

Hypoxia-induced secretion of IL-10 from adipose-derived mesenchymal stem cell promotes growth and cancer stem cell properties of Burkitt lymphoma

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Abstract In this study, we explored how the altered paracrine of adipose mesenchymal stem cells (ADSCs) contributed to the growth and cancer stem cell (CSC) properties of the Burkitt lymphoma cells. Condition mediums from normoxia or hypoxia cultured ADSC (CM-ADSC-N or CM-ADSC-H) were collected, and their effects on growth, colony formation, and apoptosis of Burkitt's lymphoma cells were investigated. Differentially expressed cytokines and inflammatory factors were compared between CM-ADSC-N and CM-ADSC-H. The involvement of differentially expressed IL-10 in growth and CSC properties of Burkitt lymphoma was investigated using both in vitro and in vivo models. Findings of this study showed that hypoxia increased IL-10 secretion from ADSCs, through which the growth and CSC properties of BL2 cells were enhanced. Intratumoral injection of CM-ADSC-H or IL-10 enhanced in vivo Burkitt lymphoma growth in nude mice model at least partly via the JAK2/STAT3 signaling pathway.

Keywords Hypoxia · IL-10 · Mesenchymal stem cell · Burkitt lymphoma

Lihua Xu and Xu Wang contributed equally to this work.

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Introduction

Tumor microenvironment (TME) is defined as a mesenchymal microenvironment surrounding tumor cells [1]. Since tumor cells and the TME are closely related and interact constantly, the behaviors of tumor cells can be influenced by extracellular signals released from the surrounding cells [2]. Recently, it was found that there is a small population of tumor-tropic adipose mesenchymal stem cells (ADSCs) in adipose tissue, which supports the formation of tumor vasculature [3]. In addition, the ADSCs may also contribute to tumor growth and vascularization of endometrial cancer xenografts [4]. In fact, the ADSCs have strong paracrine effects. However, how the cytokines and inflammation factors affect tumor behaviors are not fully revealed.

A key environmental stressor associated with solid tumor is a decreased oxygen supply, termed hypoxia [5]. Under the hypoxia environment, the paracrine effects of mesenchymal stem cells might be altered. For example, hypoxic breast tumor cells can specifically recruit mesenchymal stem cells (MSCs) by secreting IL-6, activating both STAT3 and MAPK signaling pathways to enhance migratory potential and cell survival [6]. MSCs under hypoxia can promote growth, motility, and invasive ability of breast cancer cells by increasing secretion of transforming growth factor-beta1 (TGF-beta1) [7]. Activation of hypoxia-inducible factors (HIFs) under hypoxia environment enhances bidirectional paracrine signaling between breast cancer cells and MSCs that stimulates cancer metastasis [8]. HIF1- α induced under hypoxia environment can also enhance cell survival of lymphocyte and lymphomagenesis [9]. Co-culture of pre-B acute lymphocytic leukemia cells with bone marrow-derived MSCs under hypoxia resulted in further induction of HIF1- α protein and acquisition of the glycolytic phenotype, leading to enhanced chemoresistance [10]. Burkitt's lymphoma is a solid tumor of B lymphocytes.

However, whether the HIFs affect paracrine of MSCs under hypoxia environment and how the MSCs are associated with growth of the Burkitt's lymphoma are still not fully understood.

In this study, we explored whether the paracrine of ADSCs was changed by hypoxia and how it contributes to the growth and cancer stem cell (CSC) properties of the Burkitt lymphoma cells.

Methods

Cell culture

Burkitt lymphoma cell lines Raji, Daudi, and BL2 were purchased from the American Type Culture Collection (ATCC; Manassas, VA). All cells were cultured in RPMI-1640 medium (Gibco-BRL, USA) supplemented with 10 % fetal bovine serum (HyClone, USA) in an incubator with a humidified atmosphere and 5 % CO₂ at 37 °C. Human ADSCs were purchased from Invitrogen (R7788-110, Carlsbad, CA, USA) and cultured using the prepackaged MesenPRO RS™ Medium. To collect the condition medium (CM) from ADSCs, 1 × 10⁶ passage 3 ADMSCs were cultivated in six-well plates with serum-free essential medium at either a normoxia (21 % oxygen) or hypoxia (2 % oxygen) environment. Twenty-four hours after cultivation, the CMs of normoxia (CM-ADSC-N) or hypoxia (CM-ADSC-H) were collected. The CMs were concentrated using Pierce™ Protein Concentrators (150 K MWCO, 7 ml, Thermo Fisher) according to manufacturer's instruction. Five milliliters CM was concentrated into 50 µl volume for in vivo tumor model use.

Reagents and cell transfection

Lentiviral vector encoding HIF1-α was purchased from GeneChem (Shanghai, China). To generate HIF1-α overexpression lentiviral particles, pLenti-HIF1-α and the lentiviral packaging mix were co-transfected to HEK 293T cells by using Lipofectamine 2000 (Invitrogen). Fourty-eight hours post transfection, the supernatants were harvested after the measurement of viral titers. The ready-to-use human HIF1-α shRNA lentiviral particles (sc-35561-V) were purchased from Santa Cruz Biotech (Santa Cruz). To overexpress or suppress the genes, the ADSCs were infected with corresponding lentiviral particles with the presence of 8 µg/ml polybrene (Sigma-Aldrich).

Cell proliferation and colony formation

Cells were pretreated with CM-ADSC-N (with or without IL-10 (20 ng/ml, Sigma-Aldrich) supplementation) or CM-ADSC-H (with or without anti-IL-10 (I5020-1MG, Sigma-

Aldrich)) for 48 h. Then, cell viability was determined using WST-8 assay using Cell Counting Kit-8 (CCK-8; Dojindo) according to manufacturers' instruction. To explore colony formation, soft agar colony formation assay was performed using 24-well plates according to the methods introduced in one previous study [11]. The cells were cultured in a cell incubator for 2 to 3 weeks and then were fixed with 10 % paraformaldehyde and stained with 1 % crystal violet in 70 % ethanol. Colonies (with minimal 50 cells) were counted using a stereomicroscope.

Flow cytometry analysis

The proportion of Ki67-positive BL2 cells was measured using flow cytometry. Briefly, the cells were fixed using 4 % paraformaldehyde at room temperature for 30 min, permeabilized in 0.1 % Saponin in PBS at 37 °C for another 30 min and then blocked using 4 % BSA for 30 min at 25 °C. Then the cells were incubated with primary anti-Ki67 (1:100, ab15580, Abcam) for 30 min at 22 °C. The secondary antibody used was donkey anti-Rabbit IgG H&L (PE) preadsorbed (1:200, ab7007, Abcam) for 30 min at 22 °C. The cells with positive ALDH or with active caspase-3 were quantified using ALDEFLUOR™ Kit (STEMCELL) or Fluorescein Active Caspase-3 Staining Kit (Abcam, ab65613), respectively, according to the manufacturers' instruction. All flow cytometry analysis was performed using a FACSCaliber (BD Biosciences). Data acquisition was done using CellQuest 3.2 software (BD Biosciences). Each test was performed with at least three repeats.

Chemotherapy response (IC50 measurements)

Ifosfamide (Bristol-Myers Squibb), methotrexate (Hengrui Medicine), doxorubicin (Sigma-Aldrich), vincristine (Sigma-Aldrich), cytarabine (Sigma-Aldrich), and doxorubicin (Sigma-Aldrich) are used to test the chemotherapy response of BL2 cells after treatment with CM-ADSC-H or CM-ADSC-N. Cells in the logarithmic phase were plated in 96-well plates at the density of 5 × 10³/well and were treated with fourfold serially diluted drugs for 72 h. Cell viability was measured by MTT (Sigma Aldrich) assay according to the recommended protocol. The drug concentration resulted in 50 % growth inhibition (IC50) was determined from the corresponding dose-response curve.

Western blot analysis

Total protein of the cell samples was extracted using a lysis buffer (Beyotime), and the protein concentrations were measured by BCA protein assay kit (Beyotime). The lysates were separated on 10 % SDS-PAGE and then transferred onto a PVDF membrane. After blocking with 5 % nonfat dry milk,

the membranes were incubated with primary antibodies to Bcl-2 (1:1000, ab18210, Abcam), AKT (1:2000, ab185633), phosphorylated AKT (ab18206, 1:1000), active caspase-3 (1:1000, ab77973), IL-10 (1:1000, ab9969), HIF1- α (1:1000, ab179483), JAK2 (1:500, ab39636), phosphorylated JAK2 (1:1000, ab32101), STAT3 (1:1000, ab68153), and phosphorylated STAT3 (1:500, ab30647), respectively, and then incubated with the corresponding HRP-conjugated secondary antibody (1:5000, anti-rabbit IgG, HRP, ab6721; 1:5000, anti-mouse IgG, HRP, ab6728). All primary and secondary antibodies were purchased from Abcam. Signals were visualized by using the ECL Western blotting substrate (Promega, Madison, WI, USA). The band intensity was quantified by using ImageJ software. Experiments were performed in triplicate.

QRT-PCR analysis

Total RNAs of the cells were extracted using Trizol Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instruction. The first-strand complementary DNA (cDNA) was reversely transcribed using the RevertAid first-strand cDNA synthesis kit (Fermentas, ON, Canada) according to manufacturer's instructions. The expressions of CSC marker genes (ALDH, CD133, CD44, CD24, ESA, and BIM-1) and IL-10 were detected by using the gene-specific primers (Supplementary Table 1) and SYBR[®] Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA). GAPDH was used as the endogenous control gene. All qRT-PCR analysis was performed using an ABI Prism 7500 (Applied Biosystems, Foster City, CA, USA).

Tumorsphere formation assay

Cells pretreated with CM-ADSC-N (with or without IL-10 supplementation) or CM-ADSC-H (with or without IL-10 neutralization) were suspended in defined, serum-free medium composed of DMEM-F12 (Gibco), 10 ng/ml of human recombinant basic fibroblast growth factor (bFGF; R&D Systems), 10 ng/ml of epidermal growth factor (EGF; R&D Systems), B27 (Thermo Fisher), and N2 (Thermo Fisher). Cells were fed every 48 h and cultured for 7 days. Then the tumorspheres were counted under a microscope.

ELISA analysis of growth factors and inflammatory factors in CM of ADSCs

The concentrations of growth factors (bFGF, HGF, IGF-1, SCF, and VEGF) and inflammation factors (TNF- α , CCL-14, IL-1 α , IL-6, IL-10, and IL-17) in the CM-ADSC-H or CM-ADSC-N were measured by using ELISA kits (USCN Life Science) according to the manufacturer's instruction.

Tumor models

Procedures involving animals were reviewed and approved by the Animal Care and Use Committee of the Guangzhou Medical University. All animal studies were performed in accordance with the ethical standards and according to the Declaration of Helsinki. To develop *in vivo* tumor model, 2.0×10^6 BL2 cells in 100 μ l of growth factor-reduced Matrigel (BD BioScience) were subcutaneously inoculated in the dorsal flank of C57BL/6 mice. Seven days after BL2 transplantation, CM-ADSC-N (50 μ l/mouse) or CM-ADSC-H (50 μ l/mouse) and IL-10 (5 ng/kg weight) were intratumorally injected every 5 days since day 7 for five times. Tumor volumes were calculated using the ellipsoid volume formula ($0.5 \times l \times w^2$, where l is the length and w is the width).

Statistical analysis

All statistical analysis was performed using SPSS 18.0 software. Group comparison was performed using unpaired *T* test. A two-sided *p* value of <0.05 was regarded as statistically significant.

Results

CM-ADSC-H strongly promoted the growth of Burkitt lymphoma cells

MSCs have been recently described to localize and integrate into the tumor-associated stroma, and its paracrine effect may affect motility, invasion, and metastasis of tumor cells [4]. We firstly explored how the paracrine effect of MSCs under the hypoxic condition may affect tumor growth. CM-ADSC-H treatment substantially promoted cell growth (Fig. 1a) and clonogenicity (Fig. 1b) of Raji, Daudi, and BL2 cells. Since BL2 cells had the strongest responses to CM-ADSC-H, it was selected for the following studies. Then, we investigated how the CMs might alter chemosensitivity of the Burkitt lymphoma cells. CM-ADSC-H treatment substantially decreased the sensitivity of BL2 to methotrexate, doxorubicin, vincristine, and cytarabine (Fig. 1c). In addition, it also alleviated the inhibition of doxorubicin on clonogenicity of BL2 cells (Fig. 1d). By performing flow cytometry analysis of Ki-67-positive BL2 cells, we found that both CM-ADSC-H and CM-ADSC-N treatment can significantly increase the proportion of Ki-67-positive cells, but CM-ADSC-H had a stronger effect (Fig. 1e1, e2). CM-ADSC-H also promoted cell growth (Fig. 1f1, f2) and reduced cell apoptosis (Fig. 1g1, g2) even under the treatment with doxorubicin. In addition, CM-ADSC-H significantly decreased the level of active caspase-3, but increased p-AKT and Bcl-2 under the treatment with doxorubicin (Fig. 1h1, h2).

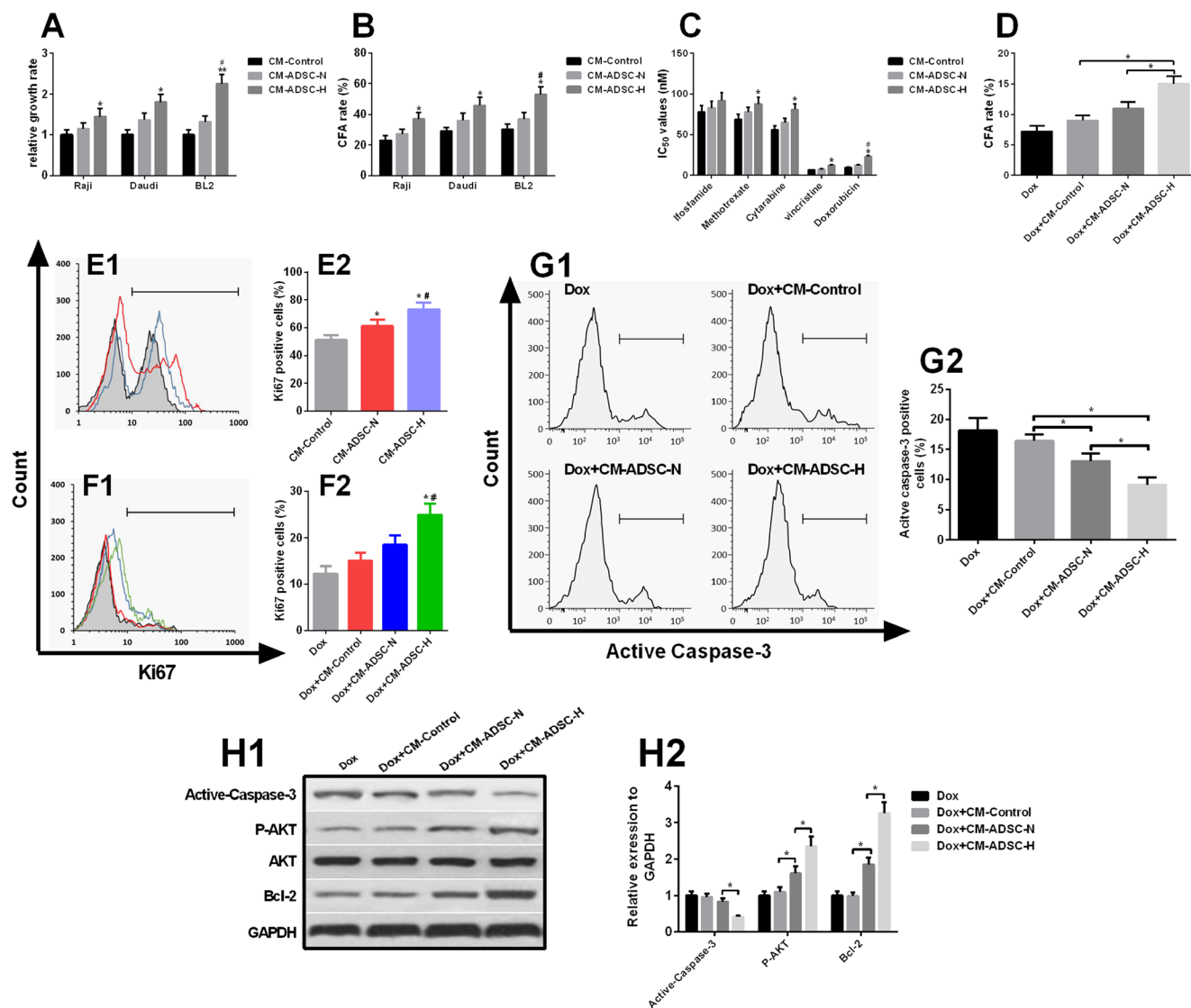


Fig. 1 CM-ADSC-H strongly promoted the growth of Burkitt lymphoma cells in vitro. **a, b** CCK-8 (**a**) and colony formation assay (CFA) (**b**) were performed to compare the effects of CM-ADSC-N and CM-ADSC-H on three Burkitt lymphoma cell lines. * vs CM-Control, # vs CM-ADSC-N. **c** The effects of CM-ADSC-N and CM-ADSC-H on chemotherapy response in BL2 cells. **d** The effects of CM-ADSC-N and CM-ADSC-H on CFA in BL2 cells under the treatment of doxorubicin (Dox). **e1, e2** Representative images (**e1**) and bar charts (**e2**) of flow cytometry analysis of the percentage of Ki67-positive cells in BL2 cells after the treatment of CM-ADSC-N and CM-ADSC-H. **f1, f2, g1, g2, h1, h2** Flow cytometry analysis of Ki67 (**f1, f2**) and active caspase-3 (**g1, g2**), and Western blot analysis (**h1, h2**) were further carried out to elucidate the potential mechanism of enhanced chemoresistance by CM-ADSC-H. Error bars show the S.D. of triplicates. *, # $P < 0.05$; **, ### $P < 0.01$

CM-ADSC-H enhanced the cancer stem cell properties of BL2 cells

Since we confirmed that CM-ADSC-H can promote the growth of Burkitt lymphoma cells, we then detected whether it changed cancer stem cell (CSC) properties of BL2 cells. CM-ADSC-H remarkably increased ALDH, CD44, BIM-1, and ESA expression (Fig. 2a). Besides, the proportion of cells with positive ALDH has increased from about 0.37 % in CM control group to around 4 % in CM-ADSC-N group and around 6 % in CM-ADSC-H group (Fig. 2b). One of the key features of CSCs is its ability to form mammospheres in

suspension culture [12]. CM-ADSC treatment increased the number and size of tumorsphere (Fig. 2c). But the difference between CM-ADSC-H and CM-ADSC-N was not evident (Fig. 2c).

Hypoxia increased IL-10 secretion from ADSCs, through which the growth and CSC properties of BL2 cells were enhanced

Results above showed that hypoxia could alter the paracrine effects of ADSCs, through which it enhanced the proliferation and CSC properties of Burkitt lymphoma cells. Then, we

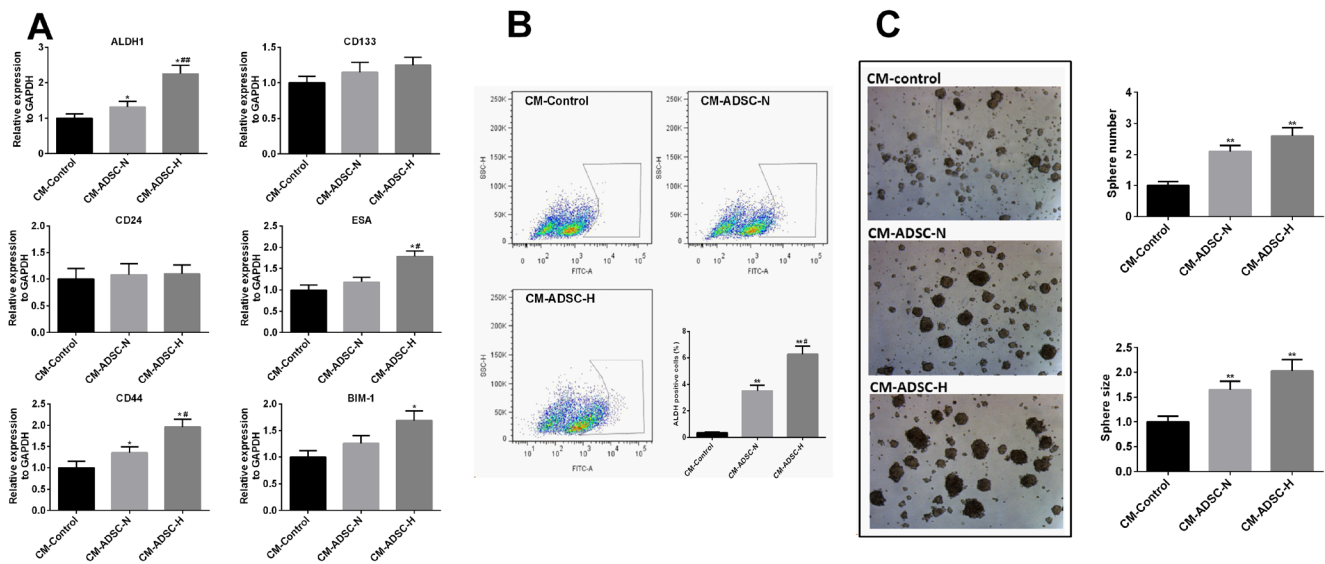


Fig. 2 CM-ADSC-H enhanced the cancer stem cell (CSC) properties of BL2 cells. **a** Quantitative PCR analysis of the series of CSC marker genes. **b, c** Flow cytometry analysis of ALDH-positive cells. **c** In sphere culture condition, the size and number of spheres formed by

BL2 cells were compared between CM-ADSC-N and CM-ADSC-H groups. Data are expressed as mean \pm S.D. $n=3$. * $P<0.05$; ** $P<0.01$ vs CM-Control; # $P<0.05$; ## $P<0.01$ vs CM-ADSC-N

investigated the underlying mechanism. Growth factors and inflammatory factors in CM-ADSC-H and CM-ADSC-N were measured by ELISA analysis. CM-ADSC-H had significantly higher concentrations of growth factors, including FGF, HGF, IGF, and VEGF (Fig. 3a), as well as inflammatory factors, including TNF- α , CCL-14, IL-1 α , IL-6, IL-10, and IL-17 (Fig. 3b). Previous studies reported that IL-10 can support the growth of Burkitt's lymphoma cells [13]. Therefore, we further explored the function of IL-10. ADSCs have a significantly higher expression of IL-10 (Fig. 3c) and HIF1- α (Fig. 3d) under hypoxia culture. By enforcing over-expression or knockdown of endogenous HIF1- α (Fig. 3e, f), we observed that IL-10 was positively related to HIF1- α expression at both mRNA (Fig. 3g) and protein (Fig. 3h) level. These results suggest that hypoxia remarkably increased the expression and secretion of IL-10 in a HIF1- α dependent manner in ADSCs.

Then, we investigated whether IL-10 is related to CM-ADSC-H that induced a higher growth rate and CSC properties of BL2 cells. Supplementation of IL-10 to CM-ADSC-N significantly enhanced its effect on promoting cell growth (Fig. 3i) and colony formation (Fig. 3j). However, adding anti-IL-10 to CM-ADSC-H substantially weakened its effect on cell growth and colony formation (Fig. 3i, j). Supplementation of IL-10 to CM-ADSC-N increased the proportion of Ki67-positive cells (Fig. 3k), while neutralizing IL-10 in CM-ADSC-H reduced Ki67-positive cells (Fig. 3k). These results suggest that IL-10 is an important component of CM-ADSC promoting the growth of BL2 cells. Then we investigated whether IL-10 is related to the CSC properties of BL2 cells. Supplementation of IL-10 to CM-ADSC-N significantly

increased its effect on promoting the expression of ALDH, CD44, ESA, and BIM-1, while neutralizing IL-10 in CM-ADSC-H abrogated its effect on promoting the expression of these four genes (Fig. 3l). Similar trends were observed when studying its effects on the number and size of tumor sphere (Fig. 3m, n).

CM-ADSC-H or IL-10 enhanced in vivo Burkitt lymphoma growth in nude mice model partially via JAK2/STAT3 signaling pathway

To investigate the effect of CM-ADSC or IL-10 on in vivo Burkitt lymphoma model, concentrated CM-ADSC-H, CM-ADSC-N, or IL-10 were injected intratumorally 7 days after BL2 cell inoculation. CM-ADSC-H injection has the strongest effect in promoting tumor growth and weight (Fig. 4a–c). By using tumor tissues, we found both CM-ADSC-N and CM-ADSC-H could significantly enhance the phosphorylation of JAK2 and STAT3, but CM-ADSC-H had a stronger effect (Fig. 4d, e). In comparison, supplementation of IL-10 to CM-ADSC-N enhanced phosphorylation of JAK2 and STAT3, while neutralize IL-10 in CM-ADSC-H weakened phosphorylation of JAK2 and STAT3 in BL2 cells (Fig. 4f, g).

Discussion

During the past years, the complex cross talk between neoplastic B cells and the tissue microenvironment has been gradually recognized [14]. There are emerging evidences showing that several types of leukemias and lymphomas

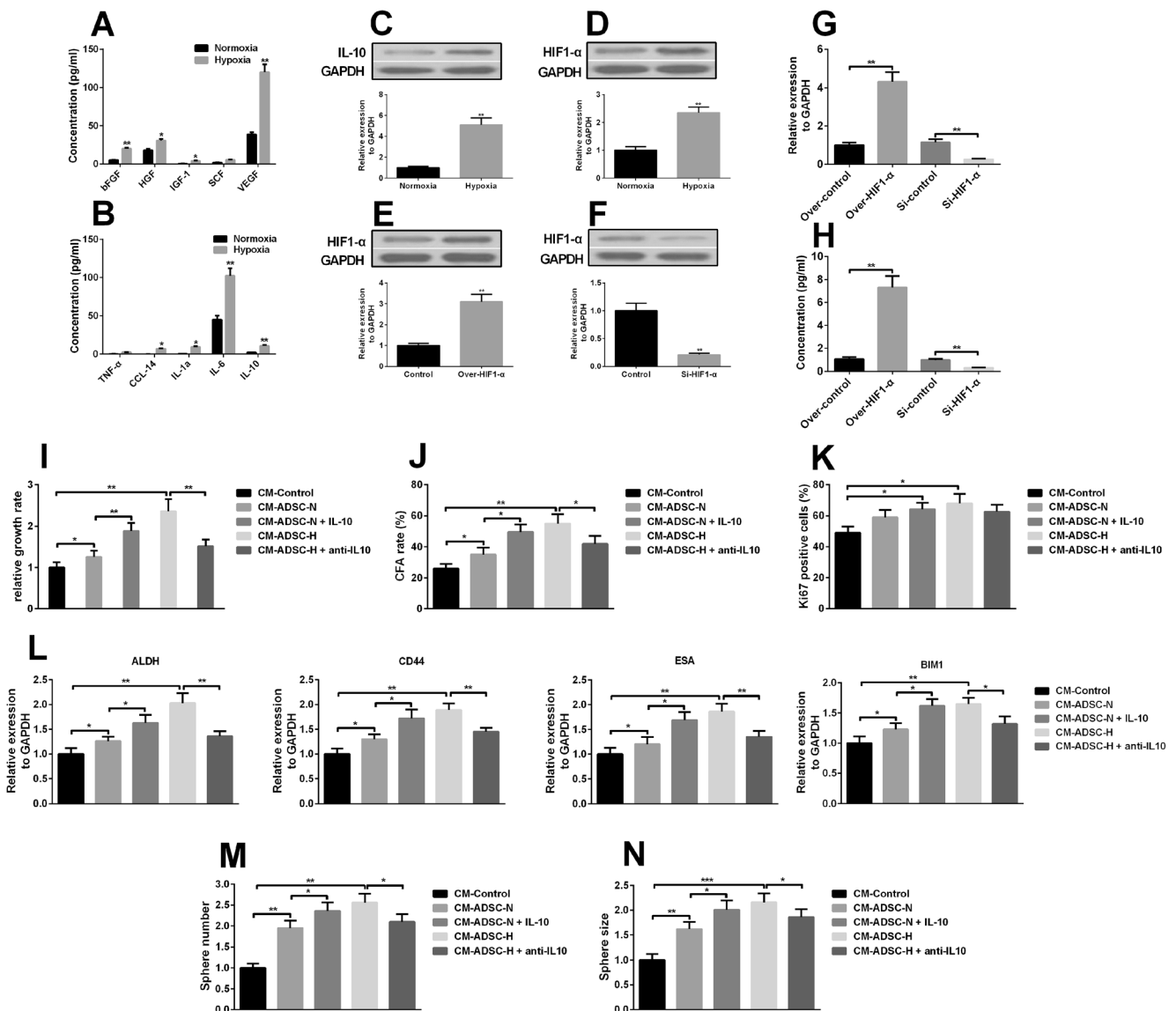


Fig. 3 Hypoxia increased IL-10 secretion from ADSCs, through which the growth and CSC properties of BL2 cells were enhanced. **a, b** Growth factors (**a**) and inflammatory factors (**b**) were evaluated by ELISA analysis. **c, d** Quantitative PCR and Western blot were conducted to confirm the upregulation of IL-17 (**c**) and HIF1- α in hypoxic ADSC. **e, f** Over-expression (**e**) and knockdown (**f**) of HIF1- α in ADSCs. **g, h** Quantitative PCR (**g**) and ELISA (**h**) were used to determine the effects of HIF1- α on

the IL-10 expression and secretion. **i–k** CCK-8 (**i**), CFA analysis (**j**), and Ki67 flow cytometry (**k**) were used to evaluate the effect of IL-10 on the proliferation of BL2 cells treated with CM-ADSC-N and CM-ADSC-H. **l** Quantitative PCR analysis of CSC marker genes in BL2 cells with indicated treatments. **m, n** The effect of IL-10 on the number (**m**) and size (**n**) of BL2 spheres formed in floating culture condition. Data are shown as mean \pm S.D. $n = 3$. * $P < 0.05$; ** $P < 0.01$

(such as follicular lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia) interact with the bone marrow/lymphoid microenvironment for proliferation, survival, and drug resistance [15, 16]. For example, MSCs can secrete adhesion molecules and integrins, which trigger important survival signals upon binding to their cognate receptors on the follicular lymphoma cells [17]. In addition, MSCs can also express pro-survival cytokines such as IL-6 and BAFF, supporting the proliferation of the lymphoma cells [18]. Co-culture of mantle cell lymphoma cells and human stromal cells led to prolonged survival and proliferation of

primary mantle cell lymphoma cells. In addition, the interactions also resulted in activation of the B cell activating factor/nuclear factor- κ B signaling axis, which contributes to reduced apoptosis, increased mantle cell lymphoma migration, and increased drug resistance [16]. Another recent study observed that after 2 weeks of co-culture with MSC, the B cells isolated from CLL patients had significantly decreased CD20 expression, leading to a higher level of resistance to rituximab-induced apoptosis [19]. Therefore, it is quite possible that the MSCs surrounding the malignant B cells might contribute tumorigenesis via paracrine effect.

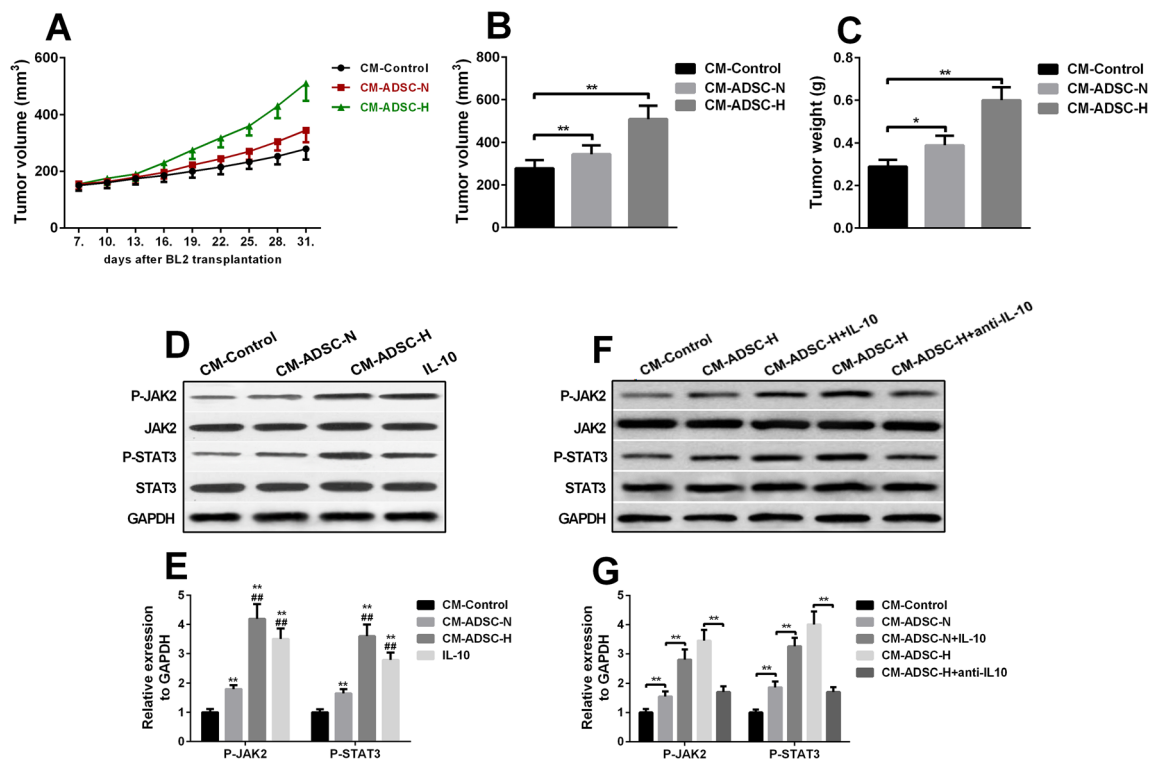


Fig. 4 Intratumoral injection of CM-ADSC-H or IL-10 enhanced the in vivo Burkitt lymphoma growth in nude mice model partially via JAK2/STAT3 signaling pathway. **a–c** Seven days after BL2 cell inoculation in nude mice, the tumor volume was measured every 3 days, and the tumor growth curves were drawn (**a**). The final tumor volume (**b**) and weight (**c**)

were calculated, $n = 6$. **d, e** Western blot analysis was performed to check the JAK2/STAT3 signal pathway using tumor tissues from nude mice. * vs CM-Control, # vs CM-ADSC-N. **f, g** JAK2/STAT3 signal pathway was further analyzed in BL2 cells. Data are shown as mean \pm S.D, $n = 3$. *, # $P < 0.05$; **, ### $P < 0.01$

The hypoxic microenvironment in the central region of solid tumors can induce molecular responses of normal and cancer cells in the local area. Previous studies found that the HIFs mediate complex and bidirectional paracrine signaling between breast cancer cells and MSCs, which stimulate breast cancer metastasis [8]. In addition, it was also observed that MSCs recruited into the hypoxic area had elevated secretion of TGF- β 1, which promotes the growth, motility, and invasive ability of breast cancer cells [7]. However, how the hypoxia affects the paracrine effects of MSCs on Burkitt lymphoma are still unclear. In this study, we found CM-ADSCs-H significantly promoted cell growth, decreased cell apoptosis, and enhanced chemoresistance of BL2 cells. Interestingly, CM-ADSCs-H also significantly enhanced the expression of CSC markers, including ALDH, CD44, ESA, and BIM-1 and stronger capability to form tumor sphere. However, the underlying mechanism has not been reported yet.

By performing ELISA assay, we observed that the CM-ADSCs-H had significantly higher concentrations of multiple growth factors and inflammation factors, including IL-10. Previous studies reported that IL-10 is an important cytokine promoting pathogenesis of lymphomas [20]. It can activate the JAK2 pathway in lymphoma and inhibit apoptosis of the lymphoma cells [21]. Epstein-Barr virus infection, one of the

major pathological causes of Burkitt lymphoma, also increases IL-10 production in mitogen-stimulated primary B cells and B cell lymphomas [22]. Therefore, we further studied the function of this cytokine. HIFs can regulate many pathways that enable tumor cells to develop metabolic adaptation to hypoxia, cell proliferation, chemotaxis, and metastasis to distant sites [23]. In addition, HIFs can also contribute to tumor aggressiveness by the governance of immature stem cell-like phenotype and related epithelial-to-mesenchymal transition (EMT)/de-differentiation in several solid tumors [24]. In lymphoma, HIF-1 α induces chemoresistance phenotype in non-Hodgkin lymphoma cell line via upregulation of Bcl-xL [25]. In this study, we found that hypoxia remarkably increased the expression and secretion of IL-10 from the ADSCs in a HIF1- α dependent manner. In addition, the IL-10 is a critical component of CM-ADSC-H, through which it promoted the growth of BL2 cells and also enhanced CSC properties of the cells. In in vivo study, we observed that IL-10 alone had a similar effect as CM-ADSC-H on enhancing Burkitt lymphoma growth in nude mouse model. Besides, CM-ADSC-H treatment also activated the JAK2/STAT3 signaling pathway. In fact, activation of this signaling pathway is related to increased chemoresistance and decreased apoptosis in B cell lymphoma [21, 26].

In conclusion, this study demonstrated that hypoxia-induced secretion of IL-10 from ADSCs can promote growth and CSC properties of Burkitt lymphoma.

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Compliance with ethical standards Procedures involving animals were reviewed and approved by the Animal Care and Use Committee of the Guangzhou Medical University. All animal studies were performed in accordance with the ethical standards and according to the Declaration of Helsinki.

Conflicts of interest None

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