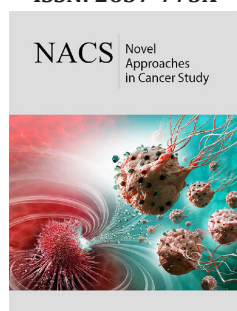


CXC Chemokine Ligand 16 Promotes the Proliferation and Migration of Hodgkin and Reed-Sternberg Cells Via the PI3K/Akt/NF- κ B Signaling Pathway

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Abstract

Hodgkin's Lymphoma (HL) is a main type of lymphoma characterized by Hodgkin's Reed-Sternberg(H/RS) cells, which involves in many cytokines and chemokines. CXC Chemokine Ligand 16 (CXCL16) was reported to be expressed in various cancer types and was previously observed by our group to highly express in H/RS cells, yet the function and mechanism of CXCL16, as well as soluble CXCL16 (sCXCL16) on the phenotypes of HRS cells needs to be fully elucidated. To investigate the effects of CXCL16 on cell proliferation, migration, cell cycle, apoptosis, and immune-phenotypes of H/RS cells, an H/RS cell line (L428) transfected with CXCL16-overexpressed lentivirus vector was established and identified; besides, recombinant sCXCL16 was also applied on L428 cell lines in the present study. Results showed that both endogenously overexpressed CXCL16 and exogenously applied recombinant sCXCL16 protein were able to promote the proliferation and migration of L428 cells, and diminished cell apoptosis, while the immune phenotypes of L428 cells showed no significant changes. Blocking the interaction between the ligand CXCL16 and its unique receptor CXCR6 with antibody suppressed the above effects. As the pathways involved were concerned, results showed that CXCL16 upregulated the expression of several phosphorylated proteins of the PI3K/Akt and NF- κ B signaling pathways, which were markedly inhibited by PI3K inhibitor LY294002 or CXCR6 antibody. The present study suggests that CXCL16 promotes the proliferation and migration of H/RS cell through its receptor CXCR6. The mechanism may involve activation of the PI3K/Akt/NF- κ B signaling pathways.

Keywords: CXC chemokine ligand 16; Soluble CXCL16; Hodgkin 's lymphoma; Hodgkin reed-sternberg; CXCR6; Signaling pathway

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Background

Hodgkin's Lymphoma (HL) is one of the most common malignant neoplasms affecting hematological and lymphoid systems. The leading causes of poor prognosis in HL correlate with tumor invasion and metastasis. Hodgkin and Reed-Sternberg (H/RS) cells, although only accounting for less than 1% of total HL tumor cells, contribute considerably to tumor progression [1]. The mechanism may involve immune escaping which was conducted by interaction of various cytokines and chemokines between tumor cells and inflammatory cells in the tumor microenvironment [2].

Accumulating evidence suggests that chemokine ligands interact with corresponding receptors to induce a variety of cell responses that affect tumor progression, such as cell proliferation, migration, invasion and metastasis. CXCL16 is a chemokine that exists in two forms: a transmembrane form (TM-CXCL16) and a soluble form (sCXCL16) which is secreted into the cell culture supernatant via the cleavage of TM-CXCL16 by a disintegrin-like metalloproteinase 10 (ADAM10) [3]. Both forms of CXCL16 interact with its unique receptor CXCR6 to exert distinct functions [4,5]. Interaction of sCXCL16 with CXCR6 has been reported in various tumors and is associated with tumor growth, metastasis, and recurrence [5-7]. Darash-Yahana [8] and Deutsch [9] highlighted that CXCL16 and CXCR6 may be expressed in

lymphoma, however, the role of the CXCL16-CXCR6 axis in lymphatic malignancies is yet to be elucidated. In our previous study, CXCL16 expression was found negatively correlated with the expression of CD99 in human and mouse lymphoma cell lines [10,11]; besides, CXCL16 were found highly expressed in several lymphoma cell lines as well as in clinical samples [11]. In diffuse large B cell lymphoma (DLBCL), co-expression of CXCL16 and CXCR6 is a risk factor for poor prognosis of patients with diffuse large B Cell lymphoma [12], while in HL, the function of CXCL16 on H/RS cells and the involved pathways needs further clarification. The present study aims to characterize the effect of sCXCL16 on the phenotypes of H/RS cells *in vitro* and to explore the role of the PI3K/Akt/NF- κ B pathways in the H/RS cell progression regulated by sCXCL16-CXCR6 axis, which may provide experimental data for potential strategy in clinical therapy.

Methods

Cell culture and transfection

L428 cells were cultured in RPMI-1640 medium (Gibco BRI, Gaithersburg, MD) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Hyclone Technologies, Logan, UT) at 37 °C in a humidified atmosphere with 5% CO₂. A CXCL16 lentivirus vector, CXCL16-pGC FU-GFP-LV, was established by recombining the CXCL16 gene with empty lentivirus vector (pGC FU-GFP-LV), identified, then transfected into L428 cells. The subclone overexpressed CXCL16 was named as CXCL16+ group. Normal L428 cells and L428 cells transfected with empty lentivirus vector were used as controls (hereafter referred to as Control-1 and Control-2, respectively). Cell morphology and Green Fluorescence Protein (GFP) were routinely observed using fluorescence microscopy. Stable expression and secretion of sCXCL16 in different cell groups were validated using quantitative RT-PCR, western blot analysis, and Enzyme-Linked Immunosorbent Assays (ELISA).

RNA isolation and quantitative RT-PCR

RNA isolation reagent was mixed with different groups of cells at a concentration of 5×10⁶ cells/mL. Total RNA isolation and cDNA generation were performed as previously described [10]. The sequences of primers used were as follows: CXCL16: forward: 5'-CGTCACTGGAAGTTGTTATTGTGGT-3'; reverse: 5'-TGGTAGGAAGTAAATGCTTCTGGTG-3'; GAPDH: forward: 5'-GCTGAGTATGTCGTGGAGTCT-3'; reverse: 5'-GTTACACCCATCACAAACAT-3'. GAPDH was used as an internal control. The relative expression ratio of CXCL16 was calculated using the 2- $\Delta\Delta$ Ct method.

Enzyme-linked immunosorbent assay

Cells were cultured in FBS-free RPMI 1640 medium at a concentration of 1 × 10⁶ cells/mL for 8 h followed by centrifugation at 1500rpm for 5min. Commercially available ELISA kits (Becton Dickinson, Franklin Lakes, NJ) were used according to the manufacturer's instructions to measure CXCL16 concentrations at 450nm.

Cell proliferation assay

Cell proliferation in two control groups, CXCL16+ group (L428 cells transfected with CXCL16-pGC FU-GFP-LV), sCXCL16 group (L428 cells treated with 100ng/mL recombinant sCXCL16), and anti-CXCR6 group (L428 cells treated with 100ng/mL CXCR6 antibody) was examined using Cell Counting Kit-8 (CCK-8; Tongren Shanghai Co., China), as previously described [11]. The sCXCL16 recombinant protein and CXCR6 antibody were purchased from Peprotech, Rocky Hill, NJ. The proliferation of L428 cells upon treatment with the PI3K/Akt inhibitor LY294002 at concentrations ranging from 0 to 50 μ M/mL was also measured.

Transwell assays

Transwell migration assays were performed in 24-well insert plates (Corning Costar, Tewksbury, MA). First, 200 μ L of cells in serum-free medium were added to the upper chambers (5 μ m pore size) and placed into wells containing 500 μ L medium supplemented with 10% FBS at 1 × 10⁵ cells/well. The plate was then incubated for 4 h at 37 °C. Cell migration to the bottom chamber was examined using CCK-8 as described above.

Flow cytometry

For cell cycle and apoptosis analysis, the cell samples were cultured and treated using commercially available cell cycle (Kaiji Co., China) or apoptosis (Dojindo Molecular Technologies, Inc., Japan) kits according to the manufacturer's instructions and subjected to flow cytometry analysis using a FACS Vantage flow cytometer with CellQuest acquisition and analysis software (Becton Dickinson, Franklin Lakes, NJ). The cell samples were collected after 24 h of culturing and resuspended in 1× PBS containing antibodies against CD15, CD30, CD19 or CD20, incubated for 30 min in the dark, and subjected to flow cytometry analysis.

Protein extraction and western blot analysis

Protein extraction and western blot analysis were performed as previously described [10]. Briefly, L428 cells were collected at different time points (0, 15, 30, 45, and 60 min) after treatment with 100ng/mL of recombinant sCXCL16. Total proteins were examined on 10% SDS-PAGE gel and electro transferred onto Polyvinylidene Fluoride (PVDF) membranes (Merck Millipores, Burlington, MA). The membranes were blocked with 5% skim milk and incubated with primary and secondary antibodies (Cell Signaling Technology, Danvers, MA) with an enhanced chemiluminescence system to reveal specific bonds. Images were captured and analyzed using a Gel Documentation System (Bio-Rad, Hercules, CA).

Statistical analysis

All images obtained from western blotting and flow cytometry experiments were representative of at least three independent experiments. The data shown were expressed as means \pm SD. Statistical analysis were performed using SPSS 17.0 software. Data were compared using one-way ANOVA, and p-values <0.05 were considered statistically significant.

Results

sCXCL16 promoted proliferation and migration of H/RS cells

The CXCL16 gene was cloned into the lentivirus vector pGC FU-GFP-LV, then transfected L428 cells. Stable expression was achieved and the secretion of sCXCL16 was assessed (Figure 1). The proliferation of different cell groups was investigated by CCK-8 assays. Results showed that sCXCL16 significantly promoted

the proliferation of H/RS cell line (Figure 1). Transwell assays demonstrated that sCXCL16 promoted the migration of L428 cells in both CXCL16+ group, which endogenously overexpressed CXCL16, and sCXCL16 group, in which 100ng/mL recombinant sCXCL16 was applied to L428 cells (Figure 1). To test whether binding to its receptor CXCR6 was essential for the effect of endogenous CXCL16 on cell proliferation and migration, CXCR6 antibody was applied at a concentration of 100ng/mL. Blocking CXCR6 effectively slowed down cell proliferation and migration (Figure 1).

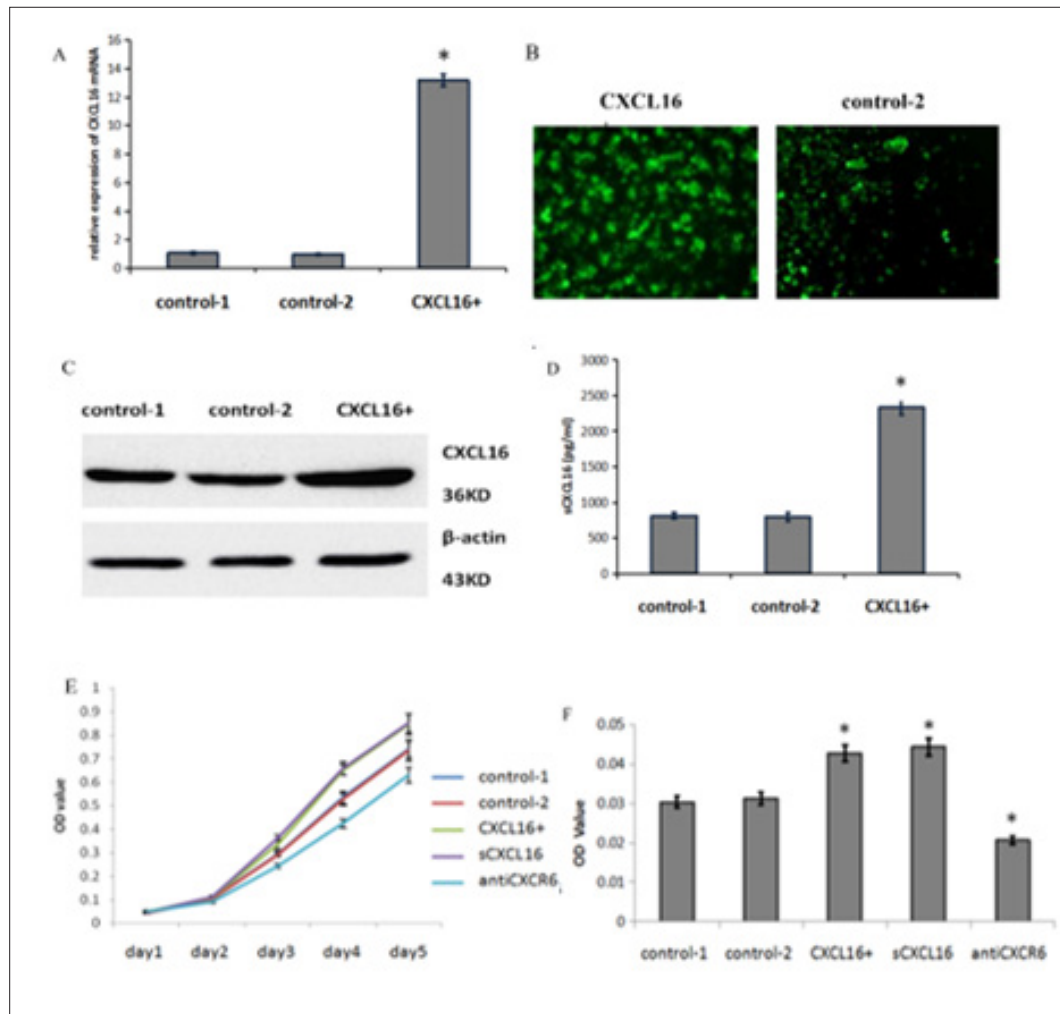


Figure 1: CXCL16 promote cell proliferation and migration of Hodgkin Reed-Sternberg cells.

A. The expression levels of CXCL16 mRNA were analysed by quantitative RT-PCR in Hodgkin Reed-Sternberg cell line L428 (control-1 group), L428 cell line transfected with empty lentivirus vector (control-2 group) and CXCL16-pGC FU-GFP-LV lentivirus vector (CXCL16+ group).

B. GFP was observed by fluorescence microscopy 120 h after transfection.

C. The expression of CXCL16 and β -actin in different groups were analysed by western blotting.

D. Soluble CXCL16 in the supernatant of cultured L428 cells were observed detected using ELISA. Proliferation

E. Chemotaxis

F. L428 cells under different treatments were assessed. 100ng/mL recombinant sCXCL16 or anti-CXCR6 were added to control-1 cells respectively. Data were expressed as the mean \pm SD and compared by one-way ANOVA. Asterisk (*) denotes significant differences ($p < 0.05$) between control and treated cells.

sCXCL16 affected cell cycle of H/RS cells and suppressed apoptosis

Flow cytometry assays were performed to investigate the effect of sCXCL16 on cell cycle and apoptosis in different cell groups. The percentage of cells in G1 phase was considerably lower in the CXCL16+ group ($42.40 \pm 1.18\%$) and sCXCL16 group ($42.26 \pm 1.36\%$) as compared with the control groups ($56.58 \pm 0.83\%$), while the percentage of cells in G2/M phase was higher in the CXCL16+ group ($27.32 \pm 0.2\%$) and sCXCL16 group ($27.6 \pm 2.25\%$) than that of the

control groups ($16.39 \pm 1.37\%$; $p < 0.05$). In contrast, treatment of normal L428 cells with CXCR6 antibody significantly increased the percentage of G1 phase cells and reduced the percentage of G2/M phase cells ($p < 0.05$) (Figure 2).

Apoptosis assays demonstrated that the percentage of apoptotic cells was diminished in the CXCL16+ and sCXCL16 groups compared with the control groups and was dramatically elevated by over 2-fold when CXCR6 antibody was applied to the normal L428 cells, the CXCL16+ group and the sCXCL16 group (Figure 2).

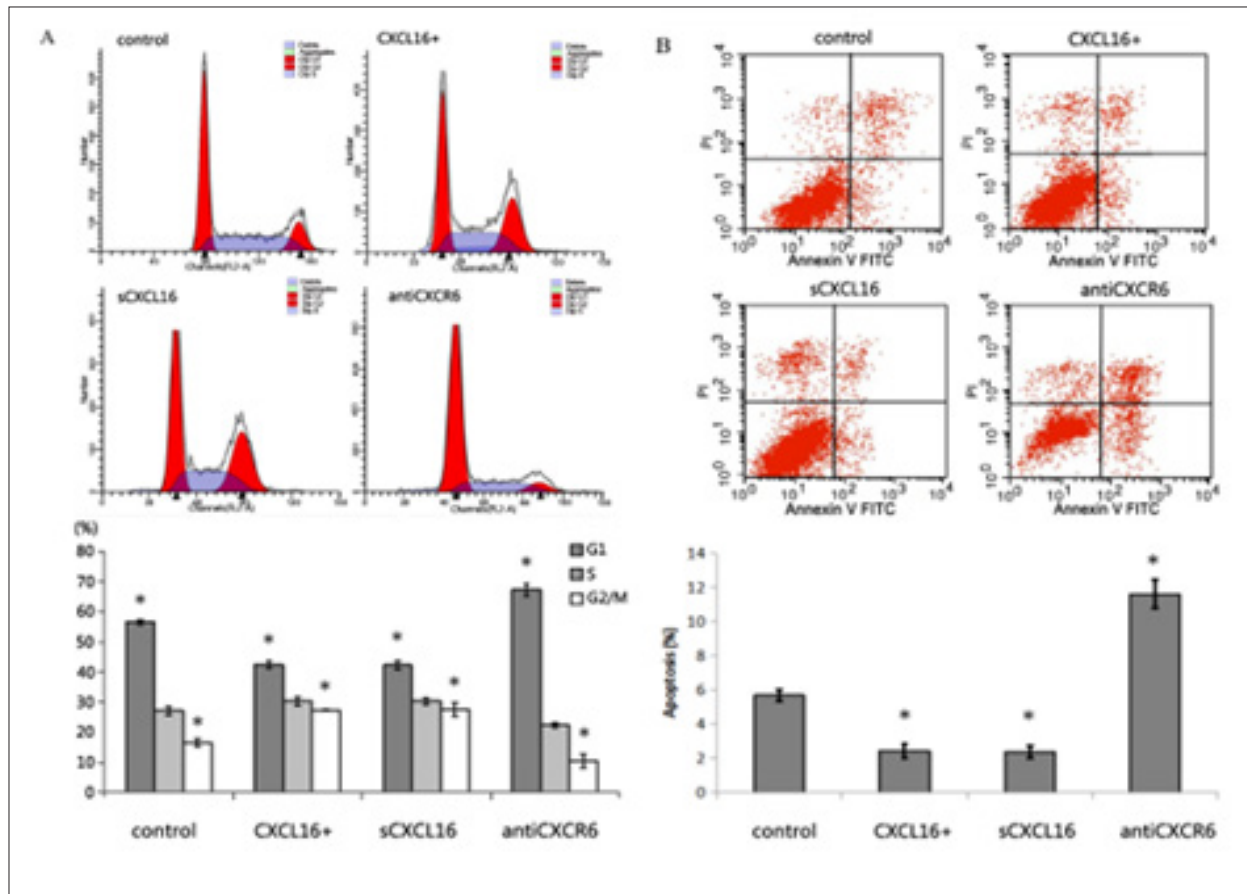


Figure 2: sCXCL16-mediated cell cycle change and apoptosis of Hodgkin Reed-Sternberg cells.

A. Cell cycles were measured to test the effects of overexpression of CXCL16 and the addition of 100ng/mL recombinant sCXCL16 or anti-CXCR6 on L428 cells. Histograms represent the percentage of L428 cells detected at different cell cycle stages.

B. Apoptosis was measured at 24 h intervals after treatments in each group. Histograms represent the percentage of apoptotic L428 cells. Flow cytometry results represent at least three independent experiments. Data were expressed as the mean \pm SD and compared by one-way ANOVA. Asterisk (*) indicates significant differences ($p < 0.05$) between control and treated cells.

sCXCL16 did not change the immune phenotypes of H/RS cells

Flow cytometry was performed to detect immune phenotypes in different cell groups. Expressions of CD19 and CD20, both are biomarkers of B-cell lymphoma instead of HL [13], were rather

low, while CD15 and CD30, which are biomarkers of HL, were highly expressed in all groups (Figure 3). There were no substantial differences in immune phenotypes observed among different groups upon CXCL16 treatment ($p > 0.05$), indicating that neither overexpression of CXCL16 or exogenously applied sCXCL16 affect the immune phenotypes of H/RS cells *in vitro*.

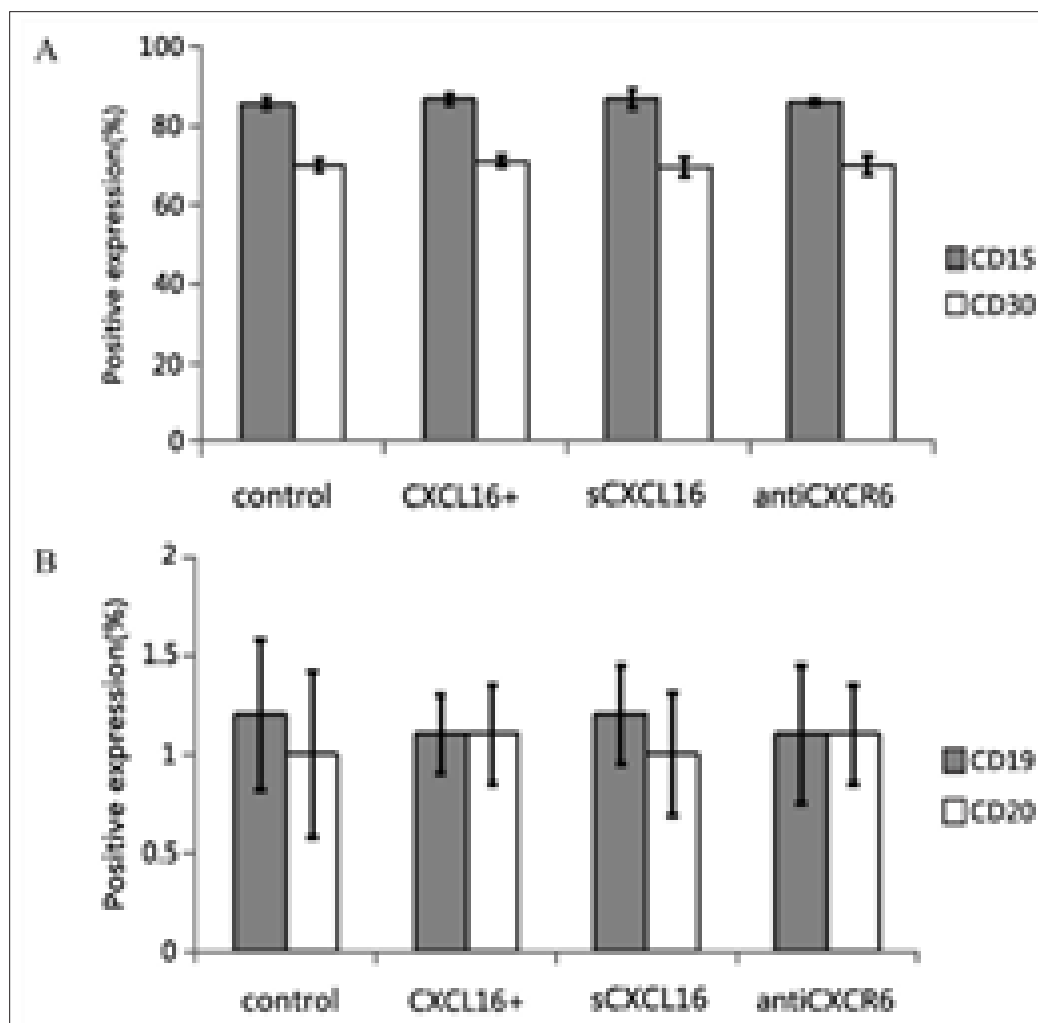


Figure 3: The immune phenotypes of L428 by applying recombinant sCXCL16.

Expression of immune phenotype markers (A) CD15, CD30, (B) CD19 and CD20 in L428 cells were measured using flow cytometry at 24h after treatments. Data were expressed as the mean \pm SD and compared by one-way ANOVA. * $p < 0.05$ vs control.

sCXCL16 regulated the PI3K/Akt/NF- κ B pathway in H/RS cells

The PI3K/Akt/NF- κ B signaling pathway plays a crucial role in regulating physiological and pathological events in cells. Dysfunction of these pathways contribute to tumor progression. Our previous studies have shown that CXCL16, including TM-CXCL16 and sCXCL16, are highly expressed in several lymphoma tissues and cell lines [11]. Elevated sCXCL16 expression was correlated with activation of the NF- κ B pathway in the H/RS cell line L428 [11]. However, the mechanism of the effects of CXCL16 on H/RS cells is not clear. To determine whether sCXCL16 could promote the activation of the PI3K/Akt/NF- κ B signaling pathways, western blot analysis was performed. Data showed that in the presence of sCXCL16, the expressions of phospho-Akt, phospho-p70S6, and phospho-I κ B were increased in a time-dependent manner, with maximum expression level reached at 45 and 60 min

after treatment with 100ng/mL recombinant sCXCL16 (Figure 4). In addition, both CXCL16 overexpression and exogenously applied recombinant sCXCL16 increased the phosphorylation of Akt, p70s6, and I κ B proteins, while blockade of CXCL16 or CXCR6 by antibodies decreased the phosphorylation of these proteins in L428 cells, suggesting that the CXCL16-CXCR6 interaction may lead to the activation of the PI3K/Akt/NF- κ B pathways (Figure 4).

To further validate the results, LY294002, an inhibitor of PI3K signaling pathway, was applied. The results showed that LY294002 inhibited L428 cell proliferation and migration in a dose-dependent manner, with the strongest effect observed at concentration of 50 μ M/mL (Figure 4). In addition, the presence of LY294002 effectively suppressed sCXCL16-induced cell proliferation and migration (Figure 4). These data provide further evidence that the functions of sCXCL16 in L428 cells are at least partially mediated through the PI3K/Akt/NF- κ B signaling pathway.

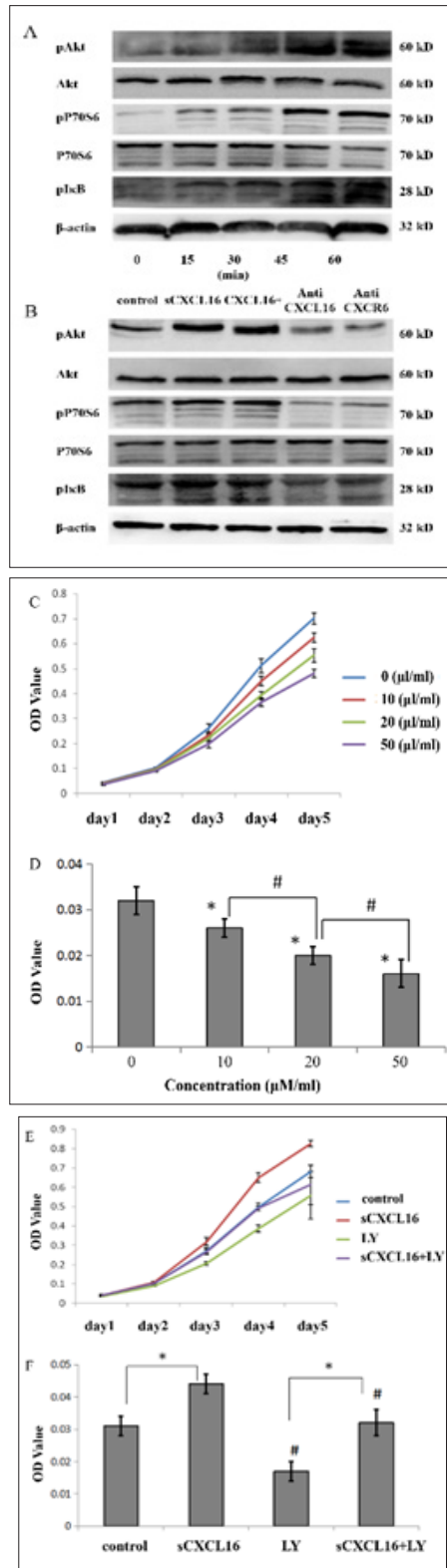


Figure 4: sCXCL16-mediated cell proliferation and migration in L428 cells through activation of the PI3K/Akt/NF-κB pathway. A-B: Western Blot analysis of expression of PI3K/Akt/NF-κB pathway-related proteins. Time-dependent effects of 100ng/mL recombinant sCXCL16 on several groups were observed in CXCL16 over-expressed cell line (A) and 100ng/mL recombinant sCXCL16 exogenously applied group (B). Effect of PI3K inhibitor LY294002 (LY) on the proliferation and migration of different groups were investigated: The concentration-dependent effects of LY294002 on the L428 cells (C, D) and effect of 100 ng/mL recombinant sCXCL16 on the L428 cells (E-F). Data were expressed as the mean ± SD and compared by one-way ANOVA. *p < 0.05 vs control.

Discussion

HL is an inflammation-associated tumor. H/RS cells, the presence of which is a hallmark of HL, secrete various cytokines and chemokines into the tumor microenvironment, contributing to development and progression of HL. Chemokines such as CXCL9 [14], CXCL10 [15], CCL5 [16], CCL17, and CCL22 [17] have been reported to participate in the crosstalk between H/RS and inflammatory cells by binding to corresponding receptors, and is associated with tumor cell growth, proliferation, migration, immunosuppression, and poor prognosis.

CXCL16 was first described in inflammatory and immune diseases [18] and was found in recent years to be correlated with tumor progression in several cancer types, including prostate cancer [5], lung cancer [7], ovarian cancer [6], and gastric cancer. Elevated CXCL16 expression has been reported to have the potential to be an independent predictor of poor clinical outcomes in cancer [19,20]. CXCL16 binds to its unique receptor, CXCR6, to induce downstream physiological and pathological outcomes. In the last decade, more evidence shows that CXCL16-CXCR6 axis could not only be a potential biomarker but an important target of clinical therapy [21-23].

Our group previously reported that CXCL16 was highly expressed in clinical tissues of HL patients and in nine human lymphoma cell lines [11] and was identified as a risk factor for poor prognosis in diffuse large B-cell lymphoma [12]. As high expression of CXCR6 was also detected in the HL cell line (L428) [11], we wondered whether regulation of CXCL16 would have any effect on H/RS cell phenotype and its extensive signaling pathways. In the present study, we used two methods to investigate the effects of CXCL16 on L428 cell lines. One was to construct a CXCL16 overexpressed lentivirus vector and transfect it into L428 cells. The second was to apply recombinant sCXCL16 protein to the cultured L428 cells. Results showed that both endogenous overexpressed CXCL16 and exogenously applied recombinant sCXCL16 promoted L428 cell proliferation and migration, and significantly suppressed cell apoptosis; meanwhile, CXCR6 antibody effectively reversed these effects, suggesting that sCXCL16 influences target cells through interaction with its unique receptor, CXCR6. Therefore, it is proposed that sCXCL16 may have an autocrine effect by co-expression with CXCR6 on H/RS cells. These results are consistent with previous studies that the CXCL16-CXCR6 axis could promote cell proliferation and migration in various tumor cells [7,20].

As the signal pathways were concerned, it is well known that the PI3K/Akt/NF- κ B signaling pathway is strongly correlated with tumor progression and considered to be an effective target in cancer chemotherapy. The CXCL16-CXCR6 axis has been reported to promote tumor cell proliferation, invasion, and metastasis via up-regulation of the PI3K/Akt pathway in pancreatic cancer [24] and ovarian cancer [6], and via the NF- κ B pathway in prostate cancer [5]. In gastric cancer, blockade of CXCR6 suppressed tumor growth through inhibition of Akt signaling [25]. In HL, reports showed that constitutive activation of PI3K/Akt/mTOR pathway contributed to cell survival [26]; downregulation of PI3K by

LY209002 [27] or RP6530 (a dual PI3K δ / γ inhibitor) [28] promoted G1 cell cycle arrest and cell apoptosis, leading to attenuated HL cell proliferation. Our previous investigation revealed that sCXCL16 was correlated with NF- κ B activation in HL [11]. The present results showed that sCXCL16 activated the PI3K/Akt/NF- κ B pathways in a time-dependent manner. Blockade of CXCL16 or CXCR6 in L428 cells reduced the activation of PI3K/Akt/NF- κ B pathway, and application of LY294002 significantly diminished sCXCL16-induced H/RS cell proliferation and migration. Together, these results provide evidence that activation of the PI3K/Akt/NF- κ B signaling pathway was possibly involved in the autocrine effect of sCXCL16 in promoting H/RS cell progression.

Immune phenotypes are important markers in different lymphoma sub-types. CD15 and CD30 are expressed in almost all H/RS cells and are commonly used as diagnostic markers for HL [29]; meanwhile, CD19 and CD20 are used to diagnose lymphoma derived from B-cell [13]. Our previous study demonstrated that up-regulation of the cell differentiation antigen CD99, which is inversely correlated with CXCL16 expression, significantly influenced immune phenotype in L428 cells; specifically, it led to the loss of cell surface markers CD15 and CD30 [11], and stimulated phenotype transformation from H/RS into B-cells. While in the present study, results revealed that sCXCL16 did not have an impact on immune phenotypes of L428 cells, indicating that differentiation or transformation of H/RS cells were not affected by CXCL16.

In summary, it is discovered in the current study that sCXCL16 promoted proliferation and migration of H/RS cells *in vitro*, which could be partially mediated by the activation of the PI3k/Akt/NF- κ B signaling pathways. These findings suggest that inhibition of sCXCL16 or CXCR6 may serve as a potential strategy for therapeutic HL.

Consent for Publication

This paper has not been published elsewhere in whole or in part. All authors have read and approved the content and agree to submit it for consideration for publication.

Competing interests

All authors declare no competing interests.

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Authors' Contributions

Conception and design: F.Liu; development of methodology: Y.Xun, H.Tang; experiments: H.Tang, Y.Xun, Y. Liang, H. Yang, D. Shen; analysis and interpretation of data: L. Fan, R. Wang, H. Liu; writing,

review, and/or revision of the manuscript: Y. Xun, F. Liu, Y. Pan; technical/material support: Y. Ai. D. Liu; study supervision: F. Liu, H. Tang. All authors read and approved the final manuscript.

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