

MiR-204 in Acute Myeloid Leukemia: A Comprehensive Review

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Acute myeloid leukemia (AML) is the most lethal of all leukemias, which is caused by genetic aberrations such as abnormal miRNA expression profiles. MicroRNA-204 is a small RNA that plays crucial physiological roles in retinal development and adipogenesis. In addition it can also impact tumor initiation, growth, and progression by regulating different processes. In AML, many studies have shown that miR204 can be considered a diagnosis and prognosis biomarker that can improve differentiation, apoptosis, survival, and response to chemotherapy by inhibiting different targets. The available, current knowledge concerning the influence of microRNA 204 on AML is summarized in this short review. Understanding the mechanism of action of miR-204 in AML could help treat and establish effective therapies.

Introduction

Acute myeloid leukemia (AML) is the most lethal of all leukemias and the second most common type of leukemia in the world with the most abbreviated survival. It is usually treated with current standard chemotherapy, which can cure only about 40-45% of younger and about 10-20% of older patients [1-3]. AML is caused by genetic aberrations; including gene mutations, chromosomal rearrangements, and abnormal miRNA expression profiles [4].

MiRNAs are a class of single-stranded, non-coding, small RNAs that play a crucial role in the posttranscriptional regulation of genes expression. A miRNA inhibits the expression of genes by linking to the three prime untranslated region or five prime untranslated region (3'-UTR or 5'-UTR) of one or more ARNm specific sequences [5, 6]. MiRNAs can play two different opposing roles that of an oncogene and that of a tumor suppressor, depending on cancer type [7]. In AML, their expression profiles vary according to AML subtypes and during the myeloid differentiation process [8, 9]. The deregulation of the miRNAs expression is a biomarker of cancer development and progression. They act as tumor suppressors that are downregulated in many types of human cancers, such as miR-503, miRNA-876, and miRNA-451 [10-12].

MiR-204 (microRNA-204) has been demonstrated to have crucial physiological roles in retinal development and formation of adipocytes from stem cells. In cancer, it influences the tumor initiation, growth, and progression by regulating angiogenesis, apoptosis, and metastasis processes. MiR-204 has many direct target genes, coding for proteins involved in tumorigenesis of different cancer types, such as BCL-2 (an apoptosis regulator) in gastric cancer, JAK2 (a tyrosine kinase) in breast cancer, RUNX2 (a transcription factor) in prostate cancer, SOX4 (a transcriptional regulator) in acute lymphoblastic leukemia, and EPHB2 (a receptor tyrosine kinase) in glioma [13, 14]. In this review, I reported the role of miR-204 in AML based on published experimental studies.

Materials and Methods

Inclusion and exclusion criteria

This study was conducted to show the role of miR-204 in AML by reviewing the published results on

this topic. The bibliographic search was conducted on the electronic databases PubMed, Scopus, and Google Scholar. By using the following keywords: “acute myeloid leukemia; AML; microRNA-204, hsa-mir-204; miR-204”. We also searched the references cited in selected studies. The selected studies were screened (by reading the title, the abstract, and the entire article); studies linked to our subject were included in the present review, while duplicate publications, case reports, reviews, and studies that not meet the purpose of the research were excluded. The search strategy retrieved 60 articles. Of these articles, 10 were eligible for the present review. The aforementioned steps concerning the selection of studies are illustrated in detail in Figure 1.

Figure 1. Flow Chart Explaining the Selection of the Included Studies.

Results and Discussion

miR-204 Biogenesis and gene role in AML

MiR-204 belongs to the miR-204/211 family. These two paralogs (miR-204, miR-211) are located in the intronic region of the two genes *TRPM3* and *TRPM1* (transient receptor potential 1/3) and have the same seed sequence, but their mature sequences differ only by one or two nucleotides, and they can target the same genes.

The *MiR-204* gene is located at chromosome 9q21.12 and produces, after several complex steps, two mature miRNAs, miRNA-204-3p and miRNA-204- 5p Figure 2 [15, 16].

Figure 2. Sequence of miR-204: A Stem-loop structure of miR-204; B mature sequences of miRNA 204-5p and 3p. (<http://mirbase.org/>).

Some genetic variations of the *miR-204* gene have been reported to be associated with higher AML risk and patient outcomes. In a case-control study by Butrym et al, the GG homozygote genotype of the polymorphism rs718447 of the *miR-204* flanking region was found to be a risk factor for AML and more frequent in patients with M0-M1 subtypes according to FAB classification, and patients with the wild-type A allele had longer survival compared with patients without allele A [17].

MiR-204 expression in AML

In terms of its expression, several studies have demonstrated that miR-204 expression is significantly lower in AML patients compared with the control groups and also showed that its expression is downregulated in human AML tissues and in many AML cell lines, such as U937, AML5, AML193, HL-60 and Kasumi-1 [18-20]. These results suggest that miR-204 might have an antitumor function and that its down- regulation contributes to dysfunctional hematopoiesis.

miR-204 expression and different variables

A cohort study by Abdelhafiz et al, showed that there was no significant association between miR-204 expression and patient's age, gender, biological parameters, cytogenetics, or FAB classification [21]. Similar results have been reported by Nie et al [18].

Regarding AML biomarkers CD, the low expression of miR-204 was significantly correlated with the presence of the biomarker for the inhibition of hematopoietic stem cell (HSCs) differentiation,

CD34, which is associated with resistance to apoptosis and bad prognosis in AML patients. A similar trend was observed in the expression of the aberrant markers CD7, CD19, and CD56 [21-23]. According to all these results, miR-204 overexpression can be used as a basis for the diagnosis of AML, but it cannot help differentiate AML subclasses.

Mechanism of miR 204 downregulation and targets

To understand the mechanisms responsible for miR-204 downregulation in AML, a few studies have been conducted and showed that there are several possible explanations for miR-204 downregulation in AML. Recently, Liang et al discovered that urothelial carcinoma-associated 1 (UCA1) could directly link to miR-204, playing the role of an endogenous sponge in AML cells; UCA1 is known as an oncogene long non-coding RNA, its expression is higher in AML cells, and it's negatively associated with the expression of miR-204. This mechanism may be an explanation for the miR-204 downregulation seen in AML [24].

In the same study, by using bioinformatics analyses, they found that SIRT1 is the putative target of miR-204. SIRT1 (NAD-dependent deacetylase sirtuin-1) is an oncogene that plays a crucial role in carcinogenesis [25]. Additionally, they found that overexpression of UCA1 positively regulates cell proliferation and inhibits apoptosis by activating the SIRT1 pathway and downregulating miR-204. However, the higher expression of miR-204 was found to inhibit the expression of the tumor promoting SIRT1 and two related proteins, iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase), that are activated by UCA1 [24].

In addition, one study has introduced another explanation for the reduced miR-204 expression in AML; Xue et al by using bioinformatics tools and luciferase assay, confirmed that the long noncoding RNA LOC285758 targets the miR-204 gene and reduces the transcription of miR-204-5p, which plays a crucial role in the regulation of the expression of E-cadherin, N-cadherin and Twist1 [26]. The LOC285758 has been reported to stimulate AML cell proliferation, to increase the viability and invasion of AML cells, and to be associated with a worse prognosis [27] Figure 3.

Figure 3. MiR204 Functions in AML. Unregulated miR-204 inhibits the expression of BIRC6, inducing apoptosis by activating the p53-dependent pathway, while it inhibits HOXA10, which induces myeloid differentiation, and it inhibits Sir1, which leads to the repressing of cell proliferation, and by inhibiting LINC00641 and HGF, it represses proliferation, migration, and invasion of AML cells.

MiR-204 has also been reported to have a tumor suppressor function in acute lymphoid leukemia (ALL). In 2015, Yin et al revealed that miR-204 is lowly expressed in T-ALL. However, miR-204 overexpression significantly suppressed the migration and invasion ability of T-ALL cells via targeting SOX4 and inhibiting its expression. The sex-determining region Y-box (SOX4) transcription factor regulates cellular differentiation and oncogenesis via the activation of the oncogenic PI3K/AKT and MAPK signaling pathways in ALL [28, 29].

Another study, by using a microarray platform, Garzon et al found that the miR-204 in AML patients with NPM1+ (mutated nucleophosmin) targets HOXA10 protein that is involved in the alteration of the myeloid differentiation process of HSCs and represents a poor prognostic factor for AML [30, 31].

A recent study by Zhang et al found that there were targeted relationships between miR-204 and the long intergenic non protein coding RNA641 (LINC00641), which has been reported to be highly present in AML tissues and cell lines. In this study, they showed that miR-204-5p overexpression or LINC00641 inhibition could inhibit cell proliferation, migration, and invasion [32, 33].

Regarding the role of miR-204 in AML cell apoptosis, Wang et al by using flow cytometry and

population in different phases of the cell cycle, revealed that the upregulation of miR-204 decreased human AML cell viability through activating cell death by arresting the cell cycle at the subG1 phase [34]. A consistent result was reported with the study by Nie et al [18]. These findings reinforce the pro-apoptotic role of miR-204 in AML. In the same study by Wang et al, miR-204 stimulated apoptosis of AML cells by targeting BIRC6. BIRC6 (Baculoviral IAP Repeat Containing 6), also named Apollon/ Bruce, is one member of the inhibitor of apoptosis proteins family (IAPs), which blocks cell death by destabilizing and degrading p53 protein by ubiquitination [34, 35].

These results indicate that miR-204 activates the p53-dependent pathway of apoptosis by increasing the expression of p53. In AML, BIRC6 overexpression is correlated with poor therapeutic response and lower survival. Similar findings were reported in children with ALL [36-38]. In another study, Schläfli et al found that BIRC6 mRNA levels are lower in CD34 positive myeloid precursors but higher in differentiated granulocytes and concluded there is an association between low BIRC6 expression and the immature myeloid phenotype, which reflects a cancer-associated deregulation [39]. These studies indicate that miR-204 acts as a tumor suppressor in AML by inhibiting cell proliferation and inducing apoptosis.

miR-204 expression, chemotherapy response, and AML patient's survival

ATO is a chemotherapy drug that is extensively used in the treatment of acute promyelocytic leukemia (APL); it activates differentiation and apoptosis in APL cells [40]. A study by Wang et al found that miR-204 reduces chemoresistance to arsenic trioxide (ATO) and stimulates its apoptotic effect in AML cells [41]. They demonstrated that the ATO plays its antileukemic role by increasing the level of miR-204, which, in turn, potentiates ATO-induced apoptosis of AML cells by suppressing BIRC6 expression, which leads to the activation of the p53-dependent apoptotic signaling pathway [40]. These results suggested that miR-204 can serve as a diagnostic and prognostic biomarker for AML and, by its proapoptotic effect, can be a very promising therapeutic target for AML treatment. In another study, Abdelhafiz et al found that AML patients with higher expression of miR-204 had a good chance of achieving complete remission post-induction therapy. However, lower miR-204 expression was found to be a poor prognostic factor when comparing survival rates and miR-204 expression level; AML patients with low expression of miR-204 have significantly shorter overall survival (OS) and disease free survival (DFS) [21]. Other studies reported similar findings and showed that low expression of miR-204 was associated with shorter survival [19, 20].

It is certain that miR-204 plays an important role in AML. However, more research will be required before introducing this miR into the clinical field.

Limitations and future research

The studies that are part of the present review have some limitations that highlight the need for additional research. First, the small number of published studies on the relationship between miR-204 and the risk of AML might influence the evaluation of this association.

Second, some studies included in this review have a small sample size, which can diminish the reliability of research results and influence their interpretation. Third, the majority of these studies have been performed in vitro, neglecting the influence of the tumor microenvironment on the expression and the role of miRNA204 and its targets. Using Cell lines such as U937, AML5, and Kasumi-1 that are studied in artificial environments where they often behave differently than actual tumors in vivo.

Fourth, AML is a multifactorial disorder related to both genetic and environmental factors;

however, these studies did not include the analysis of other factors, such as comorbidities, genetic mutations, and the state of the immune system, quality of life, healthcare, and nutritional conditions.

To overcome these limitations, I recommend that future research use the three-dimensional (D) co-model that is closer to in vivo physiological conditions, allowing a better understanding of the miR-204 role in AML and I also recommend performing environment-wide association studies (EWAS) to explore the environmental risk factors interaction effects with miRNA204 on the risk of AML.

MiRNA-based therapy is a new therapy approach that is still in the early phases of development, but it can be a promising therapeutic strategy to improve therapeutic outcomes of AML, especially with the use of advanced delivery technologies such as natural nanoparticles (exosomes) and nanoparticles [42].

In conclusion, the downregulation of miR204 in human AML cells is associated with the development and progression of AML and shorter survival. However, its upregulation decreased human AML cell proliferation, accelerated apoptosis, and reduced chemoresistance. Indeed, by restoring its expression, miR204 could be a promising biomarker and serve as a potential drug target for antileukemic therapy especially with the use of advanced delivery technologies such as nanoparticles.

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Statement of Transparency and Principles

- The authors declare no conflict of interest.
- The study was approved by the Research Ethics Committee of the authors' affiliated institution.
- The study data are available upon reasonable request.
- All authors contributed to the implementation of this research.

References

References

1. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. *Blood Reviews*. 2019; 36^{[DOI](#)}
2. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)*. 2016; 388(10053)^{[DOI](#)}
3. Bose P, Vachhani P, Cortes JE. Treatment of Relapsed/Refractory Acute Myeloid Leukemia. *Current Treatment Options in Oncology*. 2017; 18(3)^{[DOI](#)}
4. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. 2013; 381(9865):484-95. ^{[DOI](#)}
5. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004; 116(2)^{[DOI](#)}
6. Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell*. 2009; 136(2)^{[DOI](#)}

7. Garzon R, Calin GA, Croce CM. MicroRNAs in Cancer. *Annual Review of Medicine*. 2009; 60^{[DOI](#)}
8. Jongen-Lavrencic M, Sun SM, Dijkstra MK, Valk PJM, Löwenberg B. MicroRNA expression profiling in relation to the genetic heterogeneity of acute myeloid leukemia. *Blood*. 2008; 111(10)^{[DOI](#)}
9. Li Z, Lu J, Sun M, Mi S, Zhang H, Luo RT, Chen P, et al. Distinct microRNA expression profiles in acute myeloid leukemia with common translocations. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105(40)^{[DOI](#)}
10. Gupta G, Chellappan DK, Jesus Andreoli Pinto T, Hansbro PM, Bebawy M, Dua K. Tumor suppressor role of miR-503. *Panminerva Medica*. 2018; 60(1)^{[DOI](#)}
11. Ursu S, Majid S, Garger C, Semir D, Bezrookove V, Desprez P, McAllister S, et al. Novel tumor suppressor role of miRNA-876 in cholangiocarcinoma. *Oncogenesis*. 2019; 8(8)^{[DOI](#)}
12. Nan Y, Han L, Zhang A, Wang G, Jia Z, Yang Y, Yue X, Pu P, Zhong Y, Kang C. MiRNA-451 plays a role as tumor suppressor in human glioma cells. *Brain Research*. 2010; 1359^{[DOI](#)}
13. Bereimipour A, Najafi H, Mirsane ES, Moradi S, Satarian L. Roles of miR-204 in retinal development and maintenance. *Experimental Cell Research*. 2021; 406(1)^{[DOI](#)}
14. Li T, Pan H, Li R. The dual regulatory role of miR-204 in cancer. *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine*. 2016; 37(9)^{[DOI](#)}
15. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell*. 2005; 120(1)^{[DOI](#)}
16. Vitiello M, Tuccoli A, D'Aurizio R, Sarti S, Giannecchini L, Lubrano S, Marranci A, et al. Context-dependent miR-204 and miR-211 affect the biological properties of amelanotic and melanotic melanoma cells. *Oncotarget*. 2017; 8(15)^{[DOI](#)}
17. Butrym A, Łacina P, Kuliczowski K, Bogunia-Kubik K, Mazur G. Genetic variation of the gene coding for microRNA-204 (miR-204) is a risk factor in acute myeloid leukaemia. *BMC cancer*. 2018; 18(1)^{[DOI](#)}
18. Nie D, Ma P, Chen Y, Zhao H, Liu L, Xin D, Cao W, et al. MiR-204 suppresses the progression of acute myeloid leukemia through HGF/c-Met pathway. *Hematology (Amsterdam, Netherlands)*. 2021; 26(1)^{[DOI](#)}
19. Butrym A, Rybka J, Baczyńska D, Tukiendorf A, Kuliczowski K, Mazur G. Low expression of microRNA-204 (miR-204) is associated with poor clinical outcome of acute myeloid leukemia (AML) patients. *Journal of experimental & clinical cancer research: CR*. 2015; 34(1)^{[DOI](#)}
20. Moussa Agha D, Rouas R, Najjar M, Bouhtit F, Naamane N, Fayyad-Kazan H, Bron D, Meuleman N, Lewalle P, Merimi M. Identification of Acute Myeloid Leukemia Bone Marrow Circulating MicroRNAs. *International Journal of Molecular Sciences*. 2020; 21(19)^{[DOI](#)}
21. Abdelhafiz AS, Elsayed GM, Saber MM, Gameel A, Hamdy N. Low expression of miR-204 is associated with expression of CD34 and poor performance status in denovo AML. *International Journal of Laboratory Hematology*. 2020; 42(3)^{[DOI](#)}
22. Furness SGB, McNagny K. Beyond mere markers: functions for CD34 family of sialomucins in hematopoiesis. *Immunologic Research*. 2006; 34(1)^{[DOI](#)}
23. Zeijlemaker W, Kelder A, Wouters R, Valk PJM, Witte BI, Cloos J, Ossenkoppele GJ, Schuurhuis GJ. Absence of leukaemic CD34+ cells in acute myeloid leukaemia is of high prognostic value: a longstanding controversy deciphered. *British Journal of Haematology*. 2015; 171(2)^{[DOI](#)}
24. Liang Y, Li E, Zhang H, Zhang L, Tang Y, Wanyan Y. Silencing of lncRNA UCA1 curbs proliferation and accelerates apoptosis by repressing SIRT1 signals by targeting miR-204 in pediatric AML. *Journal of Biochemical and Molecular Toxicology*. 2020; 34(3)^{[DOI](#)}
25. Huffman DM, Grizzle WE, Bamman MM, Kim J, Eltoum IA, Elgavish A, Nagy TR. SIRT1 is significantly elevated in mouse and human prostate cancer. *Cancer Research*. 2007; 67(14)^{[DOI](#)}
26. Xue F, Che H. The long non-coding RNA LOC285758 promotes invasion of acute myeloid leukemia cells by down-regulating miR-204-5p. *FEBS open bio*. 2020; 10(5)^{[DOI](#)}
27. Lei L, Xia S, Liu D, Li X, Feng J, Zhu Y, Hu J, et al. Genome-wide characterization of lncRNAs in acute myeloid leukemia. *Briefings in Bioinformatics*. 2018; 19(4)^{[DOI](#)}

28. Yin J, Liang B, Zhan X. MicroRNA-204 inhibits cell proliferation in T-cell acute lymphoblastic leukemia by down-regulating SOX4. *International Journal of Clinical and Experimental Pathology*. 2015; 8(8)
29. Ramezani-Rad P, Geng H, Hurtz C, Chan LN, Chen Z, Jumaa H, Melnick A, et al. SOX4 enables oncogenic survival signals in acute lymphoblastic leukemia. *Blood*. 2013; 121(1)[DOI](#)
30. Garzon R, Garofalo M, Martelli MP, Briesewitz R, Wang L, Fernandez-Cymering C, Volinia S, et al. Distinctive microRNA signature of acute myeloid leukemia bearing cytoplasmic mutated nucleophosmin. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105(10)[DOI](#)
31. Collins CT, Hess JL. Dereglulation of the HOXA9/MEIS1 axis in acute leukemia. *Current Opinion in Hematology*. 2016; 23(4)[DOI](#)
32. Zhang Y, Yang Y, Sun Y, Chai H. [Effect of LINC00641 on Viability and Apoptosis of Acute Myeloid Leukemia Cells]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2025; 33(4)[DOI](#)
33. Wang J., Liu Z.-H., Yu L.-J.. Long non-coding RNA LINC00641 promotes cell growth and migration through modulating miR-378a/ZBTB20 axis in acute myeloid leukemia. *European Review for Medical and Pharmacological Sciences*. 2019; 23(17)[DOI](#)
34. Wang Z, Luo H, Fang Z, Fan Y, Liu X, Zhang Y, Rui S, et al. MiR-204 acts as a potential therapeutic target in acute myeloid leukemia by increasing BIRC6-mediated apoptosis. *BMB reports*. 2018; 51(9)[DOI](#)
35. Martin SJ. An Apollon vista of death and destruction. *Nature Cell Biology*. 2004; 6(9)[DOI](#)
36. Sung KW, Choi J, Hwang YK, Lee SJ, Kim H, Lee SH, Yoo KH, Jung HL, Koo HH. Overexpression of Apollon, an antiapoptotic protein, is associated with poor prognosis in childhood de novo acute myeloid leukemia. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2007; 13(17)[DOI](#)
37. Ismail EAR, Mahmoud HN, Tawfik LM, Habashy DM, Adly AAM, El-Sherif NH, Abdelwahab MA. BIRC6/Apollon gene expression in childhood acute leukemia: impact on therapeutic response and prognosis. *European Journal of Haematology*. 2012; 88(2)[DOI](#)
38. Abe S., Yamamoto K., Hasegawa M., Inoue M., Kurata M., Hirokawa K., Kitagawa M., Nakagawa Y., Suzuki K.. Bone marrow cells of myelodysplastic syndromes exhibit significant expression of apollon, livin and ILP-2 with reduction after transformation to overt leukemia. *Leukemia Research*. 2005; 29(9)[DOI](#)
39. Schläfli AM, Torbett BE, Fey MF, Tschan MP. BIRC6 (APOLLON) is down-regulated in acute myeloid leukemia and its knockdown attenuates neutrophil differentiation. *Experimental Hematology & Oncology*. 2012; 1(1)[DOI](#)
40. Norsworthy KJ, Altman JK. Optimal treatment strategies for high-risk acute promyelocytic leukemia. *Current Opinion in Hematology*. 2016; 23(2)[DOI](#)
41. Wang Z, Fang Z, Lu R, Zhao H, Gong T, Liu D, Hong L, Ma J, Zhang M. MicroRNA-204 Potentiates the Sensitivity of Acute Myeloid Leukemia Cells to Arsenic Trioxide. *Oncology Research*. 2019; 27(9)[DOI](#)
42. Martino MTD, Tagliaferri P, Tassone P. MicroRNA in cancer therapy: breakthroughs and challenges in early clinical applications. *Journal of experimental & clinical cancer research: CR*. 2025; 44(1)[DOI](#)