



Review Article

Involvement of TAL1-microRNA Axis in the Progression of T-cell Acute Lymphoblastic Leukemia



Daryush Purrahan¹, Homayon Yousefi¹, Ali Shojaeian², Reza khedri³, Mahsa Fadaei³
and Mohammad-Reza Mahmoudian-Sani^{1*}

¹Thalassemia and Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran;

²Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, Iran; ³Clinical Research Development Unit, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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Abstract

The T-cell acute lymphoblastic leukemia 1 (TAL-1) transcription factor is crucial for T-cell differentiation, but the ectopic expression in 30% of cases can disrupt normal differentiation, and promote cancer progression. This can be due to microRNA (miRNA) dysregulation or other oncogenes. The present study covers articles related to T-cell acute lymphoblastic leukemia (T-ALL), TAL-1 and miRNA, which were published in the English language from 1994 to 2023. After analyzing the research, it is evident that the TAL-1 overexpression is associated with alterations in several miRNAs, which encompass both those that suppress tumors, and those that stimulate cell growth. The interplay between TAL-1 and miRNAs exhibits diverse dynamics. For example, specific miRNAs, such as miR-223, interact with the TAL-1 gene promoter, resulting in its upregulation. In contrast, the miR-17-92 cluster indirectly influences the stability of the TAL-1 transcription complex. Typically, the interaction between TAL-1 and its associated miRNAs follows a unidirectional pattern, in which miRNAs that target TAL-1 are downregulated, leading to elevated TAL-1 levels. Nevertheless, TAL-1 exhibits a bidirectional relationship with miR-223, in which each positively affects the expression of the other. In addition, there is a cooperative interaction between miR-146-5b and TAL-1. Unlike miR-223, TAL-1 reduces the expression of miR-146-5b, thereby inhibiting tumor growth. Individuals with T-ALL, who experience disruptions in the TAL-1 and miRNA network, often face a poor prognosis, and their tumors tend to be larger. In conclusion, delving deeper into the network of miRNAs associated with TAL-1 in T-ALL offers a novel perspective on cancer prognosis and the development of improved diagnostic and treatment strategies.

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is a highly aggressive hematological disorder characterized by the presence of T-cell precursors.¹ T-ALL can develop in both children and adults, but

this can be more commonly observed in adults. Pediatric T-ALL is particularly significant since it ranks among the primary causes of cancer-related deaths in children.² Clinical presentations of T-ALL typically include symptoms, such as thrombocytopenia, fever, infection, bleeding, and the presence of several large thymus masses. T-ALL is managed through high-dose chemotherapy, which has been instrumental in improving survival rates, especially in the pediatric population.³ However, T-ALL patients face notable relapse rates. For instance, even though approximately 80% of pediatric patients treated with high-dose multi-agent chemotherapy regimens achieve a cure, at least 20% of these patients eventually experience relapse. In adult T-ALL cases, the relapse rates are approximately 40%.⁴ The exact pathogenesis of T-ALL remains unclear. Nonetheless, genetic and epigenetic changes play a significant role in the complex, multi-step transformation process of this leukemia. Among the most notable genetic changes in T-ALL are the chromosomal rearrangements and mutations that affect the T-cell-specific transcription factors.⁵ As a result, it is crucial to thoroughly investigate T-ALL cells for the presence of oncogenic

Keywords: T-cell acute lymphoblastic leukemia 1; microRNA; Gene expression; Epigenetic modification; Prognosis; Leukemogenesis.

Abbreviations: CD, cluster of differentiation; ETS, erythroblast transformation specific; FBXW7, F-Box and WD Repeat Domain Containing 7; HEB, HeLa E-box binding protein; miRNA, microRNA; MYB, v-myb myeloblastosis viral oncogene homolog; NOTCH1, neurogenic locus notch homolog protein 1; RUNX1, runt-related transcription factor 1; T-ALL, T-cell acute lymphoblastic leukemia; TAL1, T-cell acute lymphoblastic leukemia 1; UTR, untranslated region.

*Correspondence to: Mohammad-Reza Mahmoudian-Sani, Thalassemia and Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. ORCID: <https://orcid.org/0000-0002-1096-5661>. Tel: 06133750410, Fax: 06133750410, E-mail: mohamadsani495@gmail.com

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abnormalities and genetic mutations.^{2,6} One of these factors under investigation is TAL-1, which was closely examined in the present study, with particular focus on microRNAs (miRNAs) that either influence it or are influenced by it. Subsequently, a review of the clinical implications was conducted.

MicroRNAs

MiRNAs are a class of non-coding RNAs that play a crucial role in regulating gene expression. Most miRNAs are transcribed from DNA sequences into primary miRNAs. Subsequently, these primary miRNAs are processed and transformed into precursor miRNAs, eventually maturing into functional miRNAs.⁴ The majority of miRNAs primarily interact with the 3' untranslated region (UTR) of target mRNAs, thereby inhibiting translation, and promoting mRNA degradation. However, miRNAs can also interact with other regions of mRNA molecules, including gene promoters, coding sequences, and the 5' UTRs, and in some cases, these can activate or modulate transcription. There is a correlation between miRNAs and the regulation of normal hematopoiesis. MiRNAs can function as both oncogenes and tumor suppressors, depending on the specific targets and roles within the cellular pathways. Thus, miRNA deregulation can contribute to the onset and progression of cancer.⁵ Significant emphasis has been placed on molecular research on diseases, with particular attention to the miRNA expression. Based on these findings, miRNA characterization has been proven to be highly valuable in classifying patients and tailoring treatments, to achieve well-defined drug responses. This personalized approach to medicine holds the promise of more effective and targeted treatments for various diseases.⁷ Research has identified the specific role of miRNA expression in the development of T-ALL in both adults and children. Furthermore, miRNAs have the potential to be recognized as therapeutic targets or avenues for the treatment of leukemia, offering promising possibilities for improving leukemia treatment strategies.^{8,9} In the clinic, molecular characterization, particularly with emphasis on miRNA analysis, is presently being hindered by issues, such as data ambiguity, and the absence of a well-established threshold validation. Thus, conducting additional research and evidence-based meta-analyses on the miRNA expression levels in T-ALL, as potential therapeutic targets or diagnostic tools, holds the potential to offer enhanced clinical opportunities for patients. These efforts can pave the way for the more precise and effective management of T-ALL in the future.¹⁰ T-ALL is associated with numerous miRNA genes, similar to various other cancers. The examples of genes regulated by either the overexpression, or silencing of TAL1 include miR-146b-5p, miR-203, miR-17-92, miR-223, and miRNA-7. These miRNAs are involved in complex regulatory networks that influence T-ALL development and progression.¹¹

The transcription factor TAL1

The human TAL1 gene is situated on chromosome 1p32. This gene, which features a helix-loop-helix domain, binds to DNA through its regulatory regions and interacts with various binding sites, including the E-box sequence, erythroblast transformation specific (ETS), GATA binding protein (GATA), and runt-related transcription factor 1 (RUNX1) factor binding sites. These interactions are integral to its role in gene regulation and hematopoietic development.¹² TAL1 serves as a critical regulator of hematopoiesis, and inhibiting its gene expression can lead to incomplete yolk sac hematopoiesis. This highlights the essential role of TAL1 in

the formation and development of blood cells during the early embryonic stages.¹³ In an adult organism, the TAL1 expression attains its peak levels in various cell types, including hematopoietic stem cells, pluripotent and multipotent myeloid and lymphoid precursors, megakaryocytes, and erythrocytes. The role of TAL1 is notably observed in the formation of complexes, with a diverse array of transcription factors, including friend leukemia integration 1 transcription factor, LIM domain only 2, core-binding factor runt domain alpha subunit 2 translocated to 3, ETS-related gene, LIM domain binding 1,2, RUNX1, E47/E2A, LIM domain binding 1 and GATA1-3. These interactions are crucial for its function in regulating hematopoiesis and blood cell development.¹³ In order to control the transcription of downstream target genes, TAL1 collaborates with co-regulators, and a number of these are involved in histone modification. The interaction among GATA-1, TAL1, and Brg1 (a chromatin remodeling factor) plays a pivotal role in shaping the program of erythroid transcription and influencing the development of erythroid-specific chromatin structures.¹⁴ In an *in vivo* study that involved chimeric mice, it was observed that TAL1-/- embryonic stem cells were unable to contribute to hematopoiesis. This underscores the pivotal role of TAL1 in the differentiation and commitment of the hematopoietic lineage, emphasizing its significance in the formation of blood cells.¹⁵ Oncogenic transcription driven by TAL1 is clearly evident. Aberrant TAL1 expression in immature thymocytes can trigger a wide range of downstream events that impact multiple cellular processes, ultimately leading to the development of acute T-ALL. Interestingly, TAL1 functions effectively in normal hematopoiesis, and the most frequently observed gain-of-function mutation in T-ALL patients involves the activation of ectopic TAL1 transcription, further highlighting its role in leukemia pathogenesis.¹⁶ Reportedly, approximately 40–60% of T-ALL patients present with aberrant TAL1 activation. Although TAL1 has a crucial role in hematopoiesis, the regulation of its expression is significantly influenced by multiple tumor suppressors that bind to E-box proteins, such as HeLa E-box binding protein (HEB) and transcription factor 3. Through displacement events, TAL1 can collaborate with other complex agents, such as RUNX1 and GATA3, to enhance its own expression in an autoregulatory feedback loop. This process can also lead to the inhibition of the E-box protein expression (tumor suppressors). As a consequence, this disruption can result in differentiation failures, and the accumulation of mutations in neurogenic locus notch homolog protein 1 (NOTCH1), ultimately leading to the development of proliferative phenotypes and oncogenic properties.¹⁷ The translocation t(1;14)(p34;q11) that involves TAL1 in T-ALL was first reported over two decades ago. In recent research, scientists have elucidated the mechanisms underlying the thymocyte transformation by TAL1. The ChIP-seq analysis has revealed the activation of regulatory networks in TAL1-driven malignancy. TAL1 exhibits a preference for binding to E-boxes that are proximate to the RUNX, ETS, and GATA motifs in the T-cell lineage, where this plays a role in regulating genes involved in T-cell differentiation. Furthermore, TAL1 targets downstream oncogenes, such as signal transducer and activator of transcription 5A, v-myb myeloblastosis viral oncogene homolog (MYB), and human tribbles 2. These insights provide a deeper understanding of how TAL1 contributes to the development of T-ALL.¹⁸ In human T-ALL, TAL1 and its regulatory partners target genes, such as NK3 homeobox 1, cyclin-dependent kinase 6, aldehyde dehydrogenase 1 member A2, and pre-T-cell receptors. However, the precise functional roles of these targets in leukemogenesis are not fully understood at present. Thus, further research is needed to elucidate the extent to

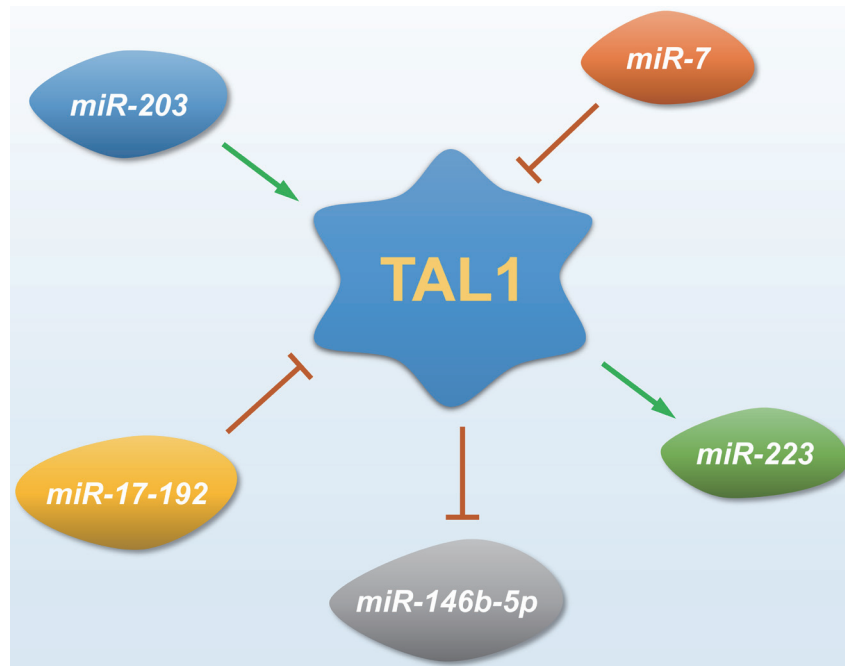


Fig. 1. The interaction between TAL-1 and its associated miRNAs follows a unidirectional pattern, in which miRNAs that target TAL-1 are downregulated, resulting in elevated TAL-1 levels. The expression of TAL-1 is positively influenced by miR-223 in a bidirectional manner, in which each positively affects the expression of the other. Furthermore, miR-146-5b and TAL-1 interact in a cooperative manner. TAL1 levels are suppressed by miR-7. MiR-17-92 causes a reduction in TAL1 levels, which leads to a decrease in TAL1 heterodimerization partners. TAL1, T-cell acute lymphoblastic leukemia 1.

which these genes contribute to the development and progression of T-ALL.¹⁹ Following its transcription, miRNAs play a regulatory role in controlling TAL1. There are instances where miRNAs that target TAL1 may be abnormally downregulated, leading to an altered TAL1 expression in T-ALL. This hypothesis underscores the physiological function of miRNAs in regulating TAL1 during normal development. The control of the TAL1 expression involves trans-acting mechanisms, epigenetic changes, and interactions between promoters and enhancers. Once TAL1 is committed to a specific hematopoietic lineage, this is silenced in the lymphatic lineage. According to a hypothesis, the subtle destabilization of mRNA, which is continued by miRNAs, can rapidly suppress the significant protein output after the mRNA transcription has ceased. A similar mechanism has been described in other physiological conditions for various miRNAs. This highlights the multifaceted regulatory roles played by miRNAs in gene expression control.²⁰ This method can substantially reduce the protein level by taking into account both the protein level threshold and the rates at which mRNA and protein degradation occur. The transition to the off-state occurs more rapidly, following even a modest suppression induced by miRNAs. MiRNAs can also function as translation suppressors, further expediting the transition to the off-state in gene expression regulation (Fig. 1).²⁰

MicroRNAs associated with TAL1 dysregulation in TAL-1 positive T-ALL

miR-7

The initial report on miR-7, which is also known as hsa-miRNA-7 in humans, was originally published in *Drosophila*. The guide strand sequence for miR-7 has demonstrated strong conservation

across various species, underscoring its profound significance in biological regulation and evolution.²¹ Beyond T-ALL, miR-7 has been recognized as a crucial regulator in various malignancies.²² In a study conducted by Jiang *et al.*, the role of miR-7 in regulating the proliferation of chronic myeloid leukemia has been considered to be noteworthy. In addition, the miR-7 expression has been associated with cell migration in various cancer subtypes. Thus, the assessment of the miR-7 expression can hold significant value in predicting breast cancer prognosis and controlling metastasis and migration, underlining its potential as a biomarker and therapeutic target in cancer research.²² Furthermore, miR-7 plays a pivotal role in fine-tuning the sensitivity to chemotherapy and modulating the resistance to various chemotherapeutic agents across different types of tumors. This underscores the multifaceted impact of miR-7 on cancer therapy and its potential as a target for improving treatment outcomes.²³⁻²⁵ The decrease in miR-7 expression shows an inverse correlation with the TAL1 expression in TAL1-positive T-ALL cells (Table 1).²⁶⁻³⁴ *In vitro* experiments have also provided compelling evidence of the ability of miR-7 to negatively regulate TAL1. Furthermore, the bioinformatics analysis has confirmed the presence of target sites for TAL1 within the miR-7 sequence. These findings collectively suggest the significant regulatory relationship between miR-7 and TAL1 in T-ALL.²⁶ Based on the available evidence, it can be concluded that miR-7 can effectively suppress TAL1 levels. The overexpression of miR-7 can lead to a significant reduction in migration, motility, and growth, and trigger apoptosis in T-ALL cells. Importantly, the observed changes in cellular behavior can be reversed by the simultaneous overexpression of TAL1. These findings underscore the potential of miR-7 to hinder tumorigenesis by inhibiting the TAL1 oncogene. Consequently, miR-7 shows promise as a prognostic biomarker and a potential therapeutic target in the clinical management of T-ALL.^{17,26}

Table 1. MicroRNAs associated with TAL-1 dysregulation in TAL-1 positive T-ALL

miR	Chromosome	Sample	Expression	Role	Correlation with TAL-1	Result	Reference
miR-7	9q21, 15q26 and 19q13	Human	↓	Tumor suppressor	Upstream of TAL-1, inverses its expression by binding to the 3'-UTR	Disease progression	26,30
miR-17-92	C13 or f 25	Human and cell line	↓, ↑	Oncogene and tumor suppressor	Upstream of TAL-1, reduces its transcription complex stability	High possible cause of disease progression	31–33
miR-223	q12 X	Cell line	↑	Oncogene	Downstream of TAL-1, has a two-way and positive correlation	Disease progression	29,34
miR-146b-5p	10q24-26	Cell line	↓	Tumor suppressor	Downstream of TAL-1, has a negative correlation	Disease progression	28
miR-203	14q32.33	–	↑	Oncogene	Upstream of TAL-1, has a positive correlation	High possible cause of disease progression	27

↑, Upregulation; ↓, Downregulation. miR, microRNA; T-ALL, T-cell acute lymphoblastic leukemia; TAL-1, T-cell acute lymphoblastic leukemia 1; UTR, untranslated region.

MiR-203

The MIR203A gene, which is situated on chromosome 14q32.33, has a critical role in transcribing miR-203, a miRNA with important regulatory functions in various biological processes.³⁵ MiR-203 is a member of the miRNA family and is known for its significant role in regulating embryonic epidermal differentiation, and the formation of the skin barrier. Multiple studies have consistently demonstrated that miR-203 undergoes dysregulation in various human malignancies. This dysregulation impacts critical cellular processes in tumor cells, including the regulation of cell proliferation, differentiation, metastasis, invasion, and apoptosis. Thus, the involvement of miR-203 in these processes underscores its importance in cancer biology and its potential as a therapeutic target in cancer treatment.³⁶ Furthermore, miR-203 has been considered to have a proto-oncogenic potential, which may contribute to the development of acute pediatric leukemia, including ALL. Moreover, the miR-203 expression is significantly correlated to various factors, including fusion genes, gender, specific chromosomes, immunophenotype, *SCL* interrupting locus-TAL1, breakpoint cluster region-abelson murine leukemia, and prednisone response in children with ALL. In addition, this is associated with fusion genes, chromosomes, gender, and *SCL* interrupting locus -TAL1 in children with acute leukemia. As a result, the miR-203 expression may serve as an indicator of poor prognosis in both ALL and acute leukemia in pediatric patients.²⁷

MiR-17-92

The miR-17-92 cluster is situated within the *MIR17HG* gene and encodes six distinct mature miRNAs. MiR-17-92 plays a crucial role in hematopoietic differentiation and has significant implications for malignancies. Its expression has been associated with various human cancers, allowing it to regulate the expression of genes involved in cell proliferation, cell cycle regulation, and cell death. Several transcription factors, including early growth response 2 gene, RUNX1, friend leukemia integration 1 transcription factor, MYC47, and tumor protein P53, have been identified as regulators of proliferation and differentiation, which can activate miR-17-92, further underscoring its role in cancer and normal cellular processes.^{37,38} Nonetheless, some uncertainties remain in the downstream transcription factors of miR-17-92, and its own transcriptional regulation.³⁹ MiR-17-92 is involved in establishing a regulatory loop with the TAL1 transcription factor. This cluster of miRNAs

inhibits the TAL1 expression, indirectly influencing the stability of the TAL1 transcription complex. Importantly, the transcription of miR-17-92 is controlled by TAL1 and its heterodimerization partner, E47. In addition, evidence suggests that miR-17-92 has a negative impact on erythroid differentiation and that this effect is contingent upon gene activation through the TAL1 complex. These interactions highlight the intricate regulatory networks at play in hematopoietic development, and the role of miR-17-92 in this context.^{39,40} This regulatory loop has an indirect impact on the stability of members within the TAL1 gene regulatory complex. When miR-17-92 is overexpressed, TAL1 protein levels are reduced, and this also decreases in E47 and HEB. In addition, both TAL1 and miR-17-92 are present in immature cluster of differentiation (CD) 34+ precursor cells, in which TAL1/E47 binds to the miR-17-92 promoter in CD34 cells. The co-occurrence of TAL1 and miR-17-92 suggests the potential association with an immature T-cell program. However, further research that involves primary T-cell materials is warranted, in order to determine whether the aberrant expression of TAL1 or miR-17-92 is a cause or consequence of the leukemic cell precursor status in T cells. This would help elucidate the intricate relationship between these factors in the context of T-cell development and leukemia.⁴¹ The transcription factor MYB plays a role in mediating the activation of the miR-17-92 transcription. This contributes to the growth-promoting effects of MYB in Philadelphia-positive leukemia cells. Notably, the direct MYB-mediated activation of miR-17-92 can also be observed in K562 cells. These findings highlight the involvement of MYB in regulating the expression of miR-17-92, which has implications for cell growth and leukemia.⁴² Indeed, it is reasonable to hypothesize that MYB and TAL1 may have direct or indirect functional interactions in the regulation of miR-17-92. TAL1 occupies a central position in the hematopoietic transcription factor network, and its association with miR-17-92 can lead to consequences for TAL1-dependent processes, such as erythroid differentiation. The deletion of miR-17-92 appears to affect all subsets of hematopoietic precursors, making these less competitive, and this is possibly the result of its influence on apoptosis. These complex interactions underscore the intricate regulatory networks at play in hematopoiesis and hematologic malignancies.²⁸ The delicate balance between TAL1 and miR-17-92 is crucial in determining the biological outcomes based on cell-type interactions. The reduction in TAL1 levels induced by miR-17-92 ultimately leads to a decrease in the level of heterodimerization partners of TAL1. Given that TAL1/E47 heterodimers

have a lower activation potential when compared to E47/E47 homodimers, miR-17-92 plays an active role in complex formation, which in turn influences cell fate, proliferation, and differentiation. The dysregulation of the TAL1/miR-17-92 axis is implicated in the development of leukemia, underscoring its significance in hematologic malignancies.

MiR-223

The gene encoding miR-223 is indeed located at locus q12 on the X chromosome. The conservation of the miR-223 sequence across different species underscores its fundamental and evolutionarily conserved role in various physiological processes. This suggests that miR-223 plays a critical role in regulating essential biological functions.⁴³ MiR-223 is tightly regulated and robustly expressed in hematopoietic cells, where it plays a significant role in modulating the activation and differentiation of myeloid cells. Researchers have extensively studied the impact of miR-223 on various myeloid cell activities, including macrophage and neutrophil activation and differentiation. Its regulatory functions in these immune cells highlight its importance in maintaining immune homeostasis and responding to immune challenges.⁴⁴ The expression of CCAAT/enhancer binding proteins alpha is induced by all-trans retinoic acid in acute promyelocytic leukemia. This induction leads to the regulation of miR-223 by binding to its promoter. Subsequently, the upregulation of miR-223 prompts the suppression of nuclear factor IA, which in turn, promotes myeloid cell differentiation. This cascade of events illustrates the critical role of all-trans retinoic acid-induced CCAAT/enhancer-binding protein alpha and miR-223 in driving myeloid cell differentiation, in the context of acute promyelocytic leukemia.⁴⁵ In the context of the TAL1-positive subtype of T-ALL, research efforts have been directed toward identifying miRNAs directly controlled by TAL1. MiR-223 has emerged as a valuable downstream target due to its distinct expression pattern following TAL1 knockdown. In addition, this plays a role in the viability of TAL1-positive T-ALL cells. The expression profile of miR-223 closely mirrors that of TAL1 during thymic development, with high levels observed in early thymocytes. However, miR-223 becomes significantly downregulated after the double-negative-2 stage of maturation. This phenomenon is attributed to the binding of the TAL1 complex to the miR-223 promoter, resulting in the upregulation of the miR-223 expression. These findings highlight the regulatory role of TAL1 in controlling the miR-223 expression during thymic development and its significance in TAL1-positive T-ALL.²⁹ The analysis of T-ALL cell lines has emphasized that miR-223 undergoes the most significant downregulation after TAL1 knockdown. The close relationship between TAL1 and miR-223 during normal thymocyte maturation suggests that the TAL1-mediated regulation of miR-223 is an integral part of a conserved developmental process. This evidence aligns with the elevated levels of miR-223 observed in T-ALL cases, which present the characteristic features of an immature cell of origin, further supporting the role of miR-223, in the context of T-ALL and its connection with TAL1.^{29,46} MiR-223 exerts its regulatory influence by inhibiting the mRNA of the F-Box and WD Repeat Domain Containing 7 (FBXW7) ubiquitin ligase through sequence-specific interactions. This inhibition leads to the upregulation of oncoproteins, including NOTCH1, Cyclin E, MYB, and MYC. Consequently, the TAL1-miR223 axis indirectly supports cell survival and proliferation through the regulation of these oncoproteins.²⁹ TAL1, in conjunction with its regulatory collaborators (RUNX1, GATA3, LIM domain Only1/2, E2A, and HEB), plays a direct role in controlling the miRNA gene expres-

sion. These intricate interactions highlight the complex regulatory network involved in T-ALL and the contribution of the TAL1-miR223 axis to disease progression.⁴⁷ The abnormal upregulation of miR-223, which is mediated by TAL1, is a critical process that enhances the growth of T-ALL cells that are positive for TAL1. The miR-223 expression sustains some T-ALL cells even after TAL1 knockdown. Notably, the miR-223 overexpression significantly diminishes the FBXW7 protein expression, while the TAL1 knockdown leads to the increase in FBXW7 protein expression, thereby reducing the levels of its substrates, including CYCLIN E, NOTCH1, MYB, and MYC. TAL1-induced miR-223 upregulation intensifies the malignant phenotype in T-ALL by repressing the tumor suppressor role of FBXW7, and this has important implications for the progression of T-ALL.²⁹ MYB, which is a leucine zipper transcription factor, acts as an oncogene and plays a significant role in both malignant and healthy hematopoiesis. In T-ALL, the elevated levels of MYB can be attributed directly to the MYB translocations through T-cell receptors, increased binding of the TAL1 complex at the MYB site, and MYB genomic replication, or indirectly to the TAL1/miR-223/FBXW7 regulatory axis. To identify miRNAs associated with the transformation of malignant and normal T cells, transcriptome data from two independent T-ALL groups and various subsets of normal T cells were analyzed. As a result, miR-193b-3p emerged as the novel miRNA capable of effectively suppressing tumor growth by targeting MYB within the context of malignant T-cell transformation. This discovery holds promise for potential targeted therapies aimed at MYB in human T-ALL, offering a potential avenue for advancing treatment options.⁴⁸ Based on these findings, it can be concluded that one of the central components of the TAL-1 function in T-ALL pathogenesis is the induction of the miR-223 expression.

MiR-146b-5p

Human miR-146b-5p is located at the genomic region 10q24-26 (104186259-104186331+), and this has been observed to be frequently associated with genetic material deletion in cancer cells. Previous researches have identified miR-146b-5p as a tumor suppressor in various types of cancer, including breast and pancreatic cancers. This miRNA plays a role in regulating cell growth, proliferation, and other oncogenic processes, and its downregulation or deletion can contribute to the development and progression of cancer.⁴⁹ TAL1 has been identified as a suppressor of miR-146b-5p. This means that TAL1 downregulates the expression of miR-146b-5p. It was observed that the miR-146b-5p expression levels were lower in TAL1-positive patient samples when compared to other T-ALL variants. Furthermore, the miR-146b-5p expression decreased in leukemia T cells, when compared to normal thymocytes, T cells, and other hematopoietic progenitor cells. The suppression of miR-146b-5p is associated with the increase in migration and invasion capabilities of T-ALL cells *in vitro*, leading to elevated levels of chemokines, and the reorganization of filamentous actin. In a human T-ALL xenotransplant model, mice survived longer when miR-146b was overexpressed in the TAL1-positive cell line. Conversely, the knockdown of miR-146b-5p accelerated the leukemia progression, and reduced the overall survival of mice, paralleling the rapid invasion of tumors into the central nervous system. In summary, miR-146b-5p is a miRNA gene that plays a crucial role in T-ALL. Its downregulation by TAL1, and possibly other oncogenes, contributes to the progression of the disease by affecting leukemia cell motility and increasing disease aggressiveness. Research has shed light on the intricate mechanisms involved in T-ALL development and progression, offering potential insights

for targeted therapies.⁸ The downregulation of miR-146b-5p by TAL1 has led to the exclusion of miR-146a/b, as a potential tumor suppressor miRNA in T-ALL. It appears that miR-146a lacks the ability to prevent leukemogenesis, possibly due to redundancy with miR-146b-5p, which is highly prevalent in hematopoietic progenitors. MiR-146b-5p is highly expressed in single-positive mature thymocytes, and its regulation occurs during the transition from dual-positive to single-positive thymocytes. This observation aligns with a model, in which the aberrant TAL1 expression partially contributes to leukemogenesis in developing thymocytes by negatively regulating miR-146b-5p. Bioinformatics analyses have shed light on the potential role of miR-146b-5p in regulating cell migration and motility by targeting various genes. MiR-146b influences the capacity of T-ALL cells in infiltrating both hematopoietic and non-hematopoietic organs, thereby delaying the leukemia progression, and acting as an effective tumor suppressor gene. It appears that the modulation of miR-146b-5p regulation impacts the progression of T-ALL by influencing leukemia cell invasion, motility, organ dissemination, and ultimately, disease aggressiveness. These findings underscore the importance of miR-146b-5p in T-ALL biology and hold promise for the development of novel therapeutic approaches in this field. Understanding the regulatory network involving TAL1 and miR-146b-5p would provide valuable insights on the mechanisms underlying T-ALL, and may offer potential targets for intervention in the treatment of this disease.^{28,50}

Conclusion

The initiation and maintenance of a specific cell type expression are governed by a regulatory network, which comprises transcription factors, miRNAs, and epigenetic modulators. When considering the substantial reduction or disruption of normal mechanisms that lead to TAL1 transcriptional silencing in the pre-leukemic stage, it becomes evident that TAL1 protein levels can be positively influenced by the simultaneous reduction in miRNA-TAL1 expression and its interactions, subsequently affecting the progression of leukemia. However, a more in-depth exploration of the upstream mechanisms involved in diminishing the expression of miRNAs that regulate TAL1 in T-ALL is warranted. Identifying the entire set of genes regulated by TAL1, including miRNAs, and elucidating its functional impact on leukemia progression may unveil novel molecular targets for T-ALL treatment. Given the modest individual effects of each miRNA on the TAL1 protein expression, which aligns with findings reported in studies on the transcriptional regulation of miRNAs at post-transcription, it remains challenging to predict whether the unregulated miRNA expression can entirely account for the high aberrant TAL1 expression in T-ALL. It is conceivable that multiple specific miRNAs simultaneously target TAL1, possibly in response to a common upstream event, contributing to its dysregulation. The complexity of these interactions underscores the need for further research, in order to fully understand the regulatory networks at play in T-ALL.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

HY, AS, MF and RK designed the study and supervised the data collection; DP and MRMS prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

References

- [1] Bornschein S, Demeyer S, Stirparo R, Gielen O, Vicente C, Geerdens E, *et al*. Defining the molecular basis of oncogenic cooperation between TAL1 expression and Pten deletion in T-ALL using a novel pro-T-cell model system. *Leukemia* 2018;32(4):941–951. doi:10.1038/leu.2017.328, PMID:29151585.
- [2] Yeoh AE, Tan D, Li CK, Hori H, Tse E, Pui CH. Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. *Lancet Oncol* 2013;14(12):e508–e523. doi:10.1016/S1470-2045(13)70452-2, PMID:24176570.
- [3] Aureli A, Marziani B, Venditti A, Sconocchia T, Sconocchia G. Acute lymphoblastic leukemia immunotherapy treatment: now, next, and beyond. *Cancers (Basel)* 2023;15(13):3346. doi:10.3390/cancers15133346, PMID:37444456.
- [4] Smolarz B, Durczyński A, Romanowicz H, Szyłło K, Hogendorf P. miRNAs in cancer (review of literature). *Int J Mol Sci* 2022;23(5):2805. doi:10.3390/ijms23052805, PMID:35269947.
- [5] Ali Syeda Z, Langden SSS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. *Int J Mol Sci* 2020;21(5):1723. doi:10.3390/ijms21051723, PMID:32138313.
- [6] Wiggins M, Stevenson W. Genetic predisposition in acute leukaemia. *Int J Lab Hematol* 2020;42(Suppl 1):75–81. doi:10.1111/ijlh.13173, PMID:32115888.
- [7] Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol* 2021;22(2):96–118. doi:10.1038/s41580-020-00315-9, PMID:33353982.
- [8] Correia NC, Barata JT. MicroRNAs and their involvement in T-ALL: A brief overview. *Adv Biol Regul* 2019;74:100650. doi:10.1016/j.jbior.2019.100650, PMID:31548132.
- [9] Wallaert A, Van Loocke W, Hernandez L, Taghon T, Speleman F, Van Vlierberghe P. Comprehensive miRNA expression profiling in human T-cell acute lymphoblastic leukemia by small RNA-sequencing. *Sci Rep* 2017;7(1):7901. doi:10.1038/s41598-017-08148-x, PMID:28801656.
- [10] Gębarowska K, Mroczek A, Kowalczyk JR, Lejman M. MicroRNA as a prognostic and diagnostic marker in T-cell acute lymphoblastic leukemia. *Int J Mol Sci* 2021;22(10):5317. doi:10.3390/ijms22105317, PMID:34070107.
- [11] Correia NC, Durinck K, Leite AP, Ongenaert M, Rondou P, Speleman F, *et al*. Novel TAL1 targets beyond protein-coding genes: identification of TAL1-regulated microRNAs in T-cell acute lymphoblastic leukemia. *Leukemia* 2013;27(7):1603–1606. doi:10.1038/leu.2013.63, PMID:23448994.
- [12] Hsu HL, Huang L, Tsan JT, Funk W, Wright WE, Hu JS, *et al*. Preferred sequences for DNA recognition by the TAL1 helix-loop-helix proteins. *Mol Cell Biol* 1994;14(2):1256–1265. doi:10.1128/mcb.14.2.1256-1265.1994, PMID:8289805.
- [13] Vagapova ER, Spirin PV, Lebedev TD, Prassolov VS. The role of TAL1 in hematopoiesis and leukemogenesis. *Acta Naturae* 2018;10(1):15–23. PMID:29713515.
- [14] Lausen J, Pless O, Leonard F, Kuvardina ON, Koch B, Leutz A. Targets of the Tal1 transcription factor in erythrocytes: E2 ubiquitin conjugase regulation by Tal1. *J Biol Chem* 2010;285(8):5338–5346. doi:10.1074/jbc.M109.030296, PMID:20028976.
- [15] Patel B, Kang Y, Cui K, Litt M, Riberio MS, Deng C, *et al*. Aberrant TAL1 activation is mediated by an interchromosomal interaction in human

- T-cell acute lymphoblastic leukemia. *Leukemia* 2014;28(2):349–361. doi:10.1038/leu.2013.158, PMID:23698277.
- [16] Smith C, Goyal A, Weichenhan D, Allemand E, Mayakonda A, Toprak U, *et al*. TAL1 activation in T-cell acute lymphoblastic leukemia: a novel oncogenic 3' neo-enhancer. *Haematologica* 2023;108(5):1259–1271. doi:10.3324/haematol.2022.281583, PMID:36632736.
- [17] Sanda T, Leong WZ. TAL1 as a master oncogenic transcription factor in T-cell acute lymphoblastic leukemia. *Exp Hematol* 2017;53:7–15. doi:10.1016/j.exphem.2017.06.001, PMID:28652130.
- [18] Smith C, Touzart A, Simonin M, Tran-Quang C, Hypolite G, Latiri M, *et al*. Harnessing the MYB-dependent TAL1 5' super-enhancer for targeted therapy in T-ALL. *Mol Cancer* 2023;22(1):12. doi:10.1186/s12943-022-01701-x, PMID:36650499.
- [19] Li Y, Liao Z, Luo H, Benyoucef A, Kang Y, Lai Q, *et al*. Alteration of CTCF-associated chromatin neighborhood inhibits TAL1-driven oncogenic transcription program and leukemogenesis. *Nucleic Acids Res* 2020;48(6):3119–3133. doi:10.1093/nar/gkaa098, PMID:32086528.
- [20] Kunze-Schumacher H, Krueger A. The role of MicroRNAs in development and function of regulatory T cells - lessons for a better understanding of microRNA biology. *Front Immunol* 2020;11:2185. doi:10.3389/fimmu.2020.02185, PMID:33013919.
- [21] Horsham JL, Ganda C, Kalinowski FC, Brown RA, Epis MR, Leedman PJ. MicroRNA-7: A miRNA with expanding roles in development and disease. *Int J Biochem Cell Biol* 2015;69:215–224. doi:10.1016/j.biocel.2015.11.001, PMID:26546742.
- [22] Zhao J, Tao Y, Zhou Y, Qin N, Chen C, Tian D, *et al*. MicroRNA-7: a promising new target in cancer therapy. *Cancer Cell Int* 2015;15:103. doi:10.1186/s12935-015-0259-0, PMID:26516313.
- [23] Jiang MJ, Dai JJ, Gu DN, Huang Q, Tian L. MicroRNA-7 inhibits cell proliferation of chronic myeloid leukemia and sensitizes it to imatinib *in vitro*. *Biochem Biophys Res Commun* 2017;494(1-2):372–378. doi:10.1016/j.bbrc.2017.10.001, PMID:28986256.
- [24] Cheng MW, Shen ZT, Hu GY, Luo LG. Prognostic significance of microRNA-7 and its roles in the regulation of cisplatin resistance in lung adenocarcinoma. *Cell Physiol Biochem* 2017;42(2):660–672. doi:10.1159/000477884, PMID:28618418.
- [25] Cui YX, Bradbury R, Flamini V, Wu B, Jordan N, Jiang WG. MicroRNA-7 suppresses the homing and migration potential of human endothelial cells to highly metastatic human breast cancer cells. *Br J Cancer* 2017;117(1):89–101. doi:10.1038/bjc.2017.156, PMID:28571043.
- [26] Sun H, Zhang Z, Luo W, Liu J, Lou Y, Xia S. MiR-7 functions as a tumor suppressor by targeting the oncogenes TAL1 in T-cell acute lymphoblastic leukemia. *Technol Cancer Res Treat* 2020;19:1533033820934130. doi:10.1177/1533033820934130, PMID:32633635.
- [27] Wang N, Pan J, Cao L, Lu J, Xiao PF, Zhao WL, *et al*. The expression and clinical significance of miR-203 in pediatric acute leukemia. *Zhonghua Xue Ye Xue Za Zhi* 2013;34(9):777–781. doi:10.3760/cma.j.isn.0253-2727.2013.09.009, PMID:24103876.
- [28] Correia NC, Fragoso R, Carvalho T, Enguita FJ, Barata JT. MiR-146b negatively regulates migration and delays progression of T-cell acute lymphoblastic leukemia. *Sci Rep* 2016;6:31894. doi:10.1038/srep31894, PMID:27550837.
- [29] Mansour MR, Sanda T, Lawton LN, Li X, Kreslavsky T, Novina CD, *et al*. The TAL1 complex targets the FBXW7 tumor suppressor by activating miR-223 in human T cell acute lymphoblastic leukemia. *J Exp Med* 2013;210(8):1545–1557. doi:10.1084/jem.20122516, PMID:23857984.
- [30] Li G, Gao L, Zhao J, Liu D, Li H, Hu M. LncRNA ANRIL/miR-7-5p/TCF4 axis contributes to the progression of T cell acute lymphoblastic leukemia. *Cancer Cell Int* 2020;20:335. doi:10.1186/s12935-020-01376-8, PMID:32714094.
- [31] Kusy S, Gerby B, Goardon N, Gault N, Ferri F, Gérard D, *et al*. NKX3.1 is a direct TAL1 target gene that mediates proliferation of TAL1-expressing human T cell acute lymphoblastic leukemia. *J Exp Med* 2010;207(10):2141–2156. doi:10.1084/jem.20100745, PMID:20855495.
- [32] Mavrakis KJ, Wolfe AL, Oricchio E, Palomero T, de Keersmaecker K, McJunkin K, *et al*. Genome-wide RNA-mediated interference screen identifies miR-19 targets in Notch-induced T-cell acute lymphoblastic leukaemia. *Nat Cell Biol* 2010;12(4):372–379. doi:10.1038/ncb2037, PMID:20190740.
- [33] Ye H, Liu X, Lv M, Wu Y, Kuang S, Gong J, *et al*. MicroRNA and transcription factor co-regulatory network analysis reveals miR-19 inhibits CYLD in T-cell acute lymphoblastic leukemia. *Nucleic Acids Res* 2012;40(12):5201–5214. doi:10.1093/nar/gks175, PMID:22362744.
- [34] Gu J, Xu H, Chen Y, Li N, Hou X. MiR-223 as a regulator and therapeutic target in liver diseases. *Front Immunol* 2022;13:860661. doi:10.3389/fimmu.2022.860661, PMID:35371024.
- [35] Peng Q, Shen Y, Zhao P, Cai S, Feng Z, Cheng M, *et al*. Biomarker exploration of microRNA-203 as a promising substrate for predicting poor survival outcome in colorectal cancer. *BMC Cancer* 2020;20(1):1003. doi:10.1186/s12885-020-07512-x, PMID:33059609.
- [36] Meng Y, Hu X, Li S, Zeng X, Qiu L, Wei M, *et al*. miR-203 inhibits cell proliferation and ERK pathway in prostate cancer by targeting IRS-1. *BMC Cancer* 2020;20(1):1028. doi:10.1186/s12885-020-07472-2, PMID:33109107.
- [37] Fang LL, Wang XH, Sun BF, Zhang XD, Zhu XH, Yu ZJ, *et al*. Expression, regulation and mechanism of action of the miR-17-92 cluster in tumor cells (Review). *Int J Mol Med* 2017;40(6):1624–1630. doi:10.3892/ijmm.2017.3164, PMID:29039606.
- [38] Mogilyansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. *Cell Death Differ* 2013;20(12):1603–1614. doi:10.1038/cdd.2013.125, PMID:24212931.
- [39] Meyer A, Herkt S, Kunze-Schumacher H, Kohrs N, Ringleb J, Schneider L, *et al*. The transcription factor TAL1 and miR-17-92 create a regulatory loop in hematopoiesis. *Sci Rep* 2020;10(1):21438. doi:10.1038/s41598-020-78629-z, PMID:33293632.
- [40] Tan TK, Zhang C, Sanda T. Oncogenic transcriptional program driven by TAL1 in T-cell acute lymphoblastic leukemia. *Int J Hematol* 2019;109(1):5–17. doi:10.1007/s12185-018-2518-z, PMID:30145780.
- [41] Tan SH, Bertulfo FC, Sanda T. Leukemia-Initiating Cells in T-Cell Acute Lymphoblastic Leukemia. *Front Oncol* 2017;7:218. doi:10.3389/fonc.2017.00218, PMID:29034206.
- [42] Spagnuolo M, Regazzo G, De Dominicis M, Sacconi A, Pelosi A, Korita E, *et al*. Transcriptional activation of the miR-17-92 cluster is involved in the growth-promoting effects of MYB in human Ph-positive leukemia cells. *Haematologica* 2019;104(1):82–92. doi:10.3324/haematol.2018.191213, PMID:30076175.
- [43] Taïbi F, Bertzinger-Le Meuth V, Massy ZA, Metzinger L. miR-223: An inflammatory oncomiR enters the cardiovascular field. *Biochim Biophys Acta* 2014;1842(7):1001–1009. doi:10.1016/j.bbba.2014.03.005, PMID:24657505.
- [44] Yuan X, Berg N, Lee JW, Le TT, Neudecker V, Jing N, *et al*. MicroRNA miR-223 as regulator of innate immunity. *J Leukoc Biol* 2018;104(3):515–524. doi:10.1002/JLB.3MR0218-079R, PMID:29969525.
- [45] Wang XS, Zhang JW. The microRNAs involved in human myeloid differentiation and myelogenous/myeloblastic leukemia. *J Cell Mol Med* 2008;12(5A):1445–1455. doi:10.1111/j.1582-4934.2008.00386.x, PMID:18554315.
- [46] Del Gaizo M, Sergio I, Lazzari S, Cialfi S, Pelullo M, Screpanti I, *et al*. MicroRNAs as modulators of the immune response in T-cell acute lymphoblastic leukemia. *Int J Mol Sci* 2022;23(2):829. doi:10.3390/ijms23020829, PMID:35055013.
- [47] Parriott G, Kee BL. E protein transcription factors as suppressors of t lymphocyte acute lymphoblastic leukemia. *Front Immunol* 2022;13:885144. doi:10.3389/fimmu.2022.885144, PMID:35514954.
- [48] Mets E, Van der Meulen J, Van Peer G, Boice M, Mestdagh P, Van de Walle I, *et al*. MicroRNA-193b-3p acts as a tumor suppressor by targeting the MYB oncogene in T-cell acute lymphoblastic leukemia. *Leukemia* 2015;29(4):798–806. doi:10.1038/leu.2014.276, PMID:25231743.
- [49] Cai J, Xu L, Cai Z, Wang J, Zhou B, Hu H. MicroRNA-146b-5p inhibits the growth of gallbladder carcinoma by targeting epidermal growth factor receptor. *Mol Med Rep* 2015;12(1):1549–1555. doi:10.3892/mmr.2015.3461, PMID:25760482.
- [50] Drobna M, Szarzyńska-Zawadzka B, Dawidowska M. T-cell acute lymphoblastic leukemia from miRNA perspective: Basic concepts, experimental approaches, and potential biomarkers. *Blood Rev* 2018;32(6):457–472. doi:10.1016/j.blre.2018.04.003, PMID:29703513.