., Grever, M.R. and Marcucci, G. Silvesterol exhibits significant in vivo and in vitro antileukemic activities and inhibits FLT3 and miR-155 expressions in acute myeloid leukemia. Journal of Haematology and Oncology. 2013; 6: 21.
23. Maki, K., Yamagata, T., Sugita, F., Nakamura, Y., Sasaki, K., and Mitani, K. Aberrant expression of MIR9 indicates poor prognosis in acute myeloid leukemia. British Journal of Haematology. 2012; 158(2): 283-285.
24. Chen, P., Price, C., Li, Z., Li, Y., Cao, D., Wiley, A., He, C., Gurbuxani, S., Kunjamma, R.B., Huang, H., Jiang, X., Arnovitz, S., Xu, M., Hong, G.M., Elkahloun, A.G., Neilly, M.B., Wunderlich, M., Larson, R.A., Le Beau, M.M., Mulloy, J.C., Liu, P.P., Rowley, J.D. and Chen, J. MiR-9 is an essential oncogenic microRNA specifically overexpressed in mixed lineage leukemia-rearranged leukemia. PNAS. 2013; 110 (28): 11511-11516.
25. Xiong, Y., Li, Z., Ji, M., Tan, A.C., Bemis, J., Tse, J.V., Huang, G., park, J., Ji, C., Chen, J., Bemis, L.T., Bunting, K.D. and Tse, W. MiR29B regulates expression of MLLT11 (AF1Q), an MLL fusion partner and low MIR29B expression associates with adverse cytogenetics and poor overall survival in AML. British Journal of Haematology. 2011; 153(6): 753-757.