REVIEW ARTICLE

MicroRNAs and JAK/STAT3 signaling: A new promising therapeutic axis in blood cancers

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Abstract
Blood disorders include a wide spectrum of blood-associated malignancies resulting from inherited or acquired defects. The ineffectiveness of existing therapies against blood disorders arises from different reasons, one of which is drug resistance, so different types of leukemia may show different responses to treatment. Leukemia occurs for a variety of genetic and acquired reasons, leading to uncontrolled proliferation in one or more cell lines. Regarding the genetic defects, oncogene signal transducer and activator of transcription (STAT) family...
transcription factor, especially STAT3, play an essential role in hematological disorders onset and progress upon mutations, dysfunction, or hyperactivity. Besides, microRNAs, as biological molecules, has been shown to play a dual role in either tumorigenesis and tumor suppression in various cancers. Besides, a strong association between STAT3 and miRNA has been reported. For example, miRNAs can regulate STAT3 via targeting its upstream mediators such as IL6, IL9, and JAKs or directly binding to the STAT3 gene. On the other hand, STAT3 can regulate miRNAs. In this review study, we aimed to determine the role of either microRNAs and STAT3 along with their effect on one another's activity and function in hematological malignancies. Copyright © 2021, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Abbreviations

JAK janus kinase
STAT signal transducer and activator of transcription
c-myc c-myelocytomatosis
Bcl-2 B-cell lymphoma 2
Mcl-1 myeloid cell leukemia 1
Bcl-XL B-cell lymphoma-extra large
CLL chronic lymphocytic leukemia
IL9 interleukin 9
PBMC peripheral blood mononuclear cell
BCR B-cell receptor
ZAP7 zeta chain of T cell receptor-associated protein kinase 70
PIAS protein inhibitor of activated STAT3
PDCD4 programmed cell death 4
PTEN phosphatase and tensin
MAPK mitogen-activated protein kinase
GFP green fluorescent protein
ALL acute lymphoblastic leukemia
CML chronic myeloid leukemia
TLGL T-cell large granular lymphocytic
ANC absolute neutrophil count
HuR human antigen R
MEG3 maternally expressed gene 3
lncRNAs long noncoding RNAs
HDAC1 histone deacetylase 1
DNMT DNA methyl transferase
SCA sickle cell anemia
YY1 Yin Yang 1
GATA1 GATA binding protein 1
EPO erythropoietin
TPO thrombopoietin
HSPCs hematopoietic stem and progenitor CD34+ cells
SOF6 suppressor of cytokine signaling 6
MPN myeloproliferative neoplasms
AEL acute erythroid leukemia
CB cord blood
LIF leukemia inhibitory factor
HIF1 hypoxia-inducible factor 1
MCL mantle cell lymphoma

Introduction

Among the intracellular defects, types of genetic mutations, deletions, unbalanced chromosomal translocation,1–7 and dysregulation of signal transducer factors including transcription factors are the most important underlying causes of acute leukemia disorders.8–7 The JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling pathway is one of the most important signaling pathways that participated in cell proliferation, differentiation, apoptosis as well as migration.8–11 Reports have suggested that dysregulation and overactivation of JAKs and STATs proteins is an influential marker in the development of hematological and non-hematological cancers.8–16 Therefore, suppressing or blocking this pathway is one of the significant therapeutic approaches for the treatment of leukemias in which this signaling pathway is impaired. Members of the STAT family, especially STAT3, are oncogenic factors, playing diverse roles in the biological function of cells covering proliferation, survival, angiogenesis along with metastasis, in particular, in undifferentiated cells.11,17–19

The STAT family cytoplasmic transcription factor includes seven DNA-binding proteins, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 which are typically activated via phosphorylation on tyrosine residues by the JAK kinase family.20 After phosphorylation, they are dimerized, and subsequently translocated into the nucleus. After that, these STAT dimers bind to specific gene promoter sequences and modify the transcription of genes involved in cellular processes adjustment, encompassing differentiation, proliferation, and apoptosis.8,17,21 STAT3 plays a significant role in tumorigenesis by affecting the expression of cell cycle regulators (e.g., c-Myc [cellular Myc], cyclin D1) and cancer-promoting genes such as members of the anti-apoptotic Bcl-2 (B-cell lymphoma 2) family (e.g., Mcl-1 [myeloid cell leukemia 1], Bcl-2, Bcl-XL [B-cell lymphoma-extra large]).22 To date, numerous strategies have been investigated or even used to find therapeutic strategies for suppressing JAK/STAT signaling.11,13,20,23,24 In continued efforts to more understanding the mechanisms of JAK/STAT3 signaling inhibition, a large number of studies have identified the pivotal role of miRNAs in the regulation of STAT3 or signaling
pathway in which STAT3 is involved. On the other hand, several studies have implied the possible role of STAT3 in regulating miRNA expression.

miRNAs are an endogenous and non-coding class of single-stranded RNAs containing 19 to 25 nucleotides, modifying gene expression post-transcriptionally through binding to the 3’ untranslated regions (3’ UTRs) leading to the promotion of the mRNA degradation or triggering the inhibition of mRNA translation. miRNAs actively contribute to a variety of cellular processes such as the production of auto-antibodies, cellular immunity, cell proliferation, differentiation, cell cycle, and apoptosis in concomitant with association with various other events such as neurodevelopment, DNA editing-repairing, and oxidative stress. It has been also robustly evidenced that the dysregulation of miRNAs expression is involved in the tumor microenvironment (TME) and drug resistance. In Figure 1, microRNA biogenesis has been shown.

In sum, numerous studies have shown that miRNAs and STAT3 may stimulate a fundamental regulatory effect on each other directly or indirectly. Herein, we have highlighted the potent role of miRNAs in the regulation of STAT3 expression and function in hematological disorders.

Interaction between miRNAs and JAK/STAT3 signaling in chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is one of the most common hematological disorders in the world and the most common adult leukemia disorder in the western hemisphere. Generally, about 95% of cases are B cells typically characterized by the accumulation of mature and small B cell phenotype expressing CD5 and CD19 immune phenotype markers, affecting peripheral blood, bone marrow (BM), and lymphatic tissues.

Relationship between IL9, STAT3, miR-A21, miR-155 in CLL

Previous studies have displayed that IL9 is commonly increased in CLL patients. Chen et al also observed that the proliferation of CLL cells was increased after using recombinant human IL9, while apoptosis was decreased. They also analyzed the relationship between the upregulation of IL9 expression and the expression levels of STAT3, P-STAT3, miR-21, miR-51 in peripheral blood mononuclear cell (PBMC) of CLL patients, and found an increase in expression of STAT3 and P-STAT3 in CLL patients. IL9 is more commonly known as Th2 cytokine, contributes to allergic diseases. Findings have presented that IL9 in addition to the involvement in T-reg and mast cell-mediated tumor immunity, may participate in growth, tumor progression, and the anti-apoptotic process. Many studies have shown that the IL9-a chain stimulates mutant JAK1 phosphorylation resulted in activation of the STAT family, in particular, STAT3.

Chen and his coworkers signified that the transfection of miR-21 and miR-21 overexpressed CLL cell lines could stimulate IL9 production in these cells, enabling IL9 production in CLL cells upon promotion of p-STAT3 cellular levels. These findings implied that an IL9 endogenous/miR-21/miR-155/STAT3 axis exists in CLL cells, which could be useful in finding new therapeutic patterns.

The relationship between miR-21 and the STAT3 signaling pathway in CLL cells

CLL cells are highly dependent on their microenvironment and the B-cell receptor (BCR) signaling pathway plays an important role in this regard. Among the proteins involved in cell-to-microenvironment interaction, the zeta chain of T cell receptor-associated protein kinase 70 (ZAP70) can improve cell response to microenvironment stimuli.

miR-21 is overexpressed in various leukemic disorders including CLL, possibly involved in the development of drug resistance and survival along with augmenting of disease progression. Besides, the presence of the relationship between miR-21 and poor prognosis in CLL as well as cell proliferation and oncogenesis has been evidenced. Carabia et al showed that stimulation of BCR signaling by the microenvironment can regulate the expression of miR-21 and its target repressor genes, including protein inhibitor of activated STAT3, programmed cell death 4 (PDCD4), and phosphatase and tensin homolog (PTEN) via the signaling pathway stimulated or progressed by mitogen-activated protein kinase (MAPK or MAP kinase) and STAT3.

The ZAP70 protein plays an important role in different signaling pathways also modulates the interaction between the cells and related microenvironments. Carabia and her colleagues analyzed the expression changes of miR-21 following ZAP70 status in CD19 B cells derived from patients who were diagnosed with CLL and found that miR-21 was highly expressed in patients with higher expression of ZAP70. Also, the study of miR-21 expression level in Ramos cell (human Burkitt’s lymphoma B cells) transfected with GFP-ZAP70 demonstrated similar results. In another study, the stimulation of the IL-6 receptor (one of the B cell receptors) on the surface of the myeloma B cells resulted in pre-miR regulation by STAT3 translocation into the nucleus. Accordingly, Carabia et al identified that the stimulation of the BCR signaling pathway caused ZAP-70 activation, which in turn, triggered an enhancement in mature miR-21 levels via inducing the STAT3 binding to the pre-miR-21 transcript promoter.

miR-155 and its association with STAT3 signaling in CLL cells

The miR-155 is involved in tumorigenesis and autoimmunity and its overexpression can lead to lymphoma onset in mice. The miR-155 regulates the proliferation and development of hematopoietic cells as well as contributed to immune cell response, production of antibodies, cytokines, and antigen expression. In this context, a study showed that overexpression of miR-155 in the murine model leads to B cell proliferation and is associated with lymphoma development. Similarly, overexpression of miR-155 has been observed in CLL accompanied by
miRNA biogenesis. The majority of genes, which encode the miRNAs, are in promoter regions of intronic genes. Firstly, RNA polymerase II transcribes the miRNA genes to the primary miRNA (pri-miRNA) form. Drosha, a type III RNase, incorporated with the cofactor protein DGCR8, binds to the primary miRNA (pri-miRNA) transcript and cleaves it, in the nucleus to form precursors-miRNAs. The pre-miRNAs are exported to the cytosol by Exportin 5 (whereas in the drosha independent pathway pri-miR are exported into the cytosol by Exportin 1 and then cleaved to pre-miRNAs form), and subsequently cleaved by Dicer (a type III RNase) to miRNA duplex form incorporation with TAR RNA binding protein (TRBP). The argonaute (AGO) family and its associated protein mediate the processing of the miRNA duplex. After unwinding and strand selection, the mature miRNA can target recognition. Next, mature miRNA binds to the RISC and so it is capable of targeting the miRNAs via complementary sites and results in translational repression or mRNA degradation.

Figure 1  miRNA biogenesis. The majority of genes, which encode the miRNAs, are in promoter regions of intronic genes. Firstly, RNA polymerase II transcribes the miRNA genes to the primary miRNA (pri-miRNA) form. Drosha, a type III RNase, incorporated with the cofactor protein DGCR8, binds to the primary miRNA (pri-miRNA) transcript and cleaves it, in the nucleus to form precursors-miRNAs. The pre-miRNAs are exported to the cytosol by Exportin 5 (whereas in the drosha independent pathway pri-miR are exported into the cytosol by Exportin 1 and then cleaved to pre-miRNAs form), and subsequently cleaved by Dicer (a type III RNase) to miRNA duplex form incorporation with TAR RNA binding protein (TRBP). The argonaute (AGO) family and its associated protein mediate the processing of the miRNA duplex. After unwinding and strand selection, the mature miRNA can target recognition. Next, mature miRNA binds to the RISC and so it is capable of targeting the miRNAs via complementary sites and results in translational repression or mRNA degradation.

Hodgkin and non-Hodgkin’s lymphoma. Other investigations have implied that IL-6 may activate STAT3 expression and function in CLL cells; on the other hand, overexpression of miR-155 has been found in CLL. Considering the results, it seems that IL6 increases the miR-155 expression, delivering proof of the concept of the important influences of miRNA in leukemia pathogenesis or therapy. In this regard, Li et al detected miR-155 overexpression in CLL cells upon exposure with rh IL-6 and verified STAT3 binding to the miR-155 promoter in rh IL-6-exposed CLL cells. Despite the direct regulation of miR-155 transcription by STAT3, they suggested that IL-6 increased STAT3 binding to the miR-155 promoter. Structural and molecular analysis verified the existence of the
two binding sites in the miR-155 gene promoter for STAT3.\textsuperscript{21} STAT3, after phosphorylation, joins to the gamma interferon activation site (GAS)-LIKE components located in the promoter region of various genes.\textsuperscript{77} Indeed, Li et al introduced two GAS-LIKE elements inside the miR-155 promoter, enabling STAT3 binding to the miR-155 promoter by these elements.\textsuperscript{21} Thus, they confirmed that IL-6 induces miR-155 activation in CLL cells via STAT3, and consequently regulates hematopoietic cell proliferation.\textsuperscript{21}

Interaction between miRNAs and JAK/STAT3 signaling in acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the high proliferation of non-mature lymphocytic cells in BM, peripheral blood, and other organs. About 4000 people have been involved annually in the United States that 75%–80% of them are children.\textsuperscript{76, 78}

Relationship between miR-451a and JAK/STAT3 signaling in Philadelphia-positive ALL (Ph\textsuperscript{+} ALL)

ALL with BCR-ABL1 gene fusion (Philadelphia chromosome-positive) in the precursor of B-lineage subtypes, which is resulted in constitutive activation of ABL tyrosine kinase, is one of the most fatal leukemia showing unfavorable prognosis\textsuperscript{79, 80}; however, commonly demonstrate an appropriate response to tyrosine kinase inhibitors (TKI).\textsuperscript{79, 80} Nevertheless, the relapses incidence rate is notable in these patients, highlighting the importance of new insights to treating this condition.\textsuperscript{91} It has been clarified that BCR/ABL fusion protein in chronic myeloid leukemia (CML), stimulates the expression of IL-6, which is a multipotent cytokine that prepares the favorable micro-environment for expansion and maintenance of the leukemic stem cells.\textsuperscript{82} Despite that BCR/ABL fusion gene is the indicator marker of Ph\textsuperscript{+} ALL, the relation between BCR/ABL fusion and IL-6 in Ph\textsuperscript{+} ALL has not yet been elucidated entirely.\textsuperscript{93} As described, IL-6 binds to its specific receptor (IL-6R) and then triggers the JAK/STAT3 signaling pathway.\textsuperscript{84, 85} In a study, Jiang et al evaluated the level of BCR-ABL expression in Ph\textsuperscript{+} ALL patients to investigate the association between BCR-ABL and miR-451 in mononuclear cells of these patients, and found that BCR-ABL has an inverse relation with miR-451.\textsuperscript{83} Bioinformatic analysis showed that IL-6R can be a target of miR-451a.\textsuperscript{86} It has been reported that miR-451a represses the proliferation of some types of cancer cells such as lung adenocarcinoma\textsuperscript{87} and renal cell carcinoma.\textsuperscript{88} Besides, in CML, miR-451a is inversely related to BCR-ABL gene expression levels, and its downregulation is paralleled to imatinib resistance.\textsuperscript{89} Examination of the underlying mechanism of miR-451a on the ALL cell line with Philadelphia chromosome-positive showed that this miRNA directly suppresses IL-6R via targeting its 3’-UTR. Jiang et al reported that BCR/ABL mRNA levels were inversely correlated to miR-451a and positively associated with serum IL-6 concentration.\textsuperscript{83} They also indicated that miR-451a downregulated the levels of phosphorylated JAK2 and STAT3 in the absence of any impact on total rates of JAK2 and STAT3, indicating the inhibitory effects of the miR-451 on IL6/JAK/STAT3 axis upon suppressing the IL6R and p-JAK and p-STAT3 downstream molecules.\textsuperscript{83} Thereby, it has been suggested that miR-451 is downregulated by BCR-ABL at Ph\textsuperscript{+} ALL patients to provide a survival advantage in leukemic cells via the IL6/JAK/STAT3 pathway. Therefore, elevation in miR-451 expression in these patients could rise the promise for the treatment of this acute and severe type of leukemia.\textsuperscript{83}

The relationship between JAK/STAT pathway and miR-146b and FASL for inducing neutropenia in T-cell large granular lymphocytic (TLGL) leukemia

T-cell large granular lymphocytic (TLGL) is a rare type of leukemia characterized by the abnormal proliferation of large granular T lymphocytes in peripheral blood.\textsuperscript{90, 91} TLGL leukemic cells are divided into two clusters, including cluster A that showed CD8\textsuperscript{+}/CD4\textsuperscript{+}/CD57\textsuperscript{+} immune phenotype, and cluster B that showed CD4\textsuperscript{+}/CD8\textsuperscript{+}/CD57\textsuperscript{+} immune phenotype.\textsuperscript{92} The underlying cause of TLGL is not fully well known, an impairment in apoptotic signals and increase in survival involve be considered as possible pathogenesis of these types of blood malignancies.\textsuperscript{93, 97}

Among these, JAK/STAT signaling is one of the well-known involved pathways in TLGL progress especially in the CD8\textsuperscript{+}/CD4\textsuperscript{+} immunophenotype which is associated with neutropenia.\textsuperscript{92, 94, 95}

The mechanism of neutropenia in TLGL is not fully understood, while degeneration of mature neutrophils and myeloid progenitors through FAS/FASL signaling has been suggested as a potent corresponding mechanism.\textsuperscript{92} Previously, it has been reported that promoted levels of soluble FASL in the blood circulation are one of the most important possible factors contributing to the pathogenesis of neutropenia in T-LGL patients.\textsuperscript{96, 97} Many studies also have the existence of the improved concentrations of soluble FASL in TLGL patients.\textsuperscript{95, 96, 98, 99} which supports neutropenia occurrence in TLGL patients. It has been observed that about 35% of TLGL patients have a hotspot mutation in STAT3, supporting the overactivation of STAT3.\textsuperscript{100, 101} Teramo et al have reported that STAT3 plays a key role in FASL transcription and showed that a promoted level of STAT3 activity is associated with a higher rate of FASL expression in TLGL patients\textsuperscript{95}; however, the molecular mechanism of FASL regulation by STAT3 has not yet been elucidated. In another study, Mariotti and her co-workers also detected elevated levels of tyrosine-phosphorylated (YP)-STAT3 in CDB\textsuperscript{+} TLGLL patients, but not in CD4\textsuperscript{+} T-LGLs patients.\textsuperscript{92} Mariotti et al revealed that FASL mRNA expression is correlated with the upregulation of STAT3 activation and inversely with the absolute neutrophil counts (ANC).\textsuperscript{92} They determined that miR-146b was downregulated in CD8\textsuperscript{+} TLGL compared to CD4\textsuperscript{+}, as well as found that there is an association between miR-146b expression and ANC levels concomitant with the levels of YP-STAT3 in T-LGLs patients.\textsuperscript{92} In addition, they found that miR-146b has an inverse correlation with STAT3 tyrosine phosphorylation, neutropenia, FASL
expression, and soluble FASL release in blood circulation,\(^{92,95}\) emphasizing the importance of the STAT3-miR146b-FasL axis in TLGL leukemia.\(^{92}\) Respecting the previous findings that STAT3 can stimulate inhibitory influence on gene expression through inducing the target genes promoter methylation,\(^{102,103}\) it has been confirmed that STAT3 stimulates miR-146b promoter methylation through regulating the expression of methyl transferase-1 in solid tumors and T lymphocytic malignancies.\(^{104}\) Regardless of the presence of correlation between STAT3 function and miR-146b cellular levels in malignant condition,\(^{104,105}\) it also has been reported STAT3 activates miR-146b in normal tissues.\(^{106,107}\) Overall, Mariotti et al suggested that STAT3 suppressed the miR-146b expression in TLGL by inducing the miR-146b promoter methylation.\(^{92}\) Considering molecular analysis, human antigen R (HuR), which plays a well-known role in mRNA stabilization and FASL expression, has been shown that can be another target of miR-146b.\(^{108}\)

Mariotti et al detected that HuR protein is an endogenous target of miR-146b in CD8\(^+\) T-LGLs, and also indicated that miR-146b downregulated the FASL expression indirectly and post-transcriptionally through reducing the HuR protein levels. Accordingly, they suggested that consistent over-activity of STAT3 in CD8\(^+\) T-LGLs resulted in the loss of miR-146b, which in turn led to the HuR protein translation, enabling FasL production and neutropenia incidence.\(^{92,95}\)

### Interaction between miRNAs and JAK/STAT3 signaling in CML

CML is a hematopoietic stem cell clonal disorder characterized by the generation of the Philadelphia chromosome (Ph\(^+\)) due to the BCR-ABL oncogenic protein fusion resulting from translocation t(9;22) and comprises about 15% of leukemia diagnosed in adults.\(^{111}\)

### The relationship between miR-147 and STAT3 signaling

The miR-147 has been identified about various cancers\(^{112-115}\) through showing dual roles, including tumorigenesis and tumor suppressor roles, in a variety of human cancers. For example, upregulation of miR-147 has been observed in human gastric and liver cancers, whereas its downregulation has been reported in human breast cancer.\(^{116}\) In a study, Han et al showed that the hypoxia-induced damage was intensified in the PC12 cell line, commonly derived from a transplantable rat pheochromocytoma, due to the attenuation in miR-147 levels.\(^{117}\) In detail, they showed that maternally expressed gene 3 (MEG3) as a long noncoding RNAs (lncRNAs) boosted hypoxia injury in PC12 cells through down-regulating miR-147, as well as demonstrated that the overexpression of MEG3 and miR-147 induced apoptosis and inhibited target cells proliferation.\(^{117}\) LncRNAs and miRNAs usually act as competing endogenous RNAs. Evaluation of the miRNAs database to identify MEG3 interacting miRNAs has revealed that miR-147 is one of the potential miRNAs in this regard. Investigations revealed that the levels of MEG3 and miR-147 expression in the KCL22 and K562, two human CML cells, were decreased in comparison to healthy BMMCs. It seems that MEG3 can bind to miR-147 and eventually reduce miR-147 expression. Li et al also observed a high level of methylation of miR-147 and MEG3 in CML patients but not in healthy individuals. Accordingly, they showed that the expression rate of the methylation-related genes, such as HDAC1 (histone deacetylase 1), DNMT1 (DNA methyl transferase 1), DNMT3A, DNMT3B, were remarkably promoted in the CML patients with accelerated phase. Therefore, they concluded that the downregulation of miR-147 and MEG3 levels in the CML patients was probably mediated by histone deacetylation and DNA methylation. Besides, they suggested that JAK2 and STAT3 can negatively regulate MEG3 upon binding to it, as well as described that MEG3 can downregulate STAT3 by suppressing the phosphorylation of JAK/STAT.\(^{118}\) In sum, they suggested that there is a negative feedback between MEG3 and STAT3. On the other hand, they showed that miR-147 and MEG3 can regulate each other negatively and adjust leukemia development, verifying that STAT3 and miR-147 indirectly affect each other through MEG3.\(^{116}\)

### The relationship between miR-574-3P and JAK/STAT3 signaling

The significant role of miR-574-3p in some cancers has been reported. For instance, miR-574-3p commonly is decreased in bladder cancer cells whereas overexpression of miR-574-3p remarkably prohibited bladder cancer cell proliferation, invasion, and migration.\(^{115}\) In addition to the miR-574-3p importance as a potential prognostic marker for breast cancer,\(^{120}\) its lower expression is noticed in the early stages of gastric cancer; however, upregulation of miR-574-3p inhibits proliferation, invasion, as well as the migration of human gastric cancer cells, line.\(^{121}\) It is also reported that miR-574-3P has a tumor-inducing role in human osteosarcoma,\(^{122}\) while triggers an inhibitory impact on esophageal squamous cell carcinoma,\(^{123}\) implying its potentially reciprocal role in a variety of human cancers. Yang et al showed that the miR-574-3P expression was significantly decreased in the peripheral blood of CML patients compared to the healthy donor. They also showed that overexpression of miR-574-3P resulted in significant inhibition of cell proliferation of human K562 CML cells and induced apoptosis, whereas suppression of miR-574-3P had a contrasting effect. They checked the TargetScan Human database and found that the IL6 can be a potential direct target for miR-574-3P. They also found that the IL6 at mRNA and protein levels was remarkably inhibited upon miR-574-3P transfection. These data showed that IL6 is a direct target for miR-574-3P and IL6 expression was negatively regulated by miR-574-3P. As known, IL6 is identified as an inflammatory cytokine involved in the pathogenesis of hematological disorders such as multiple myeloma.\(^{124}\) Maeda et al showed that IL6 may contribute to both myeloid proliferation and lymphocytopenia.\(^{125}\) They suggested that IL6 could control the cell destination of leukemic multipotent progenitor cells and may support a positive feedback loop to maintain CML progression.\(^{62}\) It is also known to be a prognostic factor for the follow-up of imatinib treatment in CML patients.\(^{126}\) It has already been
found that overexpression of IL6 significantly induces K562 CML cell proliferation, and conversely inhibits their apoptosis.\textsuperscript{127} Also, reports confirm that IL-6 can activate the JAK/STAT3 and MAPK signaling pathway and is involved in the development of CML.\textsuperscript{55} Rendering findings, Yang et al proposed that miR-574-3P can suppress the IL6/JAK/STAT3 signaling pathway through directly targeting IL6, which in turn, inhibits the proliferation and induce apoptosis in CML cells,\textsuperscript{127} describing miR-574-3p as a potent target for CML treatment.

The relationship between miR-34a and embryonic hemoglobin production in myeloid cells mediated by STAT3

Sickle cell anemia (SCA), which is characterized by abnormal hemoglobin S (Hb S) production, is one of the most common genetic hematological disorders. Annually more than 300,000 newborns are born with cyclic anemia, which is one of the most common blood disorders in the world associated with a poor prognosis.\textsuperscript{128} Despite the recent increase in new therapeutic approaches, hydroxyurea is still the principal of SCA treatment showing the competence to reduce SCA-related mortalities.\textsuperscript{129} Indeed, the most effective treatment for the cycle cell anemia is increasing Hb F production with the formula \(a_2g_2\) (a combination of two alpha chains and two gamma chains globulin) that improves clinical symptoms and consequently prolongs the patient overall survival rates.\textsuperscript{130,131} The therapeutic role of Hb F is related to its inhibitory effects on Hb S polymerization,\textsuperscript{132} which is one of the main pathogens and risk factors in patients with SCA.\textsuperscript{133} Importantly, comprehensive studies have indicated that a wide spectrum of genes is targeted by miR-34a, including the genes known as a repressor of gamma-globin, a variant of globulin chain used in hemoglobin F production, such as Yin Yang 1 (YY1), HDAC1, and STAT3.\textsuperscript{75,134–137} Scientific related software predicted the binding site for miR-34a at the 3’ UTR of STAT3,\textsuperscript{131} and also studies have shown that miR-34a interacts with STAT3 in K562 CML cells.\textsuperscript{137} Interestingly, reports have revealed that GATA1 (GATA binding protein 1) and STAT3 compete for binding to the 5’ UTR of the gamma globulin gene and an increase in GATA1 expression reverses gamma globulin gene silencing induced by STAT3.\textsuperscript{138} Besides, it has been shown that during the erythroid differentiation progresses, erythropoietin (EPO) can activate STAT3 through phosphorylation,\textsuperscript{139} leading to the inhibition of gamma globulin gene expression.\textsuperscript{138} Therefore, these data verify that STAT3 has a function in gamma globulin gene regulation. In a study, Ward et al conducted a study to determine whether miR-34a can regulate gamma-globin gene expression through targeting the negative gamma globulin regulator genes including STAT3. Achieved consequences exhibited that the total and phosphorylated STAT3 levels were significantly decreased in miR-34a-transfected K562 cells.\textsuperscript{131} They also observed that the gamma-globin mRNA and Hb F protein levels were augmented in response to overexpression of miR-34a. Respecting that the overexpression of miR-34a leads to a reduction in STAT3 and an increase in gamma-globin and Hb F expression, WARD et al reports confirmed that likely exist an indirect mechanism for gamma-globin regulation by miR-34a via STAT3 gene silencing.\textsuperscript{131} They showed that miR-34a induced the production of Hp F in K562 cells by reducing total STAT3 and phosphorylated STAT3 levels, which have a role in silencing the gamma globulin gene.\textsuperscript{131}

Interaction between miRNAs and JAK/STAT3 signaling in AML

AML is the most common acute leukemia in adults, with about 20,000 cases per year in the United States alone.\textsuperscript{140}
Association with miR-494-3p overexpression and promoting the megakaryocytopoiesis in primary myelofibrosis hematopoietic stem/progenitor cells

Thrombopoietin (TPO) is produced in the liver and acts as the main regulator in megakaryocytopoiesis and participates in megakaryocyte proliferation and differentiation. TPO has been identified as a pan-hematopoietic cytokine and is crucial for the preservation and survival of hematopoietic stem cells.\(^1\) It binds to its receptor, TPOR, on the surface of hematopoietic stem and progenitor CD34\(^+\) cells (HSPCs) and results in the activation of JAK2, which leads to STAT3 phosphorylation and induction of megakaryocytopoiesis.\(^1\)\(^2\) Studies have supported overexpression of miR-494-3P in HSPCs in patients with primary myelofibrosis (PMF).\(^1\)\(^3\) Rontauroli et al. in their study showed that an increase in expression of miR-494-3P, enhanced hematopoiesis in normal hematopoietic cells.\(^1\)\(^4\) Investigations have recommended that the suppressor of cytokine signaling 6 (SOCS6) is a target for miR-494-3p. Also, a previous study reported that SOCS6 is downregulated in HSPCs derived from PMF patients, which concurrently showed miR-494-3p upregulation.\(^1\)\(^3\) SOCS6 is an important factor in the negative regulation of the JAK/STAT signaling pathway;\(^1\)\(^4\) as well as contributes to the mechanism of myeloproliferative neoplasms (MPN) pathogenesis.\(^1\)\(^4\) Other investigations have evidenced that SOCS6 decreases the nuclear level of the STAT3 and attenuates its phosphorylation, supporting STAT3 downregulation.\(^1\)\(^4\)\(^5\) Rontauroli et al. reported that the expression level of MK antigen, including CD41 or later CD42b antigen, has superiority in CD34\(^+\) cells transfected with miR-494-3p over normal cells. These results confirmed that miR-494-3p is involved in megakaryocyte differentiation in the pathogenesis of PMF. Furthermore, STAT3 may affect TPO signaling and megakaryocytopoiesis in HSPCs.\(^1\)\(^2\) The results of the study of Rontauroli et al. demonstrated that transfection of K562 and CB (cord blood-derived) CD34\(^+\) cells with miR-494-3P decreased SOCS6 protein levels and subsequently increased STAT3 phosphorylation, ultimately leading to megakaryocyte hyperplasia observed in PMF patients.\(^1\)\(^4\)

Cluster miR-23a, miR-27a, miR-24 and association with JAK/STAT signaling pathway in acute erythroid leukemia (AEL)

Acute erythroid leukemia (AEL) (termed AML M6), is a rare subtype of AML with accounts for about 5% of all AML cases.\(^1\)\(^4\)\(^7\)\(^8\) The survival and prognosis of AEL patients are...
too worse than in other AML subtypes.\textsuperscript{149, 150} As described, STAT3 plays an important role in the progression of erythroleukemia through suppression of erythroid differentiation.\textsuperscript{151} In a study, Su et al showed that miR-23a, miR-27a, miR-24 synergistically targeted the members of the GP130/JAK1/STAT3 signaling pathway. They also showed that miR-23a, miR-27a, and miR-24 clusters were downregulated in AEL patients. They assumed that miR-23a, miR-27a, miR-24 cluster jointly targeted the GP130/JAK1/STAT3 pathway in AEL cells and induced the differentiation of these cells.\textsuperscript{152}

Other studies have presented that the JAK1 binding to the GP130 transmembrane protein and succeeding activation of STAT3 enables signaling network formation among GP130, JAK1, and STAT3.\textsuperscript{7} They concluded that overexpression of miR-23a, -27, and -24 can trigger apoptosis and inhibit the deregulated proliferation of AEL cells through the

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**Figure 4** The signals mentioned in the study in which STAT3 and miRNAs are involved.
| Cancers                        | miRNA        | Interaction between miR:503-5p and STAT3 | Suggested pathway or signaling involved | References |
|-------------------------------|--------------|-------------------------------------------|----------------------------------------|------------|
| Metastatic or paclitaxel-resistant ovarian cancer cells | miR-503-5p  | miR-503-5p binds directly to the 3’ UTRs of CD97 | miR-503-5p inhibits the CD97-mediated JAK2/STAT3 pathway | 190        |
| Early gastric cancer          | miRNA-200 Family | miR-200 family members were upregulated by IL11/STAT3 signaling | IL11/STAT3-dependent manner | 191        |
| Ovarian cancer                | miRNA-92     | STAT3 directly regulates miR-92a          | STAT3/miRNA-92/DKK1/Wnt/b-catenin signaling pathway | 192        |
| Colorectal cancer             | miR-34a      | IL6R is a direct target of miR-34/STAT3 and JAK 2 can be potentially miR-34a targets | IL-6R/STAT3/miR-34a feedback loop | 193        |
| Human gastric cancer          | MicroRNA-143 | miR-143 directly targets STAT-3            | Proliferation, migration, and invasion signaling in which STAT3 is involved | 195        |
| Cervical cancer               | miR-411      | miR-411 inhibited cervical cancer progression by directly targeting STAT3 | Proliferation and invasion signaling in which STAT3 is involved | 26         |
| Pancreatic cancer             | miR-301a     | Targeting SOCS5                           | miR-301a induces pancreatic cancer invasion and metastasis via JAK/STAT3 signaling by targeting SOCS5 | 194        |
| Breast cancer                 | MicroRNA-204 | Targeting JAK2                            | MicroRNA-204 targets JAK2 and induces cell apoptosis through the STAT3/Bcl-2/survivin pathway | 195        |
| Human renal carcinoma cells   | miRNA-133b/  | miR-133b and miR-135a may target directly the 3-UTR of JAK2 | miR-133b and miR-135a induce apoptosis signaling cascade involving JAK2, STAT3, and Bcl-2 | 196        |
|                              | miR-135a     |                                             |                                        |            |
| Pancreatic cancer cells       | miRNA let-7  | let-7 upregulates SOCS3 expression in PDAC cells | LINC00240/microRNA-124-3p/STAT3/MICA axis | 197        |
| Natural killer T cell         | miR-124-3p   | Down-regulation of miR-124-3p promotes cervical cancer progression through targeting STAT3 |                                        | 198        |
| cytotoxic activity in cervical cancer | miR-181b   | STAT3 up-regulates miR-181b through directly binding | STAT3-miR-181b-CYLD-NF-κB | 199        |
| Epigenetic switch between     | miR-146b     | miR-146b was reported as a direct target of STAT3 | NF-κB/IL-6/STAT3 pathway | 104        |
| inflammation and colorectal cancer | miR-221   | miR-221 directly targets the PDLIM2 gene that is known to be essential for restraint NF-κB | miR-221/PDLIM2 gene/NF-κB/STAT3 | 200        |
| Breast cancer cells           | miR-155      | miR-155 directly targets and inhibits the SOCS1 (the inhibitor of STAT3) | miR-155/NF-κB-STAT3 | 200        |
| AOM/DSS mice model            | miR-206      | miR-206 decreased the angiogenesis by targeting 14-3-3z | Locking the 14-3-3z/STAT3/HIF-1a/VEGF signaling | 201        |
| induced inflammatory bowel disease | miR-375   | JAK2, MAP3K8, and ATG7 are predicted target genes for miR-375 | JAK2/STAT3 and MAP3K8/ERK signaling pathways | 202        |
| Colitis-associated cancer     | miR-216a     | miR-216a directly targets JAK2             | JAK2/STAT3 pathway | 203        |
| Gastric cancer cells          | MicroRNA-216a|                                            |                                        |            |
| Papillary thyroid cancer      | miRNA-148a   | miRNA-148a promotes STAT3 and PI3K/AKT signaling |                                        | 204        |
suppressing of the GP130-JAK1-STAT3 cascade. They also reported that these miRNAs cooperatively induce erythroid differentiation via inhibiting the GP130 and suppression of the JAK1-STAT3 phosphorylation in human leukemic HEL and K562 cell lines as well as cord blood (CB)- CD34+ HSCs.152

Relationship between miR-155 and JAK/STAT3 signaling and LIFRα

Laboratory studies on leukemic cells, including HL60, show that STAT3 overexpression and leukemogenesis is depending on the phosphorylation of STAT3.153 While inhibition of STAT3 signaling leads to the induction of apoptosis in leukemic cells.154 The leukemia inhibitory factor (LIF), as known as one of the members of IL-6 family cytokines, has been reported that can induce differentiation of the M1 murine myeloid leukemic cell line. It is named LIF due to its ability to induce differentiation M1 myeloid leukemic cells.155 This protein executes its biological activity through its receptor located on the cell surface and a membrane-associated transducer (termed LIFR-a).156 Former studies determined that STAT3 can be activated by IL-6 family cytokines,157 and also revealed that IL6 family/STAT3 signaling may affect differentiation of stem and leukemic cells and other cells.158–161 LIFRα has been determined that bind to the GP-130 on the surface of leukemic cells and form heterodimers, which are capable of STAT3 activation.162 Similar to LIFRα, the fusion protein containing the cytoplasmic functional domain of LIFRα, like CT3 in TAT-CT3 fusion, a peptide domain vector, can induce STAT3 activation in HL60 cells.163 The LIFRα-CT3 fusion transfection in HL60 cells resulted in suppression of the proliferation and promoting the differentiation in HL60 myeloid cells in vitro.163 Other studies have proposed that miR-155 is a primary transcript of the third exon of the B cell integration cluster (BIC) gene,164 typically overexpressed in the BM of patients with special subtypes of AML.165–167 Other examinations have represented that IL-10 suppresses miR-155 through STAT3 activation.168 Moreover, XU et al reported that the TAT-CT3 fusion protein inhibits miR-155 expression following targeting STAT3 in HL-60 cells.155 They determined that the TAT-CT3 fusion protein negatively regulated miR-155 expression, which is overexpressed in some type of AML.155 They showed that TAT-CT3 transfection downregulated the miR-155 expression, which in turn, increased SOCS-1 and subsequently decreased STAT3 phosphorylation results in differentiation of leukemia cells.155

Table 1 (continued)

| Cancers                          | miRNA          | Interaction between miR-503-5p and STAT3                                                                 | Suggested pathway or signaling involved          | References |
|----------------------------------|----------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------|
| Natural killer T cell cytotoxic activity in cervical cancer | microRNA-124-3p | cancer cell growth by targeting PI3K signaling pathway. miR-124-3p is a direct target of LINC00240/Inhibition of miR-124-3p promotes cervical cancer progression via targeting STAT3 | LINC00240/microRNA-124-3p/STAT3/MICA axis | 198        |
| Breast cancer cell lines         | miR-146b       | a gene encoding the miR-146b is a direct STAT3 target gene/STAT3 induces miR-146b, a negative regulator in cancer/miR-146b links STAT3 to NF-kB and IL-6 as part of a negative feedback loop | miR-146b/NF-kB/IL-6/STAT3 Axis                 | 104        |
| Lung cancer                      | MicroRNA-218    | miR-218 negatively regulates IL-6 receptor and JAK3 gene expression by directly targeting the 3'-UTR of their mRNAs | IL-6/STAT3 signaling pathway                   | 205        |

The miR-17 and miR-20a and association with STAT3 and hypoxia-inducible factor 1 (HIF1)

Hypoxia-inducible factor 1 (HIF1) is an important transcription factor in response to hypoxic conditions containing two subunits including, an alpha subunit (HIF1α, oxygen-sensitive subunit) and a beta subunit (HIF1b).170,171 It also has a role in cancer biologies such as tumor growth, metastasis, and angiogenesis.172 Consistent with the previous studies,173,174 He et al showed that hypoxia...
| miRNA            | Direct target of miRNA | MiRNA expression status in malignancy | Effect on STAT3 Type of hematological disorder | Samples                                                                 | Function                                                                                                                                  | Suggested pathway or signaling involved                                                                 |
|------------------|------------------------|--------------------------------------|---------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| miR-21/miR-155   | IL9                    | Up regulated                         | N/A                             | CLL                                                                       | MEC1 CLL cell line                                                                  | pSTAT3 up regulated miR-155 and miR-21                                                                                           |
|                  |                        |                                      |                                 |                                                                           | Extra cellular IL9/ pSTAT3/miR-155/miR-21/intra cellular IL9’ positive feedback system in CLL cells                                |
| miR-21           | repressor genes, such as PIAS3 and PDCD4 and PTEN | Up regulated                         | Indirectly via STAT3 suppressor gene | CLL                                                                       | RAMOS B cell/ UE6E7T2/bone marrow stromal cell                                      | STAT3 up regulated miRNA-21                                                                                                         |
| miR-155          | N/A                    | Up regulated                         | N/A                             | CLL                                                                       | Human multiple myeloma MM1 cells                                                   | STAT3 up regulated miR-155                                                                                                         |
| miR-451a         | IL6R                   | Down regulated                       | Direct binding to down-stream of IL6R as a STAT3 activator | Ph+ ALL                                                                   | BM-MNCs/Ph+ ALL cell line SUP-B15/Ph+ ALL cell line Nalm6                        | miR-451a/IL6/JAK/STAT3 indirectly                                                                                                   |
| miRNA-146b       | HuR protein            | Down regulated                       | N/A                             | CD8 TLGLs                                                                 | PBMCs from TLGLs patient/Jurkat cells                                              | ST3/miR146b HuR/FASL axis                                                                                                          |
| miRNA-147        | N/A                    | Down regulated                       | miR-147 indirectly affects on STAT3 via affecting on MEG3 | CML                                                                       | KCL22/K562 CML cells/bMMCs                                                          | miR-147 can probably regulate STAT3 via MEG3                                                                                      |
| miRNA-574-3P     | IL6                    | Down regulated                       | Indirectly via Increase in IL6   | CML                                                                       | K562 CML cells                                                                   | miRNA-574-3P down regulated JAK/STAT3 signaling via IL6                                                                             |
| miRNA-34a        | STAT3                  | —                                    | Directly increase in STAT3       | Sickle cell anemia                                                         | K562 CML cells                                                                   | miRNA-34a down regulated STAT3                                                                                                     |
| miR-494-3p       | SOCS6                  | Up regulated                         | Indirectly via SOCS6 inhibiting | PMF                                                                       | K562/cord blood CD34+ cells                                                        | miRNA-494-3p/STAT3                                                                                                                |
| miR-23a, -27a, -24 cluster | miR-23a, -27a and -24 synergistically target the members of gp130/JAK1/STAT3 signaling pathway | Down regulated                       | Direct increase in STAT3                                                  | AEL (AML M6)                                                                       | HEL and K562 cell lines/CB-HSCS CD34+                                                                                               |
|                  |                        |                                      |                                 |                                                                           | miR-23a, -27a, -24 cluster down regulated STAT3                                                                                 |

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Ref: 48, 49, 21, 83, 206, 118, 127, 131, 144, 152
promoted cell cycle arrest and differentiation in myeloid leukemic cells.¹⁷⁵ The HIF-1α protein translocates into the nucleus and forms a heterodimer with HIF-1β and then regulates the expression of target genes through binding to hypoxia-responsive elements (HREs) located on gene promoters.¹⁷⁵ These genes, which are targeted by HIF-1, support the cells for adaptation in hypoxic conditions by affecting processes covering, apoptosis, differentiation, angiogenesis, cell growth in concomitant with metabolism, and erythropoiesis.¹⁷⁵ HIF-1α in hypoxic conditions, known as a significant indicator of solid tumors, cooperates with tumor growth, metastasis, and angiogenesis.¹⁷² He et al have shown that the HIF-1α transcription factor can induce differentiation and inhibit AML development.¹⁷³,¹⁷⁵ They showed that HIF1α decreases miR-17 and miR-20a, two members of the miR-17-92 gene cluster, via directly targeting STAT3.¹⁷⁵ It has already been found that miR-17 and miR-20a are overexpressed in solid tumors and hematological disorders such as mantle cell lymphoma (MCL), large B-cell lymphoma, and Burkitt’s lymphoma.¹⁸⁰–¹⁸² Besides, it has been shown that the miR-17-92 cluster target the HIF-1α protein.¹⁷⁵,¹⁸³–¹⁸⁵ He et al also reported that miR-17 and miR-20a were downregulated in hypoxic conditions in AML cell lines. Indeed, they indicated that HIF-1α downregulates miR-17 and miR-20a gene expression during hypoxia in AML cells. They also demonstrated that a decrease in miR-17 and miR-20a participates in the differentiation process of AML cell lines triggered by HIF-1α. Based on last year’s reports, STAT3 can be a target gene of miR-17 and miR-20a.¹⁸⁶,¹⁸⁷ On the other hand, they reported that exist two binding sites for miR-17/miR-20a at the wild-type 3′-UTR of STAT3, which enables suppressing of the STAT3 protein expression via directly targeting its 3′-UTR post-transcriptionally.¹⁷⁵ In total, He et al concluded that miR-17 or miR-20a abrogated HIF-1α-induced growth arrest and differentiation in AML cells through binding to STAT3 transcript and inhibiting its expression.¹⁷⁵

The miR-21 and miR-17-92 cluster and their association with STAT3

Acute myeloid leukemia (AML) with t(8;16)(p11;p13) is an uncommon leukemia subtype with representative clinical features, including presentation as coagulation disorder, recurrent extramedullary involvement accompanied by poor prognosis.¹⁸⁸ Further, AML blast cells with t(8;16) show a frequent hemophagocytosis and myelomonocytic phase of differentiation.¹⁸⁸,¹⁸⁹ The oncogenic miRNAs cluster miR-17-92 and miR-21, which are usually upregulated in other cancers, are commonly downregulated in the t(8;16) AML 191. In this regard, assessment of the expression levels of the known transcription factors of cluster miR-17-92 and miR-21 genes, such as STAT3 in 7 t(8;16) AML patients and 36 patients with other AML cytogenetic subtypes approved STAT3 downregulation in the t(8;16) AML patients 191. In 2013, Beya et al found that STAT3 expression was downregulated in patients with t(8;16) translocation, and miR-21 was regulated at the transcriptional level by STAT3.¹⁸⁹ Based on these results, the decrease in miR-21 and likely decrease in miR-17-92 cluster has an association with a decrease in STAT3 in AML with t(8;16).¹⁸⁹
miRNAs regulate a variety of cellular processes, including inflammation, proliferation, survival, metastasis, invasion, and angiogenesis, all of which can also be triggered by activated STAT3 by binding to DNA and other stimulants, leading to tumor growth (Fig. 2, 3). Furthermore, the important role of miRNAs in regulating the JAK/STAT3 signaling pathway has been proven. For a better understanding of the interaction between STAT3 and miRNAs in leukemic cells, the complete signaling pathways have been shown in Figure 4. To determine the role of STAT3, one of the most important transcription factors in many cancers, including leukemia, we focused on studies regarding the role of miRNAs in the regulation JAK/STAT3 signaling pathway in hematological disorders. For a better understanding of the relationship between microRNAs and STAT3, here we have summarized the role of both factors in some cancers and more comprehensively in blood malignancies in two separate tables (Table 1, 2). To sum up, it can be concluded that therapeutic approaches especially multimodal treatments for modifying the STAT3 signaling pathway can lead to improved therapeutic outcomes in patients suffering from various hematological disorders, in particular, leukemia; however, the accomplishment of comprehensive clinical trials before using STATs inhibitors should be considered.

Author contributions

All authors contributed to the conception and the main idea of the work. M.S.D, T.A.M.M, H.S.R, and M.S.M drafted the main text, figures, and tables. S.D, N.S and S.S took part in the conceptualization and scientific editing of the manuscript. F.M and E.Z drew the figures. M.A, A.A and R.A helped in revision. M.J and M.F.H supervised the work and provided the comments and additional scientific information. All authors read and approved the final version of the work to be published.

Consent for publication

All authors consent to the publication of the manuscript in Genes & Diseases.

Conflict of interests

Authors declare no conflict of interests.

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