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MiR-155 regulates lymphoma cell proliferation and apoptosis through targeting SOCS3/JAK-STAT3 signaling pathway

X.-D. LI, X.-M. LI, J.-W. GU, X.-C. SUN

Dental Department, Yan'an People's Hospital of Shaanxi Province, Yan'an, Sh[illegible]xi, China

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Abstract. – OBJECTIVE: Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway participates in regulating cell proliferation, differentiation, and apoptosis, and related to lymphoma. Suppressors of cytokine signaling 3 (SOCS3) is a negative regulator of the JAK-STAT signaling pathway. SOCS3 reduction and miR-155 up-regulation are associated with lymphoma pathogenesis. Bioinformatics analysis showed the complementary binding site between miR-155 and SOCS3. This study aimed to investigate the role of miR-155 in regulating SOCS3/JAK-STAT signaling pathway and affecting diffuse large B cell lymphoma (DL[illegible]) cell proliferation and apoptosis.

PATIENTS AND METHODS: DLBCL [illegible]mor sample was collected from the patients [illegible]r hospital. Lymphatic tissue derived from rea[illegible] lymphoid hyperplasia patients were selected [illegible] control. MicroRNA-155 (MiR-15[illegible] SOCS3 e[illegible]pressions were detected. D[illegible]uc[illegible]e assay was used to verify the tar[illegible]ed relat[illegible]ship between miR-155 and SOC[illegible]CI-LY1[illegible]lls were cultured in vitro and divi[illegible]to[illegible], including miR-NC, [illegible]R-155 [illegible]or, pIRES2-Blank, pIRES2-SO[illegible]3, and mi[illegible] + pIRES2-SOCS3 group[illegible]CS3, p-JA[illegible]p-JAK2, p-STAT3, and [illegible]vi[illegible]pressions w[illegible]e tested. Cell apoptosis and pr[illegible]ation were detected by flow cy[illegible]metry.

RES[illegible]: MiR-155 expres[illegible]significantly increas[illegible], while SOCS3 level [illegible]clined in DLBCL tis[illegible]ompar[illegible] with control. MiR-155 targeted r[illegible]ed[illegible]OCS3 expression. MiR-155 inhibitor a[illegible]IRES2-S[illegible]S3 transfection mark[illegible] up-r[illegible]ted [illegible]CS3 expression, reduced [illegible]K1, p-J[illegible]TAT3, and Survivin levels, att[illegible]ated cel[illegible]liferation, and enhanced cell ap[illegible]osis in OCI-LY10 cells.

[illegible]ONS: Down-regulation of miR-155 [illegible]ibit[illegible]BCL cell proliferation and facilitated [illegible]optosis through up-regulating SOCS3 expres[illegible]o suppress JAK-STAT3 signaling pathway.

Key Words:

MiR-155, SOCS3, JAK-STAT3, Lymphoma, Proliferation, Apoptosis.

[illegible]rodu[illegible]

Lympho[illegible]kind of mal[illegible] tumor that takes plac[illegible]n the [illegible]hoid and hematological system, such as lymph[illegible]s, spleen, thymus, and extr[illegible]lymphatic t[illegible] and organs[1,2]. Lymp[illegible]a is associated with [illegible]mmune cell cancera[illegible], thus belonging immune system malignant t[illegible]or. Lympho[illegible]ontains Hodgkin's lymphoma ([illegible] and non-H[illegible]kin's lymphoma (NHL). NHL is t[illegible]ior ty[illegible]ccounting for more than 90%[3]. Althou[illegible] development has been achieved [illegible] surgical resection, whole body standard che[illegible]py, local radiotherapy, and biological [illegible] therapy, about 60% patients still obtain non-ideal curative effect[4,5].

Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway excessive activation is closely related to multiple cancers occurrence, development, invasion, and metastasis by promoting cell proliferation and antagonizing apoptosis[6-9]. Suppressors of cytokine signaling 3 (SOCS3) is one of the members of SOCS family that can block cytokines response to negatively regulate JAK-STAT signaling pathway. SOCS3 down-regulation is associated with tumor occurrence, metastasis, drug resistance, and poor prognosis[10-13]. SOCS3 expression significantly reduced in NHL tissue, indicating that SOCS3 plays a tumor suppressor gene role in NHL[14]. MiRNA is a type of endogenous single-stranded noncoding RNA at the length of 22-25 nt discovered from eukaryote. It plays a degrading or inhibiting role on mRNA by binding with the 3'-UTR. MiRNA that accounts for 1% gene amount regulates more than 30% of human gene expressions[15]. Numerous studies revealed that miRNA abnormal expression and function play a crucial role in multiple tumor pathogeneses, including lymphoma[16,17]. MiR-155 was found to play

Corresponding Author: Xiaochen Sun, MD; e-mail: xiaochensunr@126.com

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an oncogene role in lymphoma[18] and related to lymphoma disease degree and poor prognosis[19]. Bioinformatics analysis showed the complementary binding site between miR-155 and SOCS3. This study aimed to investigate the role of miR-155 in regulating SOCS3/JAK-STAT signaling pathway and affecting lymphoma cell proliferation and apoptosis.

Patients and Methods

Main Reagents and Materials

Human diffuse large B cell lymphoma (DLBCL) OCI-LY10 cells were purchased from Shanghai Yubo biological technology co., Ltd. (Shanghai, China). RPMI-1640 medium, Opti-MEM, penicillin, and streptomycin were purchased from Gibco BRL. Co. Ltd. (Grand Island, NY, USA). FBS was got from Gemini Bio Products (Woodland, CA, USA). EasyPure RNA Kit and Real-time PCR reagent TransScript Green One-Step qRT-PCR SuperMix were obtained from TransGen Biotech (Beijing, China). Mouse anti-human Survivin, JAK1, p-JAK1, JAK2 [illegible] p-JAK2 antibodies were purchased fr[illegible] A[illegible]cam (Cambridge, MA, USA). Rabbit a[illegible]human STAT3, phosphorylated STAT3 (p-ST[illegible]), SOCS3, and β-actin antibodies were bo[illegible] from Cell Signaling Technolog[illegible] (Bever[illegible] MA, USA). Goat anti-rabbit [illegible]nti-mouse secondary antibodies w[illegible] got fro[illegible] Bio-Rad Laboratories (Hercules, [illegible]USA). [illegible]nexin-V/PI apoptosis detectio[illegible] kit [illegible] Affinity BioReage[illegible] (Hangz[illegible] China). Cell proliferation det[illegible] kit Click-[illegible]U Alexa Fluor 488 Flo[illegible]ry Assay K[illegible]s obtained from Mo[illegible]cular P[illegible] (Eugene, OR, USA). Dual-Glo® [illegible]uciferase A[illegible] System and pMIR lucifer[illegible] reporter gene pla[illegible] were provided by P[illegible]ega (Madison, WI, USA). Lipofectamine [illegible] was [illegible]ved from Invitrogen Life Technolog[illegible]sbad, CA[illegible]USA).

[illegible]cal In[illegible]on

[illegible]tal of 2[illegible]LBCL patients received treatme[illegible] between May 2016 and Oct 2016 in Yan'an P[illegible]pital of Shaanxi Province and [illegible]other 32 patients suffered from reactive lym[illegible] hyperplasia were enrolled. The lymphatic ti[illegible]nd tumor tissue were collected. The study was approved by the Ethics Committee of Yan'an People's Hospital of Shaanxi Province. All the patients signed the informed consent.

Cell Culture

OCI-LY10 cells were cultured in RPMI-1640 medium containing 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Th[illegible]lls were passaged at 1:4.

Dual-luciferase Reporter Ge[illegible] Assay

The PCR products containing [illegible]ll length of SOCS3 gene 3'-UTR seg[illegible]nt we[illegible]ned to pMIR. Next, it was transf[illegible]ed into D[illegible]mpetent cells and sequen[illegible] to select the p[illegible] with correct sequen[illegible]hen, p[illegible]R-SOCS3 [illegible]UTR-wt (or pM[illegible]R-S[illegible]UTR-mu[illegible] was co-transfected w[illegible] HEK[illegible]ells us[illegible] Lipofectamine 200[illegible]ogether with[illegible]15[illegible]imic (or miR-NC, o[illegible]55 inhibitor[illegible] luciferase activity w[illegible] dete[illegible]ccording to the Dual-Glo® Luciferase Assay ma[illegible]fter cultured for 48 h.

S[illegible]CS3 Overexpression Plasmid [illegible]nstruction

[illegible]he CDS reg[illegible] fragment of SOCS3 gene was a[illegible]ified and co[illegible]ected to pIRES2 plasmid after dig[illegible] by Xh[illegible] and BamH I. Then it was transforme[illegible]109 competent cells and screened [illegible] penbritin. Next, the plasmid was extracted [illegible]uenced. It was named as pIRES2-SOCS3, [illegible]RES2-Blank was treated as control.

Cell Transfection and Grouping

OCI-LY10 cells were cultured *in vitro* and divided into five groups, including miR-NC, miR-155 inhibitor, pIRES2-Blank, pIRES2-SOCS3, and miR-155 + pIRES2-SOCS3 groups. Nucleotide fragments and Lipofectamine 2000 were added to Opti-MEM and incubated at room temperature for 30 min, respectively. Then they were added to the cells cultured in Opti-MEM. After 6 h incubation, the medium was changed back to RPMI 1640 medium containing 10% FBS and 1% penicillin-streptomycin. The cells were used for detection after 72 h.

qRT-PCR

Total RNA was extracted using EasyPure RNA Kit and adopted for PCR reaction by TransScript Green One-Step qRT-PCR SuperMix. The reaction system contained 1 μg RNA template, 0.3 μM primers, 10 μl 2×TransStart Tip Green qPCR SuperMix, 0.4 μl RT Enzyme Mix, 0.4 μl Dye II, and ddH$_2$O. The reverse transcription condition was 37°C for 15 min and 98°C for 5 min. The PCR reaction was composed of 45°C reverse transcription for 5 min, 94°C pre-denaturation for 30 s, followed

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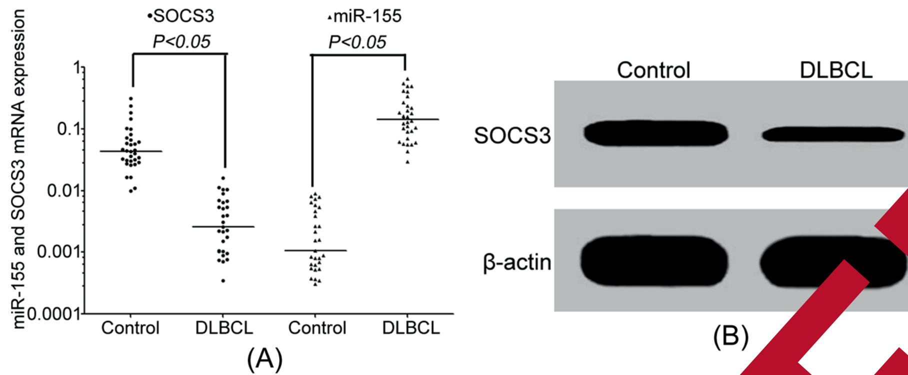
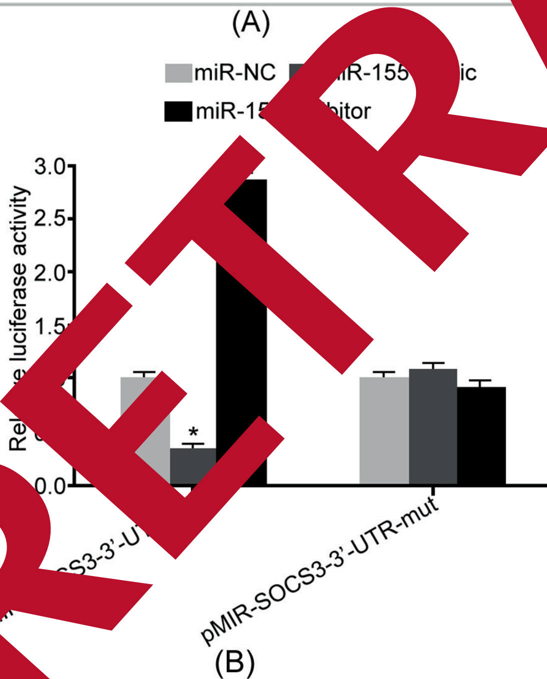


Figure 1. MiR-155 up-regulated, while SOCS3 reduced in DLBCL tissue. ***(A)*** qRT-PCR de[illegible]R-155 an[illegible]SOCS3 mRNA expressions. ***(B)*** Western blot detection of SOCS3 protein expression.

by 40 cycles of 94°C for 5 s and 60°C for 30 s. Real-time PCR was performed on Bio-Rad CFX96/ CFX connect to test the relative expression.

Western Blot

Total protein was extracted by RIPA from cells. A total of 40 μg protein was separated by



Fig[illegible]e 2. MiR-155 targeted regulated SOCS3 expression. (A) The binding site between miR-365 the 3'-UTR of DJ-1 mRNA. (B) Dual luciferase assay. *p<0.05, compared with miR-NC.

8%-10% sodium la[illegible] sulfate-polyacrylamide gel [illegible]horesis (SD[illegible]GE) for 3 h and trans[illegible]ed to membrane. Ne[illegible], the membrane was b[illegible]cked and incubated with primary antibody at 4[illegible] overnight [illegible]CS3, JAK1, p-JAK1, JAK2, p[illegible]2, STAT3[illegible] STAT3, Survivin, and β-actin at [illegible] 1:20[illegible] 1:800, 1:2000, 1:800, 1:2000, 1:800, [illegible]and 1:10000, respectively). Then, [illegible]e membrane was incubated with horseradish [illegible]ase (HRP) labeled secondary antibody [illegible]) for 60 min after washed by phosphate buffered saline-tween 20 (PBS-T) for three times. At last, the protein expression was detected by enhanced chemiluminescence (ECL).

EdU Staining

The cells were added to 10 μM EdU solution at 37°C for 120 min. After incubated for 48 h, the cells were digested by trypsin and collected. After washed with phosphate-buffered saline (PBS) containing 1% bovine serum albumin (BSA) and fixed in 100 μl Click-iT® fixative for 15 min, the cells were penetrated by 100 μl 1×Click-iT® saponin-based permeabilization and wash reagent at room temperature for 15 min. Next, the cells were incubated in 500 μl reaction liquid containing PBS, $CuSO_4$, Alexa Fluor 488, and Buffer additive at room temperature for 30 min. Then the cells were washed by 3 ml 1×Click-iT® saponin-based permeabilization and wash reagent for 1 time. At last, the cells were resuspended in 500 μl 1×Click-iT® saponin-based permeabilization and wash reagent and tested by Beckmann FC 500 MCL/MPL flow cytometry.

Flow Cytometry

The cells were resuspended in 500 μl binding buffer and incubated in 5 μl Annexin V-FITC and

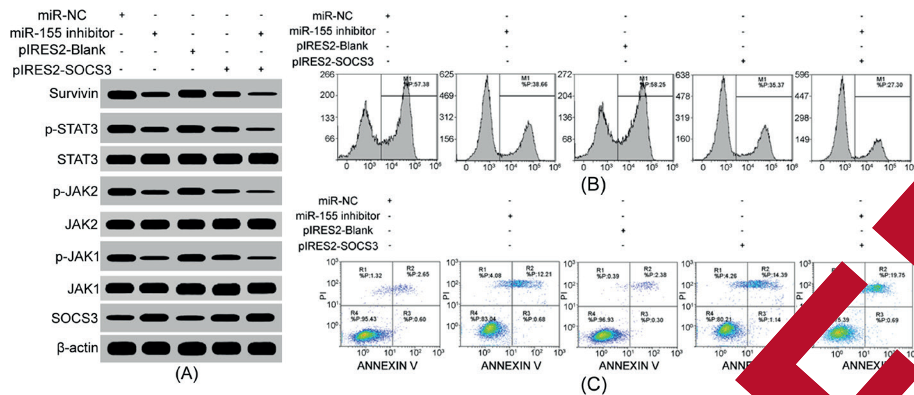


Figure 3. Down-regulation of miR-155 attenuated JAK-STAT3 signaling pathway acti[illegible], pro[illegible] apoptosi[illegible] inhibited proliferation. ***(A)*** Western Blot detection of protein expression. ***(B)*** Flow cyto[illegible]y detectio[illegible] proli[illegible]tion. ***(C)*** Flow cytometry detection of cell apoptosis.

5 µl PI avoid of light for 15 min. Next, the cells were added with 5 µl PI and tested on Beckmann FC 500 MCL/MPL flow cytometry to evaluate cell apoptosis.

Statistical Analysis

All data analyses were performed by the SPSS 18.0 software (Chicago, IL, USA). The mea[illegible]ment data were depicted as mean ± stan[illegible]viation and compared by *t*-test. $p<0.05$ was [illegible]sidered as statistical significance.

Results

MiR-155 Up-Regulate[illegible] While S[illegible]CS3 Reduced in DLBCL Tissu[illegible]

Quantitative RT-[illegible]R (qRT-[illegible]) showed that SOCS3 mRNA si[illegible]cantly redu[illegible] while miR-155 elevated i[illegible] ne[illegible]or tissue fr[illegible] DLBCL patients compared wit[illegible]trol (Figure 1A). Western blot [illegible]ealed that S[illegible] protein markedly reduce[illegible] DLBCL tissue co[illegible]ed with control, indic[illegible]g miR-155 up-regulation may play a role in [illegible]ing S[illegible]S3 and promoting DLBCL pathoge[illegible]gure 1B).

[illegible]155 [illegible] Regulated SOCS3 Ex[illegible]ssion

[illegible]croRNA.org online prediction showed the t[illegible]ng site between miR-155 and 3'-[illegible]TR of SOCS3 mRNA (Figure 2A). Dual luci[illegible]e assay revealed that miR-155 mimics or in[illegible]or transfection significantly declined or increased the relative luciferase activity of HEK293 cells, indicating the regulatory relationship between miR-155 and SOCS3 mRNA.

Down-regulation [illegible]iR-155 Att[illegible]ed JAK-STA[illegible] Signaling P[illegible]way Activity, Pro[illegible]oted Cell [illegible]optosis and Inhibited Proliferation

[illegible]iR-155 in[illegible]tor and/or pIRES2-SOCS3 tr[illegible]fection sig[illegible]cantly up-regulated SOCS3 exp[illegible], red[illegible]d p-JAK1, p-JAK2, p-STAT3, and Su[illegible]vels (Figure 3A), attenuated cell [illegible]roliferation (Figure 3B), and enhanced cell apop[illegible]igure 3C) in OCI-LY10 cells.

Discussion

JAK-STAT signaling pathway is first found in interferon study. It is discovered to be activated by multiple cytokines and growth factors, and mediates various cytokines signal transduction[20]. JAK-STAT signaling pathway is mainly composed of tyrosine kinase associated receptor, STAT, and JAK[6].

JAK-STAT signaling pathway activation is associated with tumor pathogenesis by up-regulating Bcl-2, Survivin, Cyclin D1, and c-Myc[21,22]. As an oncogene transcription factor, STAT3 is an important member of STAT family that plays a critical role in a variety of cancer pathogenesis[23,24]. JAK-STAT3 participates in multiple biological processes, such as cell proliferation, cycle, and apoptosis, thus, is associated with tumor occurrence, development, invasion, and metastasis, including lung cancer[6], colorectal cancer[9], prostate cancer[7], and pancreatic cancer[8]. As the strongest member of SOCS family, SOCS3 plays a negative regulatory role in JAK-STAT3 signaling pathway by inhibiting JAK kinase binding with receptor to suppress JAK phosphorylation or

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competitive binding with JAK to restrain STAT3 phosphorylation via N-terminal kinase inhibitory region (KIR)[11,13]. SOCS3 is related to multiple cancers' occurrence, metastasis, drug resistance, and poor prognosis, such as breast cancer[11], prostate cancer[13], lung cancer[12], and pancreatic cancer[10]. SOCS3 expression significantly reduced in NHL tissue, indicating that SOCS3 plays a tumor suppressor gene role in NHL[14]. MiR-155 was found to play an oncogene role in lymphoma[18] and related to lymphoma disease degree and poor prognosis[19]. Bioinformatics analysis showed the complementary binding site between miR-155 and SOCS3. This research aimed to investigate the role of miR-155 in regulating SOCS3/JAK-STAT signaling pathway and affecting lymphoma cell proliferation and apoptosis.

Our investigation showed that miR-155 mimics or inhibitor transfection significantly declined or increased the relative luciferase activity of HEK293 cells, indicating the regulatory relationship between miR-155 and SOCS3 mRNA. SOCS3 significantly reduced, while miR-155 elevated in the tumor tissue from DLBCL patients compared with control, indicating miR-155 up-regulation may play a role in reducing SOCS3 and promoting DLBCL pathogenesis. Slezak-Prochazka et al[25] reported that miR-155 expression in B-cell lymphoma abnormally up-regulated. Zhong et al[26] demonstrated that miR-155 increased in DLBCL compared with reactive lymphadenitic hyperplasia and was correlated with complete remission, overall response rate, and poor prognosis. Munch-Petersen et al[illegible] [illegible] overexpressed limit[illegible] in tumo[illegible] of DLBCL by nucleic acid hybridization in [illegible] technique. Huang et al[28] revealed that miR-155 [illegible] markedly elevated in activated B-cell-like (ABC) DLBCL tissue compared with germinal center B-cell-like (GCB) DLBCL tissue [illegible] lower invasion and malignancy. Moreover, miR-155 expression was apparently higher in OCI-Ly3 and OCI-Ly10 compared with that in SU-DHL6 and SU-DHL16. Merkel et al[illegible] exhibited that miR-155 increased in lymphoma and played an oncogene role. In [illegible] study, miR-155 content was significantly higher in DLBCL tissues, suggesting that miR-155 [illegible] carcinogenic factor, which is similar to Zhong et al[26] and Munch-Petersen et al[27]. Molavi et al[14] showed that promoter methylation enhanced SOCS3, while SOCS3 mRNA expression reduced in B-cell lymphoma cell line Jeko, Mino, and Rec-1 compared with healthy bone marrow mononuclear cells, which is in accordance with our results. Further detection demonstrated that miR-155 inhibitor and/or SOCS3 over-expression plasmid transfection markedly upregulated SOCS3 expression, reduced p-JAK1, p-JAK2, p-STAT3, and Survivin levels, attenuated cell proliferation, and enhanced cell apoptosis in OCI-LY10 cells. Huang et al[28] found that miR-155 targeted inhibited PIK3R1 (p85[illegible]) expression and enhanced PI3K-AKT signaling pathway, whereas down-regulation of miR-155 attenuated PI3K-AKT signaling pathway and restrained DLBCL cell line OCI-Ly3 and SU-DHL16 proliferation. Sandhu et al[29] revealed that miR-155 promoted OCI-Ly3 cell proliferation, enhanced colony formation, and inhibited apoptosis by targeting HDAC4 expression. Dagan et al[illegible] discovered that miR-155 overexpression facilitated lymphoma cell migration and a[illegible]c ability by inhibiting HGAL expression, which may promote lymphoma cell dissemination, progression, invasion, and pathogenesis. Merkel et al[18] demonstrated that inhibition of miR-155 suppressed lymphoma cell proliferation *in vitro* and *in vivo*. In this work, miR-155 down-regulation markedly attenuated OCI-Ly10 malignancy. Molavi et al[14] reported that SOCS3 over-expression apparently suppressed STAT3 phosphorylation, downregulated Cyclin D1, BCL2, and BCL-XL expressions, and induced apoptosis in B-cell lymphoma cell line Mino and Rec-1. At present, the role of miR-155 in regulating SOCS3 expression and DLBCL cell proliferation and apoptosis has not been reported. This investigation showed that miR-155 plays a role in suppressing SOCS3 expression and promoting DLBCL pathogenesis. Down-regulation of miR-155 increased SOCS3 expression and blocked JAK-STAT3 signal transduction to inhibit lymphoma cell proliferation and accelerated cell apoptosis. This study only collected DLBCL tissue and investigated the impact of miR-155 on SOCS3-JAK-STAT3 signaling pathway and DLBCL cell proliferation and apoptosis, while whether miR-155 may regulate other types of B-cell lymphoma is still unclear.

Conclusions

MiR-155 over-expression plays a role in inhibiting SOCS3 and promoting DLBCL pathogenesis. Down-regulation of miR-155 inhibited DLBCL cell proliferation and facilitated apoptosis through up-regulating SOCS3 expression to suppress JAK-STAT3 signaling pathway.

Acknowledgments

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Conflict of interest

The authors declare no conflicts of interest.

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