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November 16, 2023

Review

New therapeutic axis in blood malignancies involving microRNAs and JAK/STAT3 signaling

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Abstract

Cancers of the blood stemming from genetic or environmental abnormalities are included in the broad category of blood diseases. Some forms of leukemia may respond better to therapy than others, and there are a number of factors that contribute to the failure of current medications to effectively address blood diseases, including drug resistance. Many different factors, both inherited and acquired, may cause leukemia, which is characterized by the uncontrolled growth of one or more cell lines. Oncogene signal transducer and activator of transcription (STAT) family transcription factor STAT3, in particular, plays a crucial role in the initiation and development of hematological illnesses as a result of mutations, malfunction, or hyperactivity. In addition, research indicates that microRNAs, as biological molecules, may promote or inhibit tumor growth in different types of cancer. Additionally, it has been found that STAT3 has a robust connection to miRNA. For example, miRNAs may control STAT3 by targeting its upstream mediators such as IL6, IL9, and JAKs or directly binding to the STAT3 gene. However, STAT3 has the ability to control miRNAs. The purpose of this review was to identify the function of microRNAs and STAT3 and how they interact with one another in hematological malignancies.

Keywords: Interleukin, Janus kinase, Leukemia, microRNAs, signal transducer, activator of transcription 3

Introduction

Particularly in undifferentiated cells, members of the STAT family, and STAT3 in particular, are oncogenic factors with a wide range of cellular functions they regulate, including proliferation, survival, angiogenesis, and metastasis.11,17,18,19. The JAK kinase family typically activates the STAT family cytoplasmic transcription factor by phosphorylating tyrosine residues on STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6.20 Once activated, STATs dimerize and are translocated into the nucleus, where they are responsible for regulating gene expression. 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.25, 26, 27, 28, 29. On the other hand, several studies have implied the possible role of STAT3 in regulating miRNA expression.30, 31, 32. MicroRNAs (miRNAs) are a type of endogenous, non-coding, single-stranded RNA that range in length from 19 to 25 nucleotides and alter gene expression post-transcriptionally by binding to the 3′

untranslated regions (3′ UTRs) and thereby promoting the mRNA's degradation or triggering the inhibition of mRNA translation, respectively.33, 34, 35 miRNAs actively contribute to a wide range of cellular processes, including In conclusion, multiple studies suggest that miRNAs and STAT3 may induce a basic regulatory influence on each other, either directly or indirectly.44, 45, 46, 47 Herein, we have emphasized the powerful significance of miRNAs in regulating STAT3 expression and activity in hematological diseases.

Chronic lymphocytic leukemia (CLL) and the crosstalk between microRNAs and the JAK/STAT3 signaling pathway.

An accumulation of mature and small B cells expressing CD5+ and CD19+ immune phenotype markers, affecting peripheral blood, bone marrow (BM), and lymphoid tissues, characterizes chronic lymphocytic leukemia (CLL), one of the most common hematological disorders worldwide and the most common adult leukemia disorder in the western hemisphere.48.

Association of CLL-Related Genes IL9, STAT3, miR-A21, and miR-155

Studies have shown that IL9 levels are often elevated in CLL patients,48 and Chen et al. found that CLL cell proliferation was enhanced and apoptosis was reduced when they used recombinant human IL9. 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.48 IL9 is more commonly known as Th2 cytokine, contributes to allergic diseases.50 Findings have presented that IL9 in addition to the involvement in T-reg and mast cell-mediated tumor immunity,51 may participate in growth, tumor progression, and the anti-apoptotic process.48 Many studies have shown that the IL9-a chain stimulates mutant JAK1 phosphorylation resulted in activation of the STAT family, in particular, STAT3.52, 53, 54 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.48 These findings implied that an IL9 endogenous/IL9 exogenous/miR-21/miR-155/STAT3 axis exists in CLL cells, which could be useful in finding new therapeutic patterns.48

In CLL cells, miR-21 is associated with the STAT3 signaling pathway.

Among the proteins involved in cell-to-microenvironment interaction, the zeta chain of T cell receptor-associated protein kinase 70 (ZAP70) can enhance cell response to microenvironmental stimuli in CLL cells.49,55 The B-cell receptor (BCR) signaling pathway plays an important role in this regard. miR-21 is overexpressed in various leukemic disorders including CLL,56,57 possibly involved in the development of drug resistance and survival along with augmenting of disease progression.58 Besides, the presence of the relationship between miR-21 and poor prognosis in CLL59 as well as cell proliferation and oncogenesis has been evidenced.60 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 (PIAS3),61 programmed cell death 4 (PDCD4),62 and phosphatase and tensin homolog (PTEN)63 via the signaling pathway stimulated or progressed by mitogen-activated protein kinase (MAPK or MAP kinase) and STAT3.49 The ZAP70 protein plays an important role in different signaling pathways also modulates the interaction between the cells and related microenvironments.49 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. Similar findings were seen in a study of miR-21 expression level in Ramos cells (human Burkitt's lymphoma B cells) transfected with GFP-ZAP70.49 In yet another study, 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.64 Thus, Carabia et al.

The role of miR-155 in CLL cells and its connection to STAT3 signaling

The miR-155 is involved in tumorigenesis and autoimmunity65 and its overexpression can lead to lymphoma onset in mice.66 The miR-155 regulates the proliferation and development of hematopoietic cells21 as well as contributed to immune cell response, production of antibodies, cytokines, and antigen expression.67,68 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.66 Similarly, overexpression of miR-155 has been observed in CLL56,69,70 accompanied by Hodgkin and non-Hodgkin's lymphoma.68,71,72 Other investigations have implied that IL-6 may activate STAT3 expression and function in CLL cells73,74; on the other hand, overexpression of miR-155 has been found in CLL.56,69,70,75,76 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.21 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. They concluded that IL-6 induced STAT3 binding to the miR-155 promoter despite the fact that STAT3 directly regulates miR-155 production. Structural and molecular analysis confirmed the presence of two STAT3 binding sites in the miR-155 gene promoter.21 Phosphorylated STAT3 associates with gamma interferon activation site (GAS)-LIKE components in the promoter region of various genes.77 In fact, Li et al introduced two GAS-LIKE elements within the miR-155 promoter, allowing STAT3 binding to the miR-155 promoter by these elements.21

Acute lymphoblastic leukemia (ALL) is characterized by a crosstalk between microRNAs and the JAK/STAT3 signaling pathway. High proliferation of immature lymphocytic cells in bone marrow (BM), peripheral blood, and other organs characterizes the acute lymphoblastic leukemia (ALL), a heterogeneous hematologic illness.

In Mojdeh Mahmoudian and colleagues' study, it was discovered that certain microRNAs showed increased expression in BC tumor compared to the adjacent tissues. Specifically, hsa-miR-25-3p, -29a-5p, -105-3p, and -181b1-5p were upregulated, while hsa-miR-335-5p and -339-5p were downregulated. The upregulation or downregulation of these candidate microRNAs was found to be associated with TNM stages, except for hsa-miR-339-5p. Additionally, with the exception of hsa-miR-105-3p, each candidate microRNA correlated with HER-2 status. Furthermore, the analysis of ROC curves revealed that the combination of these six microRNAs could potentially serve as a biomarker to differentiate between tumor and non-tumor breast tissue samples.

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) and the JAK/STAT3 signaling pathway.

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 prognosis79,80; however, commonly demonstrate an appropriate response to tyrosine kinase inhibitors (TKI).79,80 Nevertheless, the relapses incidence rate is notable in these patients, highlighting the importance of new insights to treating this condition.81 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.82 Despite that BCR/ABL fusion gene is the indicator marker of Ph+ ALL, the relation between BCR/ABL fusion and IL-6 in Ph+ ALL has not yet been elucidated entirely.83 As described, IL-6 binds to its specific receptor (IL-6R) and then triggers the JAK/STAT3 signaling pathway.84,85 In a study, Jiang et al evaluated the level of BCR-ABL expression in Ph+ 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-451.83 Bioinformatic analysis showed that IL-6R can be a target of miR-451a.86 It has been reported that miR-451a represses the proliferation of some types of cancer cells such as lung adenocarcinoma87 and renal cell carcinoma.88 Besides, in CML, miR-451a is inversely related to BCR-ABL gene expression levels, and its downregulation is paralleled to imatinib resistance.89 Examination of the underlying mechanisms of miR-451a on the ALL cell line with Philadelphia chromosome-positive showed that this mi-RNA directly suppresses IL-6R via targeting its 3′-UTR. According to research by Jiang et al.,83 serum IL-6 concentration was positively correlated with BCR/ABL mRNA levels, and miR-451a downregulated the levels of phosphorylated JAK2 and STAT3 without affecting total rates of JAK2 and STAT3,

indicating the inhibitory effects of the miR-451 on the IL6/JAK/STAT3 axis by suppressing the IL6R and p-JAK and p-Therefore, increased miR-451 expression in these individuals may have therapeutic potential for dealing with this rapidly progressing form of leukemia.83

Neutropenia in T-cell large granulocytic (TLGL) leukemia: role of the JAK/STAT pathway, miR-146b, and FASL

T-cell large granular lymphocytic (TLGL) is a rare type of leukemia characterized by the abnormal proliferation of large granular T lymphocytes in the peripheral blood.90,91 TLGL leukemic cells are divided into two clusters, cluster A displaying a CD8+/CD4/CD57+ immune phenotype and cluster B displaying a CD4+/CD57+ immune phenotype.92 Although the exact cause of TL. It has been reported that increased 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.96,97 Many studies also have the existence of the improbable but plausible mechanism of degeneration of mature neutrophils and myeloid progenitors through FAS/FASL signaling.92 Teramo et al. reported that STAT3 plays a key role in FASL transcription, and they demonstrated that an increased rate of FASL expression in TLGL patients was associated with a higher level of STAT3 activity95. 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 CD8+ T-LGLL patients, but not in CD4+ T-LGLs patients.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).92 They determined that miR-146b was downregulated in CD8+ TLGL compared to CD4+,92 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.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, 109, 110 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 hypothesized that persistent STAT3 activity in CD8+ T-LGLs led to miR-146b loss, which in turn led to HuR protein translation, which in turn enabled FasL synthesis and neutropenia incidence.92,95

CML-related miRNA-JAK/STAT3 signaling interaction

CML is a clonal disease of hematopoietic stem cells that generates the Philadelphia chromosome (Ph+) as a consequence of the BCR-ABL oncogenic protein fusion caused by translocation t(9:22), accounting for roughly 15% of adult-onset leukemias.111.

miR-147 and STAT3 signaling: a possible link

The miR-147 has been shown to have both tumorigenic and tumor suppressive functions in a wide range of human cancers112, 113, 114, 115. Han et al. demonstrated that the hypoxia-induced damage was exacerbated in the PC12 cell line, commonly derived from a transplantable rat pheochromocytoma, due to the attenuation in miR-147 levels.117 Specifically, they demonstrated that maternally expressed gene 3 (MEG3) as a long noncoding RNAs (lncRNAs) boosted apoptosis in response to hypoxia. The miRNAs database evaluation for miRNAs that interact with MEG3 has

uncovered miR-147 as a possible miRNA in this respect. Two human CML cell lines, KCL22 and K562, were shown to display lower amounts of MEG3 and miR-147 when compared to healthy BMMCs. It seems that MEG3 may bind to miR-147, resulting in decreased expression of miR-147. Additionally, Li et al. found that miR-147 and MEG3 were highly methylated in CML patients compared to healthy controls. Accordingly, they revealed that the expression rate of the methylation-related genes, such as HDAC1 (histone deacetylase 1), DNMT1 (DNA methyl transferase 1), DNMT3A, DNMT3B, were dramatically enhanced in the CML patients with accelerated phase. They reasoned that because histone deacetylation and DNA methylation were implicated in the downregulation of miR-147 and MEG3 levels in CML patients, that these mechanisms must be responsible for the observed findings. In addition, they proposed that MEG3 may be downregulated by STAT3 by inhibiting the phosphorylation of JAK/STAT118, and they reported that JAK2 and STAT3 can negatively regulate MEG3 upon binding to it. They also demonstrated that miR-147 and MEG3 may adversely control one another and fine-tune leukemia development, thus providing more evidence that STAT3 and miR-147 have indirect effects on one another via MEG3.118.

miR-574-3P and JAK/STAT3 signaling: a possible link

It has been shown that miR-574-3p plays a crucial function in the development of some malignancies. MiR-574-3p is important as a potential prognostic marker for breast cancer,120 and its lower expression is observed in the early stages of gastric cancer; however, upregulation of miR-574-3p inhibits proliferation, invasion, and the migration of human gastric caner cells.119, 120. The expression of miR-574-3P was found to be considerably lower in the peripheral blood of CML patients compared to that of a healthy donor in a study conducted by Yang et al. They also demonstrated that overexpressing miR-574-3P significantly reduced cell growth and promoted apoptosis in human K562 CML cells, whereas downregulating miR-574-3P had the opposite effect. After searching the TargetScanHuman database, they discovered that IL6 could be a direct miR-574-3p target. They also discovered that miR-574-3p transfection significantly reduced IL6 expression (both mRNA and protein levels). These results demonstrated that miR-574-3p regulates IL6 expression negatively and that IL6 is a direct target of this miRNA. 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.82 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.127 Also, reports confirm that IL-6 can activate the JAK/STAT3 and MAPK signaling pathway and is involved in the development of CML.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,127 describing miR-574-3p as a potent target for CML treatment.

The role of STAT3 in mediating the connection between miR-34a and myeloid cell-derived embryonic hemoglobin synthesis.

Sickle cell anemia (SCA) is a hereditary blood condition that causes aberrant synthesis of hemoglobin S (Hb S). 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.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.129 Indeed, the most effective treatment for the cycle cell anemia is increasing Hb F production with the formula $\alpha 2\gamma 2$ (a combination of two alpha chains and two gamma chains globulin) that improves clinical symptoms and consequently prolongs the patient overall survival rates.130,131 The therapeutic role of Hb F is related to its inhibitory effects on Hb S polymerization,132 which is one of the main pathogens and risk factors in patients with SCA.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 STAT3.75,134, 135, 136, 137 Scientific related software predicted the binding site for miR-34a at the 3′ UTR of STAT3,131 and also studies have shown that miR-34a interacts with STAT3 in K562 CML cells.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 STAT3.138 Besides, it has been shown that during the erythroid differentiation progresses, erythropoietin (EPO) can activate STAT3 through phosphorylation,139 leading to the inhibition of gamma globulin gene expression.138 Therefore, these data verify that STAT3 has a function in gamma globulin gene regulation. In a research, Ward et al performed a study to examine if miR-34a may control gamma-globin gene expression via targeting the negative gamma globulin regulator genes including STAT3. The results demonstrated a substantial reduction in total and phosphorylated STAT3 levels in miR-34a-transfected K562 cells,131 as well as an increase in gamma-globin mRNA and Hb F protein levels. WARD et al reports confirmed that there likely exist an indirect mechanism for gamma-globin regulation by miR-34a via STAT3 gene silencing.131 They demonstrated that miR-34a induced the production of Hb F in K562 cells by reducing total STAT3 and phosphorylated STAT3 levels, which play a role in silencing the gamma globulin gene. About 20,000 people in the United States are diagnosed with AML every year.140 It is the most frequent form of adult acute leukemia.

The liver secretes thrombopoietin (TPO), which has a role in megakaryocyte proliferation and differentiation and is the primary regulator of megakaryopoiesis. Overexpression of miR-494-3P in HSPCs has been observed in patients with primary myelofibrosis (PMF), and this may contribute to the pathogenesis of this disease.141,142,143 Rontauroli et al. identified TPO as a pan-hematopoietic cytokine that is essential for the maintenance and survival of hematopoietic stem cells.141 Upon binding to its receptor, TPOR, on the surface of SOCS6 is an important factor in the negative regulation of the JAK/STAT signaling pathway,145 and also contributes to the mechanism of myeloproliferative neoplasms (MPN) pathogenesis144. Moreover, previous research has reported that SOCS6 is downregulated in HSPCs derived from PMF patients, with concomitant miR-494-3p upregulation.143 These findings provided further evidence that miR-494-3p plays a role in the etiology of PMF via regulating megakaryocyte differentiation. In addition, STAT3 may have an effect on TPO signaling and megakaryocytopoiesis in HSPCs, as shown by the findings of a study by Rontauroli et al.,144 which showed that transfection of K562 and CB (cord blood-derived) CD34+ cells with miR-494-3P reduced SOCS6 protein levels, which in turn increased STAT3 phosphorylation and led to the megakaryocyte hyperplasia seen Association between the JAK/STAT signaling pathway in acute erythroid leukemia (AEL) with the miR-23a, miR-27a, and miR-24 cluster.

About 5% of all cases of acute myeloid leukemia (AML) are acute erythroid leukemia (AEL), also known as AML M6.147,148 The survival and prognosis of AEL patients are too worse than in other AML subtypes.149,150 As described, STAT3 plays an important role in the progression of erythroleukemia through suppression of erythroid differentiation.151 A study by Su et al. showed that miR-23 They also found that clusters of microRNAs miR-23a, miR-27a, and miR-24 were all downregulated in people with AEL. Overexpression of miR-23a, -27a, and -24 can trigger apoptosis and inhibit the deregulated proliferation, so they hypothesized that these three miRNAs worked together to target the GP130/JAK1/STAT3 pathway in AEL cells and induce differentiation.152 Other studies have shown that the JAK1 binding to the GP130 transmembrane protein and subsequent activation of STAT3 enables signaling network formation among GP130, JAK1, and ST In addition, they found that these miRNAs work together to drive erythroid differentiation in human leukemic HEL and K562 cell lines and cord blood (CB)- CD34+ HSCs by decreasing GP130 and suppressing JAK1-STAT3 phosphorylation.152

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, 159, 160, 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 LIFRa, the fusion protein containing the cytoplasmic functional domain of LIFRa, like CT3 in TAT-CT3 fusion, a peptide domain vector, can induce STAT3 activation in HL60 cells.163 The LIFRa-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) gene164 typically overexpressed in the BM of patients with special subtypes of AML.165, 166, 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, through STAT3 direct binding to miRNA gene promoter.155 Also, miR-155 negatively regulates SOCS-1 in AML cells, known as the main negative regulator for the JAK/STAT signaling pathway.169 XU and his colleagues showed that the TAT-CT3 fusion protein can induce differentiation in HL60 myeloid cells. TAT-CT3 transfection was shown to reduce miR-155 expression, which in turn boosted SOCS-1 and decreased STAT3 phosphorylation, resulting in leukemia cell differentiation.155

STAT3 and hypoxia-inducible factor 1 (HIF1) are linked to miR-17 and miR-20a.

Hypoxia-inducible factor 1 (HIF1) is an important transcription factor in response to hypoxic conditions containing two subunits including, an alpha subunit (HIF-1a, oxygen-sensitive subunit) and a beta subunit (HIF-1b).170,171 It also has a role in cancer biologics such as tumor growth, metastasis, and angiogenesis.172 Consistent with the previous studies,173,174 He et al showed that hypoxia promoted cell cycle arrest and differentiation in myeloid leukemic cells.175 The HIF-1a protein translocates into the nucleus and forms a heterodimer with HIF-1b 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-1a 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-1a transcription factor can induce differentiation and inhibit AML development.173,175, 176, 177, 178, 179 They showed that HIF1a 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, 181, 182 Besides, it has been shown that the miR-17-92 cluster target the HIF-1a protein.175,183, 184, 185 He et al also reported that miR-17 and miR-20a were downregulated in hypoxic conditions in AML cell lines. The results supported the hypothesis that HIF-1a suppresses miR-17 and miR-20a expression in AML cells in response to hypoxia. They also revealed that a reduction in miR-17 and miR-20a contributes in the differentiating process of AML cell lines driven by HIF-1a. He et al. concluded that miR-17 or miR-20a abrogated HIF-1a-induced growth arrest and differentiation in AML cells by binding to STAT3 trans-acting elements.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

Association between STAT3 and the miR-21/miR-17-92 cluster

Acute myeloid leukemia (AML) with t(8;16)(p11;p13) is a rare leukemia subtype with characteristic clinical features, such as presentation as a coagulation disorder and recurrent extramedullary involvement, as well as a poor prognosis.188,189 AML blast cells with t(8;16) also exhibit a high frequency of hemophagocytosis and a

myelomonocytic In this respect, examination 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. Based on the findings of Beya et al. (2013), miR-21 was transcriptionally regulated by STAT3 in patients with t(8;16) translocation, and a decrease in miR-21 and probably a decrease in the miR-17-92 cluster is associated with a decrease in STAT3 in AML with t(8;16) translocation.189

Conclusion

By binding to DNA and other stimulants, active STAT3 promotes tumor development (Figures 2 and 3), which is in turn facilitated by miRNAs, which control a wide range of cellular activities including inflammation, proliferation, survival, metastasis, invasion, and angiogenesis. In addition, miRNAs have been shown to play a crucial function in controlling the JAK/STAT3 signaling pathway. Figure 4 depicts the whole signaling pathways involved in the interaction between STAT3 and miRNAs in leukemic cells. We concentrated on research into the function of miRNAs in the control of the JAK/STAT3 signaling pathway in hematological illnesses to better understand the function of STAT3, one of the most essential transcription factors in many malignancies, including leukemia. We have reviewed the roles of microRNAs and STAT3 in various cancers and more extensively in blood malignancies in two tables (Table 1, Table 2) for your convenience. Patients with a wide range of hematological disorders, including leukemia, may benefit from therapeutic approaches, particularly multimodal treatments aimed at modifying the STAT3 signaling pathway; however, it is important to complete extensive clinical trials before resorting to STATs inhibitors.

Funding: N/A

Conflicts of Interest: The authors declare that they have no competing interests

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