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Interleukin-14 Prevents Cytarabine or Irradiation Induced Neutropenia through JAK/STAT3 Signaling

Shengnan Xu[1#], Chaoqiong Ye[1#], Zhihua Wu[1], Chuying Wen[1], Wenhui Huang[1], Cong Deng[1], Jiaye Hua[1*], Wei Xie[1*], Min Xiao[1*]

[1]Department of Hematology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510260, China
[#]These authors contributed equally to this work.

ABSTRACT

Background: Severe neutropenia significantly increases the risk of bacterial infections. Recent studies have shown that the cytokine interleukin 14 (IL-14) plays an important role in immune cells, but its potential role in neutropenia induced by cytarabine (ara-c) or irradiation is unclear.

Objective: To investigate the role of IL-14 in ara-c or irradiation-induced neutropenia.

Methods: Two neutropenia models were induced by ara-c or irradiation. Neutrophil count was confirmed through flow cytometry and routine blood tests. IL-14 was used to assess the impact on neutropenia. IL-14 expression was analyzed using qPCR, Western blotting and ELISA. A IL-14 receptor (IL-14R) knockout mice model was utilized to confirm the role of IL-14R/STAT3 signaling *in vivo*.

Results: The results indicated that IL-14 treatment promoted proliferation and increased neutrophil counts in both bone marrow and peripheral blood, while IL-14R knockout suppressed this process. Furthermore, the downstream molecule of IL-14R, STAT3, showed enhanced phosphorylation levels in the presence of IL-14. Finally, we explored the source of IL-14 in the bone marrow, and found that lymphocytes secreted the highest levels of IL-14. Serum levels of IL-14 were significantly reduced in patients after chemotherapy.

Conclusions: These results indicate that IL-14 prevents ara-c or irradiation-induced neutropenia by regulating lymphocytes and activating the IL-14R/STAT3 pathway in neutrophils. This evidence suggests that IL-14 is a potent cytokine for treating ara-c or irradiation-induced neutropenia.

Keywords: Cytarabine, Interleukin 14, Irradiation, Neutropenia, STAT3

*Corresponding author:
Department of Hematology, The Second Affiliated Hospital of Guangzhou Medical University, No. 250, Changgang Avenue, Guangzhou, Guangdong
Wei Xie,
Email: weiwei_xie@aliyun.com
Jiaye Hua,
Email: jy1016aa@163.com
Min Xiao,
Email: zoufeimed2017@126.com

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INTRODUCTION

Neutrophilic granulocytopenia is a condition where the absolute peripheral blood neutrophil count is below 1.5×10^9/L in children under10 years of age, below 1.8×10^9/L in children aged 10–14 years, and below 2.0×10^9/L in adults.When the granulocytes drop severely below 0.5×10^9/L, the condition is referred to as agranulocytosis (1). Severe neutropenia can trigger bacterial infections and even threaten the patient's life (2). Chemotherapy is one of the main treatments for cancer, and a series of side effects caused by chemotherapy are inevitable (3). Myelosuppression is the most common limiting toxic side effect of chemotherapy, and febrile neutropenia (FN) caused by myelosuppression is a serious complication after chemotherapy (4, 5). FN causes various infections, reduces patients's quality of life , prolongs the interval between chemotherapy treatments, reduces treatment efficacy , and even leads to the death of some patients, and therefore, requires adequate attention (6). Cytosine arabinoside (ara-c) is a pyrimidine antimetabolite that has been widely used in the treatment of acute myeloid leukemia for an extended period, achieving certain curative effects (7). Once ara-c enters the human body, it is converted into ara-c triphosphate, which inhibits DNA synthesis. It is an S-phase-specific drug (8). Ara-c has the ability to induce apoptosis of HL-60 cellsand down-regulate the B-cell lymphoma-2 gene (9). Its common toxicities include myelosuppression and gastrointestinal disturbances (10).

Radiation therapy has a history of more than 100 years and it is an important method of clinical tumor treatment at present (11). Clinical oncology radiotherapy mainly consists of three areas: radiotherapy physics (radiotherapy technology), clinical radiobiology, and tumor radiotherapy (12). Among these, radiation therapy technology is the most advanced at the current stage and is considered the most important method of comprehensive tumor treatment (13). Although radiotherapy is effective, its side effects are very noticeable (14). During the process, radiation not only targets tumor cells, but also affects normal tissue surrounding them (15). As a result, neutropenia is a common complication after radiotherapy. While there are several drugs available for treating neutropenia, they all come with varying degrees of side effects. Therefore, findingnew and more effective treatments is an urgent issue.

IL-14, also known as high molecular weight B-cell growth factor, was first discovered by Professor Ambrus in the United States (16). In 1993, the structure of its encoding gene was determined (17). This cytokine is produced by activated T lymphocytes and malignant B lymphocytes (17, 18). IL-14 is not only an important lymphokine for regulating the function of B cells, but its receptor is also a crucial functional molecule on B cells. It is closely related to certain B-cell tumors and autoimmune diseases(19-21). Despite various evidence showing the significant role of IL-14 in immune regulation, its function in immune cells has yet to be fully understood. The role of IL-14 in ara-c and irradiation induced neutropenia is also unknown. We wondered if IL-14 could prevent ara-c and irradiation induced neutropenia. In this study, we observed the protective effects of IL-14 against ara-c and irradiation induced neutropenia in a mouse model and further explored the origin of IL-14 in the bone marrow (BM). These findings suggest that IL-14 may have translational potential in neutropenia management.

MATERIALS AND METHODS

Mice

IL-14R$^{-/-}$ mice and 12-week-old C57BL/6 mice were obtained from the Shanghai Model Organisms Center (Shanghai, China). Sex-matched littermate mice at 12 weeks of age were used for experiments unless atated otherwise. All animals were given a standard diet and kept in pathogen-free cages

at a constant temperature and humidity. The circadian rhythm was kept at 12 hours. The method used for euthanizing mice involved placing them in a closed container and gradually increasing the CO2 concentration until respiratory and cardiac arrest occurred. The experiments were conducted in accordance with institutional guidelines and approved by the Guangzhou Medical University Animal Care and Use Committee. All procedures involving mice were approved by the comittee. Animal acre and procedures were carried out following the guidelines of the National Institutes of Health for Animal Use and Care. The first day of treatment with ara-c or irradiation was considered day 0. C57BL/6 mice were divided into three groups: the ara-c group (neutropenia model group, n=36), the irradiation group (neutropenia model group, n=36) and the control group (n=18). C57BL/6 mice used in IL-14 treatment were divided into four groups: the ara-c group treated with IL-14 (treatment group, n=18), the ara-c group treated with PBS (control group, n=18), the irradiation group treated with IL-14 (treatment group, n=18), and the irradiation group treated with PBS (control group, n=18). IL-14R$^{-/-}$ mice were divided into three groups: the ara-c group (n=18), the irradiation group (n=18) and the control group (n=18). Animals were included in the study if their neutrophil count was significantly reduced (<0.5×10^9/L). Animals were excluded if they did not meet the inclusion criteria or if they died prematurely. All mice were assigned to groups randomlyusing a hardware random number generator. The testing order of each animal was randomized daily.Our study followed the ARRIVE guidelines.

Cells

Primary cultured osteoclasts, lymphocytes, osteocytes, osteoblasts, and endothelial cells were prepared as previously described (22).

Flow Cytometry Analysis

Cell staining was performed following the standard procedure for flow cytometryanalysis. The antibodies used were as follows (eBioscience, San Diego, CA, USA, unless otherwise specified): FITC-conjugated anti-CD11b (catalog number: 11-0112), PE-conjugated anti-Gr-1 (catalog number: 12-9668), APC-conjugated anti-Edu (Invitrogen, Carlsbad, CA, USA), and p-STAT3 (catalog number: 17-9033).

Routine Blood Tests

Neutrophil counts in the peripheral blood of mice were measured using an automated whole blood analyzer (Sysmex KX.21, Japan).

Ara-c-induced Neutropenia Mouse Model and IL-14 Treatment

C57BL/6 mice, 3 months old, half male and half female, were randomly assigned to different groups. ara-c (C1768, Merck, Germany) was administered intraperitoneally (IP) at a dose of 100 mg/kg/day for 10 days. Recombinant murine IL-14 (MBS5310830; MyBioSource, San Diego, USA) was also injected IP at a dose of 100 μg/kg/day for 10 days. Control mice recieved 1×PBS. After 11 days, mice were sacrificed and bone marrow (BM) and peripheral blood (PB) were collected for flow cytometry analysisand neutrophil count analysis.

Irradiation-induced Neutropenia Model and IL-14 Treatment

C57BL/6 mice, 3 months old, half male and half female, were randomly assigned to groups. The mice were exposed to 0.3Gy of irradiation per day for 15 days to induce neutropenia. Recombinant murine IL-14 (MBS5310830; MyBioSource, San Diego, USA) was injected IP at a dose of 100 μg/kg/day for 14 days. Mice were sacrificed on day 16 and BM and PB were collected for flow cytometry and neutrophil count analysis.

Conditioned Medium Collected from Lymphocytes, Osteoclasts, Osteoblasts, Endothelial Cells, Osteocytes, and BMSC Cultures

Cell isolations were conducted following the methods outlined in previous literature (22, 23).

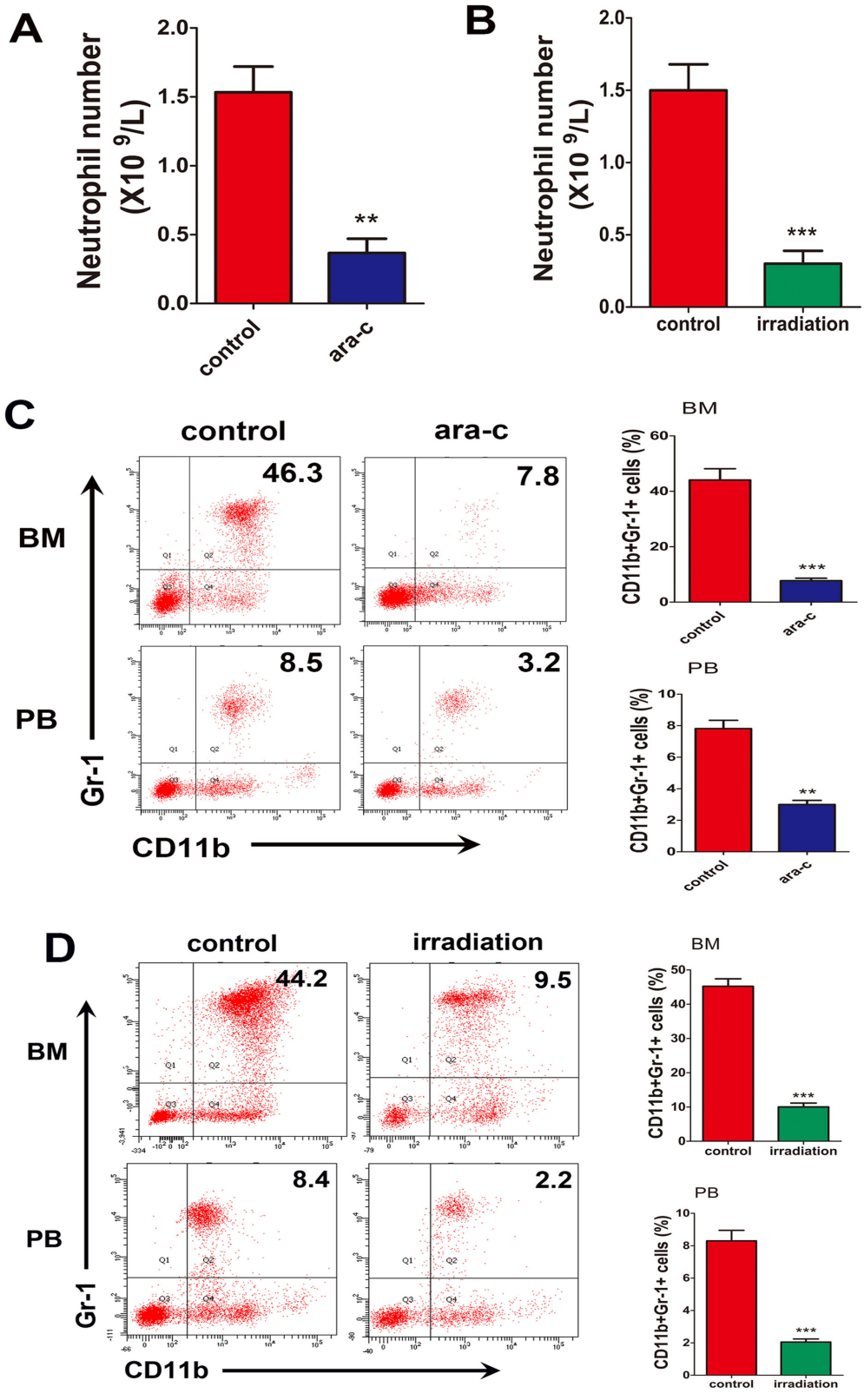

Fig. 1. ara-c or irradiation induced neutropenia. Bone marrow (BM) and peripheral blood (PB) were collected on day 11 after exposure to ara-c or day 16 after exposure to irradiation. (A) PB neutrophil count in ara-c and control mice (n=6). (B) PB neutrophil count in irradiation and control mice (n=6). (C) The percentages of BM and PB $CD11b^{+}Gr\text{-}1^{+}$ cells were analyzed by flow cytometry in ara-c and control mice (n=6). (D) The percentages of BM and PB $CD11b^{+}Gr\text{-}1^{+}$ cells were analyzed by flow cytometry in irradiation and control mice (n=6). Each experiment was repeated at least three times and data are expressed as mean±SD. $^{**}p<0.01$, $^{***}p<0.001$.

Quantitative RT-PCR

An RT-PCR kit (R123, Q341; Vazyme Biotech Co., Ltd., Nanjing, China) was used to extract RNA and complete the PCR procedure according to the manufacturer's directions. GAPDH was used as a control. The primer sequences were as follows: IL-14: forward, TATCTTTCTGCGTTGGAGATGGT; reverse, GCCCTGTGCTTTCAGGCATA (from Primer Bank) ; GAPDH: forward, AAATGGTGAAGGTCGGTGTGAAC; reverse,CAACAATCTCCACTTTGCCACTG (22).

Western Blotting

Western blotting was performed according to methods previously reported in the literature (22). GAPDH (#5174) (Cell Signaling Technology) and IL-14R antibody, obtained from Professor Ambrus (Washington University, USA), were used.

Enzyme-linked Immunosorbent Assay (ELISA)

The IL-14 concentration was measured using ELISA kits [MBS166857 for humansamples or MBS011250 for mouse samples, MyBioSource, San Diego, USA].

Clinical Samples

Serum samples were collected from patients with acute myelocytic leukemia (AML) before and after chemotherapy. Informed consent was obtained from all patients.The study protocols regarding human subjects were in line with the principles of the Declaration of Helsinki and were approved by the Clinical Research Ethics Committee of The Second Affiliated Hospital of Guangzhou Medical University.

Statistical Analysis

All experiments in this study were repeated three times. ANOVA was used for multiple comparisons; otherwise, Student's unpaired *t*-test was used for statistical analysis. Results were considered significant at $*p<0.05$, $**p<0.01$, and $***p<0.001$. All statistical analyses were performed using SPSS software version 25.0, and GraphPad Prism software 7.0.

RESULTS

ara-c and Irradiation Both Induce Neutropenia in Mice

To induce neutropenia, mice were exposed to ara-c or irradiation, respectively. Analysis using a whole-blood cell analyzer showed a significant decrease in neutrophil count in mice treated with ara-c and irradiation compared to the control group (Fig. 1A, 1B). Flow cytometric analysis revealed a sharp decrease in the percentage of $CD11b^{+}Gr\text{-}1^{+}$ cells in the PB and BM of mice treated with ara-c and irradiation (Fig. 1C, 1D). These results demonstrated that ara-c and irradiation can induce neutropenia.

ara-c and Irradiation Inhibit Proliferation of Promyelocytes in Neutropenic Mice

Next, we examined the mRNA levels of IL-14 in BM neutrophils and serum levels of IL-14 in mice with ara-c and irradiation-induced neutropenia and controls. Levels of IL-14 mRNA and serum were both significantly lower in mice with ara-c and irradiation-induced neutropenia than in the controls (Fig. 2A-2D). BM cells with EdU staining showed that the proliferation rate of $CD11b^{int}Gr\text{-}1^{int}$ cells (promyelocytes) sharply decreased in mice with ara-c and irradiation-induced neutropenia (Fig. 2E, 2F). This evidence demonstrated that ara-c and irradiation each inhibited the proliferation of promyelocytes in mice.

IL-14 Prevents ara-c or Irradiation Induced Neutropenia

We investigated the effect of IL-14 on ara-c or irradiation-induced neutropenia models. IL-14 increased the neutrophil count in mice treated with ara-cand irradiationd compared with ara-c or irradiation alone (Fig. 3A, 3B). Similarly, the frequency of $CD11b^{+}Gr\text{-}1^{+}$ cells in BM and PB significantly increased in cells treated with IL-14 (Fig. 3C, 3D).

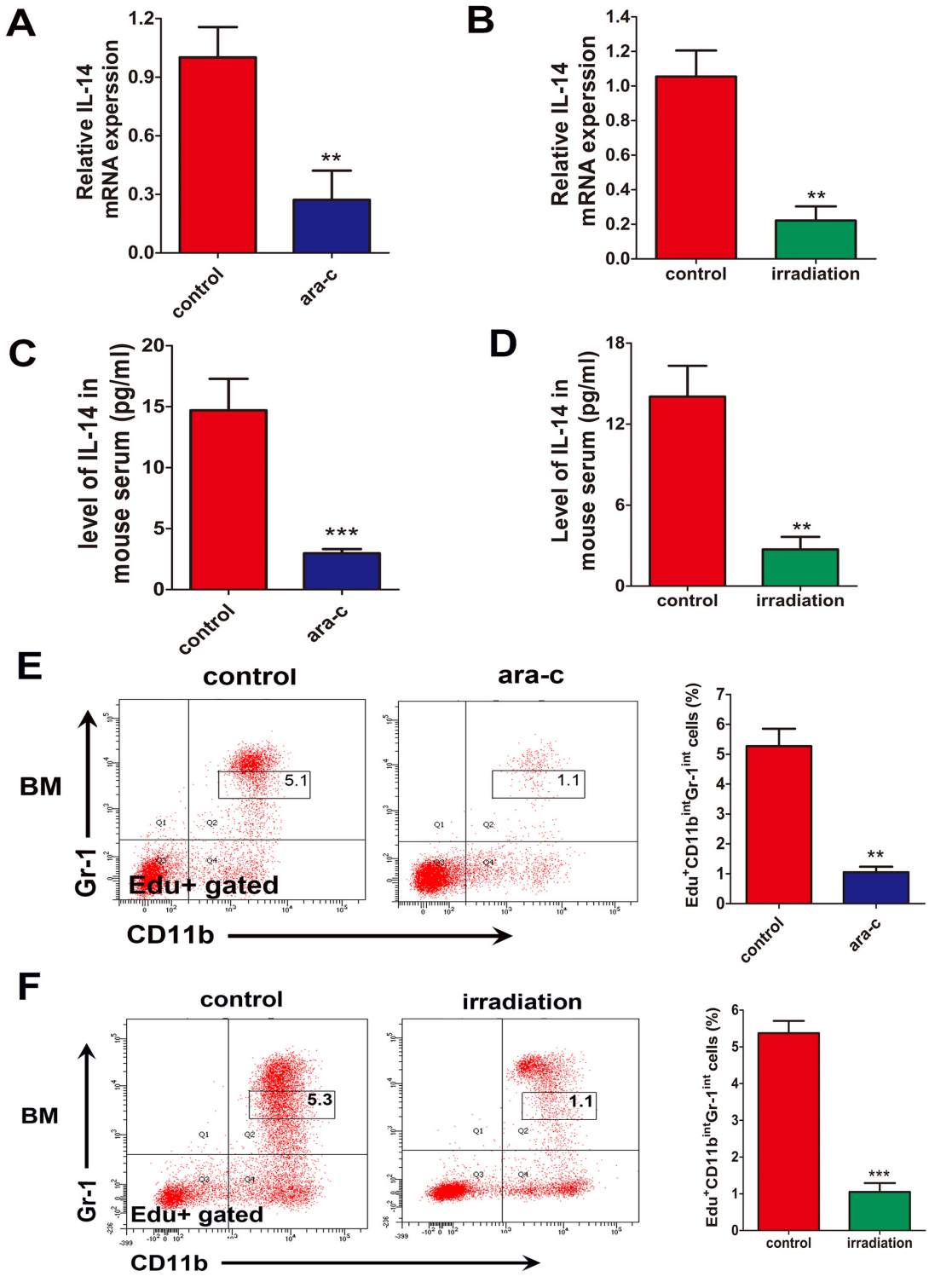

Fig. 2. ara-c or irradiation inhibits proliferation of promyelocytes in neutropenia. Bone marrow (BM) and peripheral blood (PB) were collected on day 11 after exposure to ara-c or day 16 after exposure to irradiation. (A) The IL-14 mRNA levels of BM cells from ara-c and control mice were examined by RT-PCR (n=6). (B) The IL-14 mRNA levels in BM cells from irradiation and control mice were examined by RT-PCR (n=6). (C) Levels of IL-14 in the serum of ara-c and control mice were examined by ELISA (n=6). (D) IL-14 serum levels in irradiation and control mice were examined by ELISA (n=6). (E) Flow cytometry analysis of the proliferation rate of $CD11b^{int}Gr\text{-}1^{int}$ cells in the BM from ara-c and control mice (n=6). (F) Flow cytometry analysis of the proliferation rate of $CD11b^{int}Gr\text{-}1^{int}$ cells in the BM of irradiation and control mice (n=6). Each experiment was repeated at least three times and data are expressed as mean±SD. $^{**}p<0.01$, $^{***}p<0.001$.

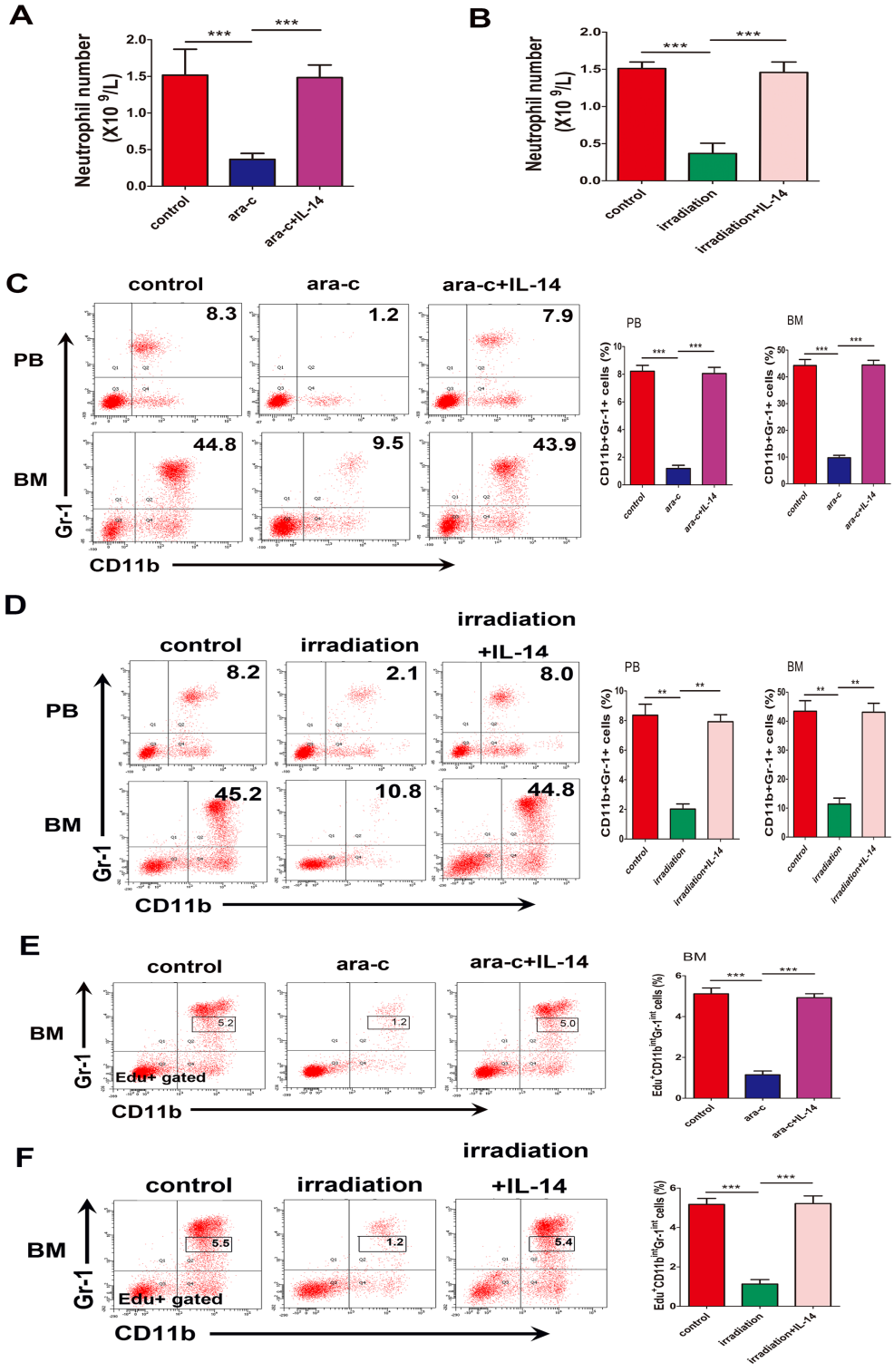

Fig. 3. IL-14 prevents ara-c or irradiation induced neutropenia. (A) Mice were intraperitoneally injected with ara-c followed by IL-14 injection 24 hours later. Neutrophil count in peripheral blood (PB) was measured on day 11 (n=6). (B) Irradiated mice were intraperitoneally injected with IL-14 for 15 days. PB neutrophil counts were measured on day 16 (n=6). (C) Flowcytometry analysis was used to determinethe percentages of bone marrow (BM) and PB $CD11b^{+}Gr\text{-}1^{+}$ cells were d by flow cytometry in the BM and PB of treated mice (n=6). (D) Flowcytometry analysis was used to determine the percentages of $CD11b^{+}Gr\text{-}1^{+}$ cells in the BM and PB (n=6). (E) The proliferation rate of $CD11b^{int}Gr\text{-}1^{int}$ cells in the BM was analyzed using flow cytometry (n=6). (F) The percentage of $Edu^{+}CD11b^{int}Gr\text{-}1^{int}$ cells in the BM was determined using flow cytometry (n=6). Each experiment was repeated at least three times and data are expressed as mean±SD. **p<0.01, ***p<0.001.

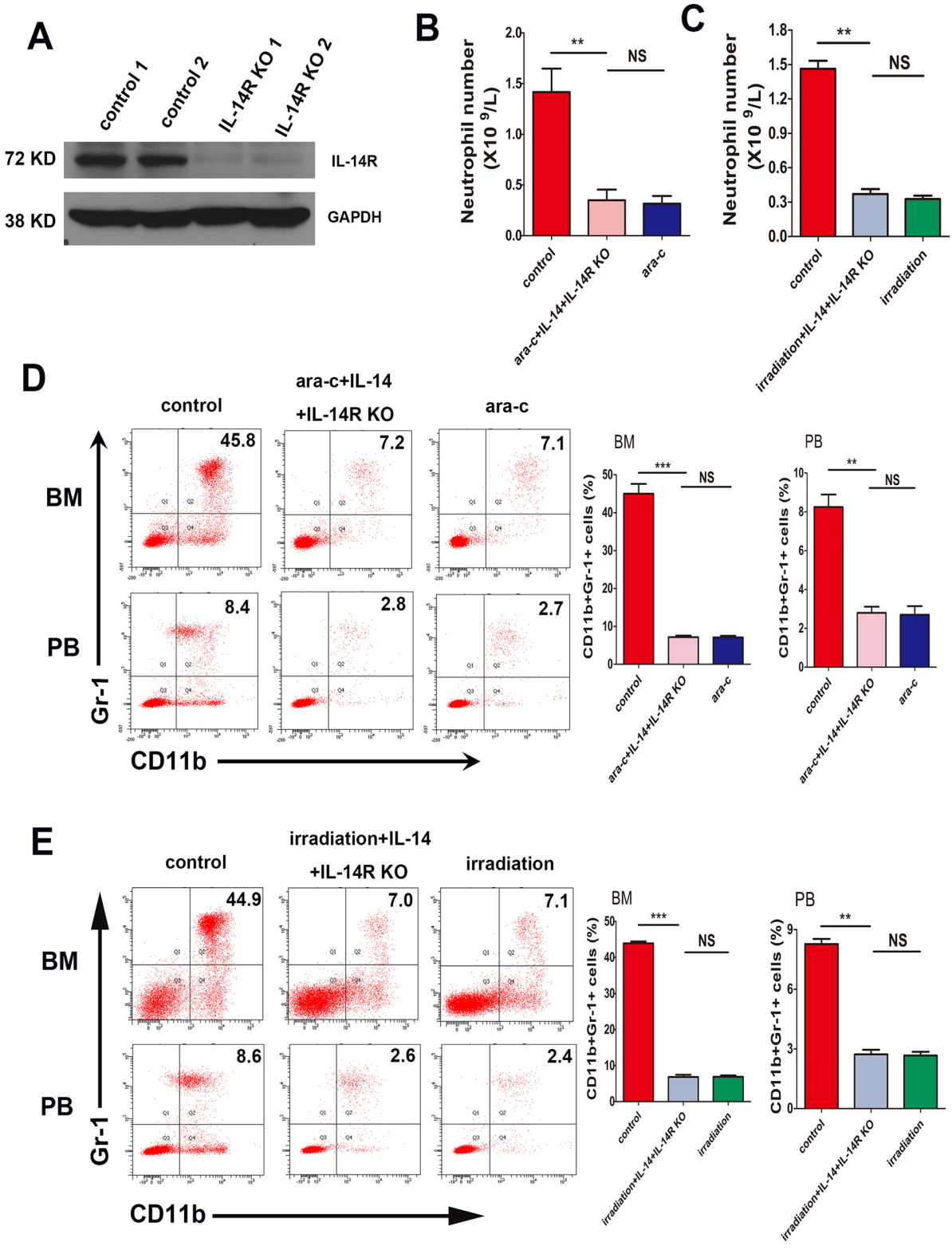

Fig. 4. IL-14 prevents ara-c or irradiation induced neutropenia via IL-14R. (A) Identification of knockout effects of IL-14R in bone marrow (BM) cells examined by western blot. GAPDH served as a loading control. (B) Peripheral blood (PB) neutrophil counts in mice treated with ara-c (n=6). (C) PB neutrophil counts in mice treated with radiation (n=6). (D) The percentage of $CD11b^{+}Gr\text{-}1^{+}$ neutrophils was analyzed by flow cytometry in the BM and PB of mice treated with ara-c (n=6). (E) The percentage of $CD11b^{+}Gr\text{-}1^{+}$ neutrophils was analyzed by flow cytometry in the BM and PB of irradiated mice (n=6). Each experiment was repeated at least three times and data are expressed as mean±SD. $^{**}p<0.01$, $^{***}p<0.001$. NS represents no significant difference.

The proliferation inhibition of CD11b^{int}Gr-1^{int} cells (promyelocytes) was almost completely reversed with IL-14 treatment (Fig. 3E, 3F). These findings indicated that IL-14 reversed ara-c– and irradiation-induced neutropenia.

IL-14 Prevents ara-c and Irradiation Induced Neutropenia through IL-14R

IL-14 can signal through IL-14R and activate STAT3. We studied the impact of IL-14 on neutropenia by using IL-14R knockout in mice with ara-c– and irradiation-induced neutropenia. IL-14R knockout suppressed the expression of IL-14R (Fig. 4A) and entirely eliminated the therapeutic benefits of IL-14 on ara-c- and irradiation-induced neutropenia (Fig. 4B–4E). These findings indicate that IL-14 prevents ara-c- and irradiation-induced neutropenia through IL-14R.

IL-14 Prevents ara-c- and Irradiation-induced Neutropenia by Activating the IL-14R/STAT3 Pathway

We then investigated how IL-14 was

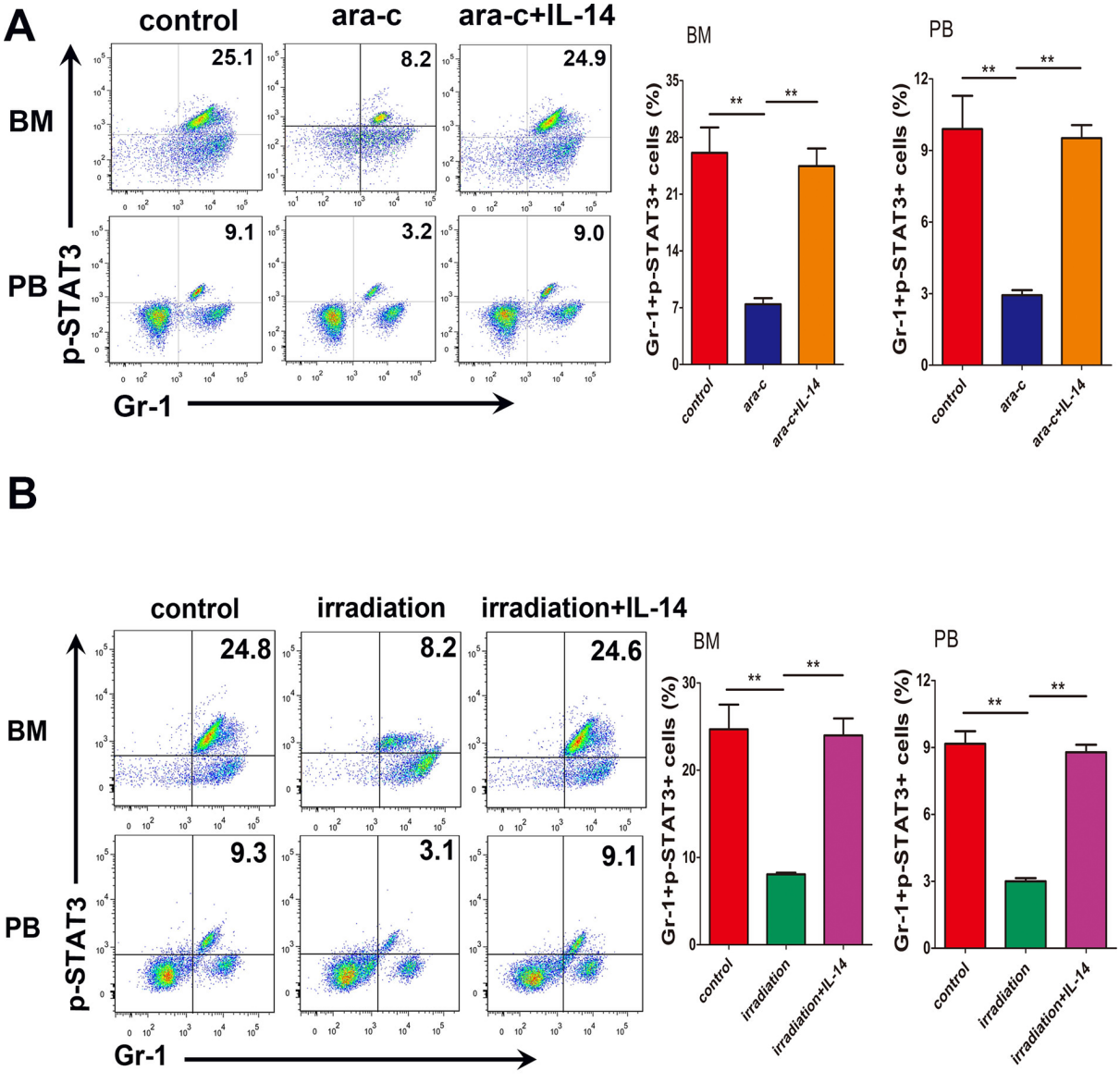

Fig. 5. IL-14 prevents ara-c or irradiation induced neutropenia by activating STAT3. (A) Percentages of Gr-1^{+}p-STAT3^{+} cells analyzed by flow cytometry in the bone marrow (BM) and peripheral blood (PB) of mice treated with ara-c or ara-c+IL-14 (n=6). (B) Percentages of Gr-1^{+}p-STAT3^{+} cells analyzed by flow cytometry in the BM and PB of mice treated with radiation or radiation+IL-14 (n=6). Each experiment was repeated at least three times and data are expressed as mean±SD. **p<0.01, ***p<0.001.

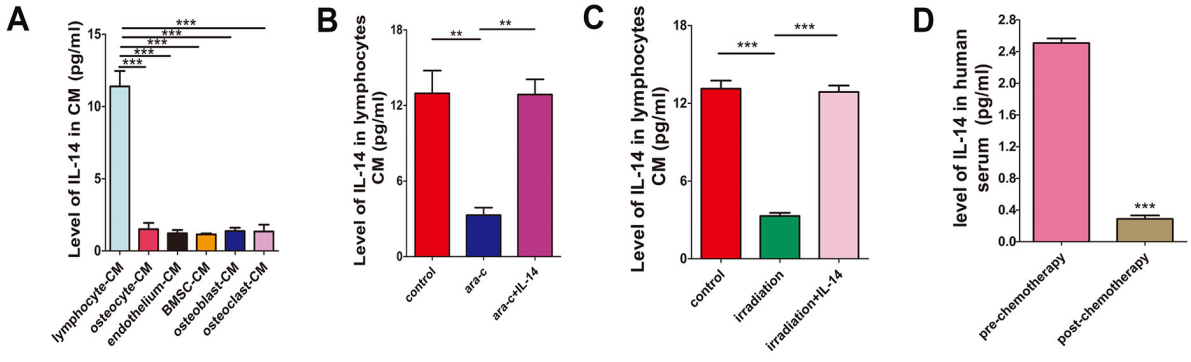

Fig. 6. IL-14 prevents ara-c or irradiation induced neutropenia via regulating lymphocytes in bone marrow (BM). (A) Conditioned medium (CM) from osteocytes, BMSCs, osteoclasts, lymphocytes, osteoblasts, and endothelial cells of C57BL/6 mice were obtained to measure IL-14 levels by ELISA (n=6). (B) The CM from the lymphocytes was obtained to measure IL-14 levels by ELISA (n=6). (C) The CM from the lymphocytes was obtained to measure IL-14 levels by ELISA (n=6). (D) IL-14 serum levels in patients before and after chemotherapy with ara-c (n=30). Each experiment was repeated at least three times and data are expressed as mean±SD. **p<0.01, ***p<0.001.

involved in neutropenia, specifically its impact on p-STAT3 expression. Levels of p-STAT3 in BM cells increased with IL-14 treatment compared to treatment with ara-c or irradiation alone. The proportion of Gr-1^+p-STAT3^+ cells was also higher with IL-14 treatment (Fig. 5A, 5B). These findings indicate that IL-14 prevents ara-c and irradiation-induced neutropenia by activating the IL-14R/STAT3 pathway.

IL-14 Prevents ara-c- and Irradiation-induced Neutropenia by Regulating Lymphocytes in the BM

We explored the origin of IL-14 inthe BM. Among osteocytes, BMSCs, osteoblasts, lymphocytes, osteoclasts, and endothelial cells, lymphocytes secreted the highest level of IL-14 (Fig. 6A). IL-14 produced by lymphocytes sharply decreased withara-c or irradiation treatment, and IL-14 accelerated the recovery of lymphocytes (Fig. 6B, 6C). These findings demonstrate that IL-14 prevents ara-c and irradiation-induced neutropenia by regulating lymphocytes. Finally, we investigated the serum IL-14 levels in patients before and after chemotherapy, and the level of serum IL-14 decreased in post-chemotherapy patients (Fig. 6D). These results further indicate that IL-14 effectively prevents ara-c or irradiation-induced neutropenia.

DISCUSSION

As is well known, chemotherapy and radiation therapy are the primary treatments for cancer, with neutropenia being the most common limiting toxic side effect of these therapies (24). While there are several drugs clinically used for neutropenia, they all come with varying degree of side effects (25-28). Therefore the search for new and more effective treatments is an urgent issue. Recent studies have shown that IL-14 plays a significant role in immunity (29-33), yet its potential role in neutropenia induced by ara-c or irradiation remains unclear. In this study, we observed the protective effects of IL-14 against ara-c and irradiation induced neutropenia in a mouse model. Our in vivo and in vitro evidence suggests that lymphocytes in the bone marrow play a crucial role in supporting CD11b$^+$Gr-1^+ cell expansion and neutrophil formation through the production of IL-14 and activation of IL-14R/STAT3 signaling. This underscores the important contribution of lymphocyte-produced IL-14 to neutrophil formation. This evidence indicates that IL-14 is a potent cytokine for treating ara-c or irradiation induced neutropenia.

IL-14 is a high molecular weight B-cell growth factor that is produced by B cells, T cells, and dendritic cells (16). Although first

reported in 1985, the role of IL-14 has not been fully clarified. Several human diseases and animal models suggest a role for IL-14 in conditions such as psoriasis, periodontitis, thyroiditis, pulmonary fibrosis, and acute pancreatitis (29-33). Despite the current lack of genetic IL-14 ablation effects on neutrophil development, our results clearly show that IL-14, secreted primarily by lymphocytes, stimulates $CD11b^{+}Gr\text{-}1^{+}$ cell expansion and neutrophil formation in vivo and in vitro, highlighting its role in innate immunity. IL-14 acts through the IL-14R. Although IL-14R has been shown to be expressed on the surface of several tumor cells as well as on the surface of peripheral blood lymphocytes in primary desiccation syndrome (17, 18, 34), there are some important questions that need to be addressed. In particular the nature of the IL-14 receptor and its paradoxical function on immune cell development and tumor regulation need further clarification. Some researchers successfully constructed an IL-14α transgenic mouse model to verify the function of the IL-14α gene in autoimmune development, . They found that most IL-14α transgenic mice developed B-cell malignant lymphoma (19). After measuring serum IL-14α expression in lymphoma patients before and after treatment, researchers observed a sharp decrease in IL-14α expression in the serum of patients after treatment (35). The expression of IL-14α mRNA has been identified in high-grade B-cell tumors in vivo, and IL-14 antisense oligonucleotides have been shown to inhibit these tumors in vitro (36). A previous report demonstrated that IL-14α is highly expressed in several super-refractory human blastoid-variant mantle-cell lymphoma (MCL-BV) cell lines (Jeko-1, Mino, DB, JMP1,Z138C), as well as in primary MCL-BV cells (37). It is suggested that IL-14α plays an important role in the rapid proliferation of MCL-BV cells and B-cell non-Hodgkinlymphomas (NHL-B). These data suggest that IL-14 and IL-14R have an important role in lymphoid tumorigenesis. Blocking the pathway of IL-14 and/or IL-14R may be a useful target for treating patients resistant to conventional chemotherapy.

The main clinical modalities for treatingneutropenia today are antibiotics and granulocyte colony-stimulating factor (G-CSF) (38, 39). Administration of Bone marrow growth factors (e.g., G-CSF) is the only approved treatment for preventing neutropenia. However, their expensive cost, limited indications, and high number of side effects , such as infections restrict their use (40). Therapeutic strategies and novel drugs are therefore urgently needed. Our results indicate that IL-14 supports neutrophil development. In conclusion, the current study suggests that IL-14 prevents ara-c and irradiation induced neutropenia by stimulating the IL-14R/STAT3 pathway. These results provide further evidence supporting the role of IL-14 as a promising therapeutic agent for the treatment of neutropenia.

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AUTHORS' CONTRIBUTION

S.X. and M.X. designed the experiment. S.X., C.Y. and Z.W. conducted the cell experiments. C.W. and W.H. carried out the mouse experiments. C.D. helped to collect the data, and J.H., W.X.,and M.X. conceived the project and drafted the paper.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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