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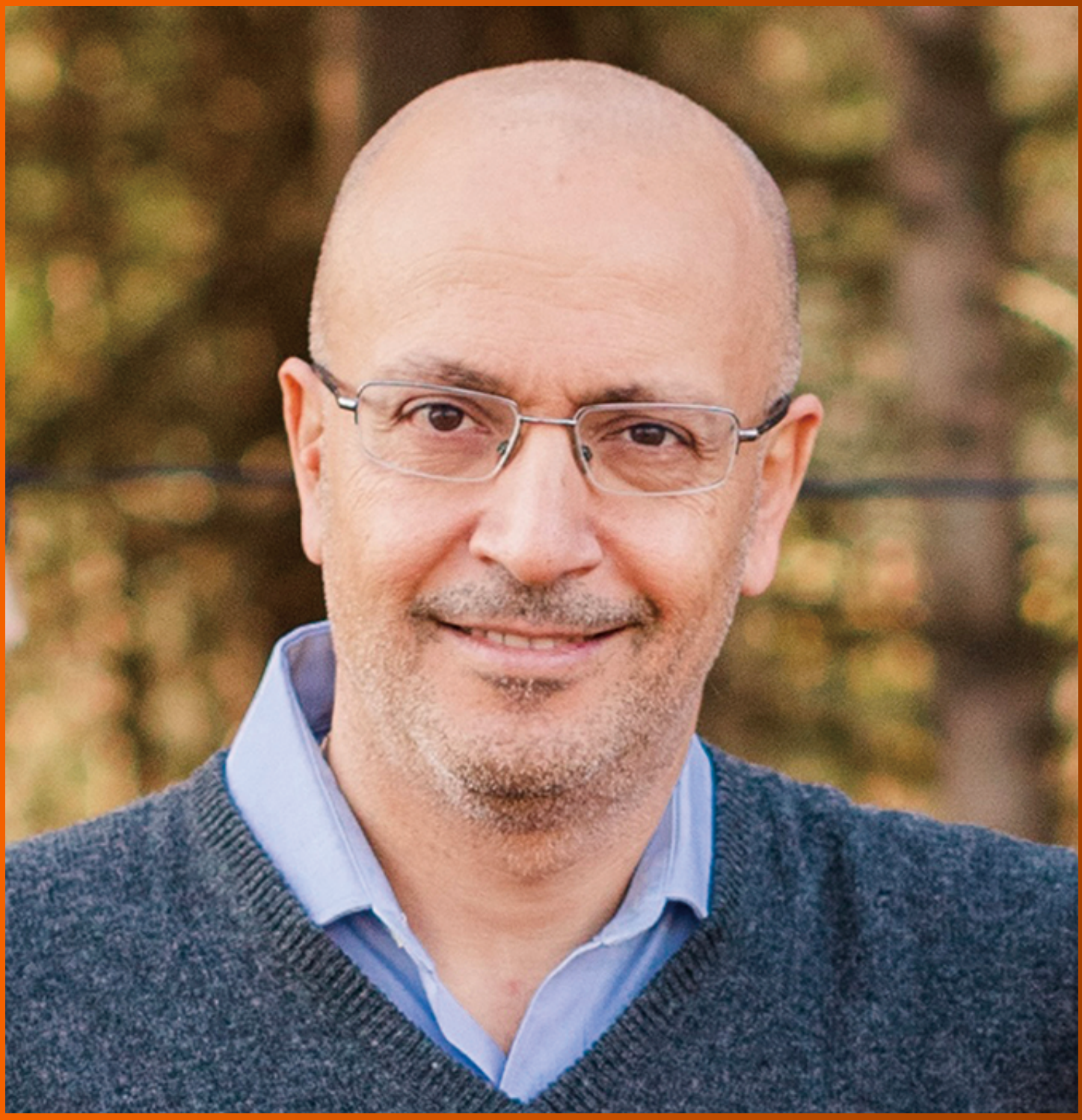

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ORIGINAL ARTICLE

Observational Study

Effect of T-regulatory cells and interleukin-35, interleukin-10, and transforming growth factor-beta on diffuse large B-cell lymphoma

Hao Wu, Hui-Cong Sun, Gui-Fang Ouyang

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Abstract

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma that affects B lymphocytes. It can develop in the lymph nodes and can be localized or generalized. Despite DLBCL being considered potentially curable, little research has been conducted on the relationship between the body's immune response and DLBCL.

AIM

To study the expression and significance of T-regulatory cells (Tregs) interleukin (IL)-35, IL-10, and transforming growth factor-beta (TGF-β) in DLBCL.

METHODS

Data from 82 patients with DLBCL who were initially admitted to The First Affiliated Hospital of Ningbo University (Zhejiang Province, China) between January 2017 and June 2022 and treated with standard first-line regimens were reviewed. Three patients were lost to follow-up; thus, 79 patients were included in the statistical analysis and then divided into three groups according to the evaluation of clinical efficacy: Incipient (new-onset and treatment-naïve), effectively treated, and relapsed-refractory. Thirty healthy individuals were included in the control group. The expression of peripheral blood T lymphocytes and their associated factors IL-35, IL-10, and TGF-β in the four groups were observed.

RESULTS

In contrast to the successfully treated and normal control groups, both the incipient and relapse-refractory groups exhibited greater proportions of CD4-positive (+) Tregs ($P < 0.05$), whereas the proportion of CD8+ Tregs did not differ

substantially between the groups. Serum levels of IL-35 and IL-10 in the incipient and relapsed-refractory groups were higher than those in the effectively treated and normal control groups ($P < 0.05$). There was no statistically significant distinction in the expression level of TGF-β between the groups ($P > 0.05$). The correlation between IL-35 and IL-10 concentrations was significantly positive, with a correlation coefficient of 0.531 ($P < 0.05$). The correlation between IL-35 and TGF-β concentration was significantly positive, with a correlation coefficient of 0.375 ($P < 0.05$). The correlation between IL-10 and TGF-β concentration was significantly positive, with a correlation coefficient of 0.185 ($P < 0.05$). The expression concentrations of IL-35, IL-10 and TGF-β were apparently and positively correlated ($P < 0.05$).

CONCLUSION

Tregs IL-35, and IL-10 may be closely associated with the occurrence and development of DLBCL and the detection of related indices may be helpful in the analysis of disease prognosis.

Key Words: Diffuse large B-cell lymphoma; T-regulatory cells; Interleukin-35; Interleukin-10; Transforming growth factor-beta; Immune response

Core Tip: To study the expression and significance of T-regulatory cells (Tregs) interleukin (IL)-35, IL-10, and transforming growth factor-beta (TGF-β) in diffuse large B-cell lymphoma (DLBCL). Seventy-nine patients were enrolled and divided into three groups according to the evaluation of clinical efficacy: Incipient, effectively treated, and relapsed-refractory. Thirty healthy individuals comprised the control group. The expression of Tregs and their associated factors IL-35, IL-10, and TGF-β in the four groups were analyzed. Finally, we found that Tregs, IL-35, and IL-10 are closely associated with the occurrence and development of DLBCL, which may be helpful in the analysis of disease prognosis.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a malignant tumor of the lymphohematopoietic system with high aggressiveness, rapid growth, and clear heterogeneity in clinical presentation, morphological features, immunological phenotypes, and molecular genetic characteristics. DLBCL is the most common type of non-Hodgkin lymphoma (NHL) in China, accounting for approximately 30%–40% of NHL cases among adults[1]. The etiology of DLBCL is complex and diverse, although it is generally believed that environmental and genetic factors contribute significantly to its pathogenesis[2]. In recent years, the concept that immune regulatory disorders may cause DLBCL has attracted increasing attention[2]. However, little is known about its pathogenesis.

The immune response is negatively regulated by a subset of lymphocytes known as T-regulatory cells (Tregs), which also aid in the immunological surveillance of the body and persistent tumor cell infection. These factors are crucial for preserving self-tolerance and preventing excessive immune damage. Regulatory cells (Tregs) have been a focus of interest in oncology research, and recent studies have reported correlations between Treg expression levels and various solid and hematological tumors, including leukemia"[3,4].

Interleukin (IL)-35 is a member of the IL-12 family and plays an important role in immunosuppression. It is a dimeric protein consisting of the IL-12α and IL-27β chains, encoded, respectively, by two independent genes, *IL-12A* and *EBI3*. IL-35, produced by Treg secretion, suppresses inflammatory responses in immune cells[5]. In contrast to the other known members of the IL-12 family, T cells do not express IL-35. Instead of engaging in immunostimulatory or proinflammatory activities, Tregs secrete IL-35 and contribute to its inhibitory action. IL-35 is primarily released by Tregs, but it is also produced by other cell groups with regulatory potential. It represents a novel potential target for regulating Treg behavior and treating autoimmune and cancerous diseases[6].

However, few studies have investigated the exact mechanism(s) of action of Tregs and their associated cytokines in DLBCL. As such, this study investigated the pathogenesis of Tregs and cytokines in DLBCL and assessed their clinical correlation by simultaneously comparing the expression levels of Tregs and related factors between patients with DLBCL and healthy individuals examined simultaneously.

MATERIALS AND METHODS

Clinical data

Among the 82 patients with DLBCL, 3 were lost to follow-up, and 79 patients were included in the statistical analysis, including 53 males and 26 females, with a median age of 39 years (range, 18–77 years), who visited The First Affiliated Hospital of Ningbo University (Zhejiang Province, China) and were confirmed by the pathology center between January 2017 and June 2022. All patients had complete data, and their diagnoses were confirmed by pathological tissue biopsy and/or immunohistochemical marker staining, with diagnostic criteria based on the 2016 World Health Organization lymphoma classification criteria[7]. Ann Arbor staging was performed based on imaging and bone marrow findings. Risk stratification for all patients was based on clinical data, including International Prognostic Index (IPI), age-adjusted IPI, presence of B symptoms (persistent fever > 38 °C for > 3 d without an infectious cause; weight loss ≥ 10% within 6 mo; night sweats), bone marrow aspiration smear results, cervicothoracic, abdominal, and pelvic computed tomography and/or magnetic resonance imaging findings, extranodal involvement, treatment, recurrence, and metastasis. All patients were followed up from the date of diagnosis to October 2022 as inpatients, outpatients, or *via* telephone interviews, and three patients were lost (loss ratio of follow-up, 3.8%), with a median follow-up of 30 mo (range, 3–60 mo). Clinical data were collected during the pre-treatment period, and the follow-up content was determined mainly based on patient involvement at the time of initiation and relevant abnormal laboratory investigations. Patients were divided into three groups according to the evaluation of clinical efficacy: Incipient (new-onset and treatment-naïve), effectively treated, and recurrent-refractory. Thirty healthy individuals comprised the normal (healthy) control group. The hospital's medical ethics committee approved the informed consent form, which was signed by all patients and those in the control group.

Efficacy evaluation

All patients started treatment with R-CHOP or a similar first-line treatment regimen. According to the National Comprehensive Cancer Network (NCCN) lymphoma guidelines for efficacy determination, patients were evaluated for efficacy after every two regular chemotherapy sessions and again after every two subsequent courses of treatment, which were classified as complete response (CR), CR unconfirmed (CRu), partial response (PR), stable disease, progressive disease, and relapse (those who had achieved CR/CRu in the previous period). The first three classifications were considered effective, whereas the latter three were considered ineffective.

According to the criteria for determining efficacy in the NCCN lymphoma guidelines for NHL, patients who achieved CR after treatment were defined as the effectively treated group (n = 45). The two categories of patients who were unable to achieve CR, CRu, or PR after treatment and those who developed a new site of involvement or progressed to > 50% of the original site after achieving CR or PR were defined as the relapse-refractory group (n = 34).

Assay methods

Approximately 5 mL of heparin-anticoagulated venous blood was drawn from each group of fasted subjects; one was centrifuged at 1500 r/min to obtain serum, and the other was centrifuged using a Ficoll-paque density gradient method to isolate peripheral blood single nuclei cells, and stored at -80°C, and thawed just once before use to prevent deterioration. Expression levels of the cytokines IL-35, IL-10, and TGF-β in the serum were measured using ELISA. Levels of CD4-positive (+), CD8+, and Tregs among single-nucleated cells were measured using flow cytometry. All procedures were performed according to the manufacturer's instructions. Standard curves were prepared using an enzyme marker as required for analysis.

Statistical methods

McDonald reported that analysis of variance (ANOVA) remains robust to skewed data and that Welch's ANOVA test results are more accurate if the variance is not homogeneous[8]. Comparisons of variance and correlations were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, United States). Analysis of variance (ANOVA) was used for chi-square comparisons between groups, whereas the least significant difference method was used for multiple comparisons. Welch's ANOVA was used for multiple comparisons with the Games-Howell test for variance dissimilarity. Differences with $P < 0.05$ were considered to be statistically significant.

RESULTS

Serum expression levels IL-35, IL-10 and TGF-β across subgroups

Serum expression levels of IL-35 and IL-10 in the incipient and relapsed-refractory groups were higher than those in the effectively treated and normal control groups ($P < 0.05$). There was no statistically significant difference between the incipient and relapsed-refractory groups ($P > 0.05$). Additionally, there was no statistically significant distinction in the expression level of TGF-β between the groups ($P > 0.05$). Further details are summarized in Table 1.

Comparisons revealed significant differences in the concentrations of IL-35 and IL-10 between the groups ($P < 0.05$). According to multiple comparisons, the expression levels of IL-35 and IL-10 were higher in the incipient and relapse-refractory groups than in the groups with effective therapy and normal control groups.

Pearson's correlation analysis was used to examine the concentrations of the three cytokines. Based on these results, the correlation between IL-35 and IL-10 concentrations was significantly positive, with a correlation coefficient of 0.531 ($P < 0.05$). The correlation between IL-35 and TGF-β concentration was also significantly positive, with a correlation coefficient

Table 1 Serum expression levels of interleukin (IL)-35, IL-10, transforming growth factor beta across the subgroups

Group	*n*	IL-35 (pg/mL)	IL-10 (pg/mL)	TGF-β (pg/mL)
Incipient	79	166.79 ± 132.69	38.31 ± 30.92	653.3 ± 610.26
Effectively treated	45	115.8 ± 81.47	26.55 ± 18.75	602.5 ± 709.82
Relapse-refractory	34	234.29 ± 156.62	53.87 ± 36.79	720.54 ± 447.53
Control	30	107.34 ± 66.6	24.57 ± 20.25	416.69 ± 339.78
F value		8.47[c]	7.562[c]	1.686
P value		< 0.001	< 0.001	0.172
Multiple comparison		Expression levels of IL-35 in both the incipient and relapsed-refractory groups were higher than those in the effectively treated and normal control groups	Expression levels of IL-10 in the incipient and relapse-refractory groups were higher than effective therapy and normal control groups	/

[c]Indicates the use of Welch's analysis of variance (*i.e.*, McDonald reported that analysis of variance) test.
Data presented mean ± SD unless otherwise indicated. IL-35: Interleukin-35; IL-10: Interleukin-10; TGF-β: Transforming growth factor beta.

of 0.375 ($P < 0.05$). Similarly, the correlation between IL-10 and TGF-β concentration was significantly positive, with a correlation coefficient of 0.185 ($P < 0.05$). The expression concentrations of IL-35, IL-10 and TGF-β were evidently and positively correlated between the two ($P < 0.05$). Further details are presented in Table 2.

Comparison of the proportions of CD4+, CD8+, and Tregs across subgroups

Based on the results of multiple comparisons, the proportions of CD4+ cells and Tregs in the incipient and relapse-refractory groups were significantly higher ($P < 0.05$). However, the proportion of CD8+ Tregs did not differ substantially between the groups. ($P > 0.05$) (Table 3).

DISCUSSION

DLBCL is a malignant tumor of the lymphohematopoietic system that can affect the entire body and is the predominant type of NHL among the Chinese population, accounting for approximately 30%-40% of cases[1]. Tumor tissues are often extremely aggressive, with significant heterogeneity in their clinical presentation, morphological features, immunological phenotypes, and molecular genetic characteristics. DLBCL can occur at any age, and its incidence tends to increase with advancing age, with a slightly higher incidence in males than in females. The specific pathogenesis of DLBCL remains under investigation, and the hypothesis that it is caused by an immune disorder has attracted attention[2].

Tregs are a subset of suppressor T cells that regulate immune function in the body and play a crucial role in maintaining autoimmune tolerance and immune homeostasis, thereby maintaining the tolerance of the immune system to its own components. Elevated Treg percentages have been observed in patients with Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, and acute leukemia[9,10]. Some studies have reported that the percentage of Tregs is increased in cancer patients and that tumor cells can produce Tregs to suppress the onset of immune responses in the antitumor microenvironment, thereby reducing the effectiveness of cancer immunotherapy[11]. In addition, it has been reported that CD4+ and CD8+ Treg cell pools are disrupted in patients with B-cell NHL[12]. However, the mechanism of action has not yet been fully elucidated. Analysis of CD4+ and CD8+ Tregs in single-nucleated cells extracted from blood samples of different groups of patients using flow cytometry revealed that the proportion of CD4+ Tregs increased in the incipient and relapsed-refractory groups, whereas the proportion of CD8+ Tregs without distinction and the proportion of Tregs decreased as the disease improved, suggesting that Tregs may play a role in the pathogenesis and progression of DLBCL.

Some studies have shown that DLBCL tumor cells overexpress IL-35[5]. In this study, we found that the serum concentrations of IL-35 and IL-10 were significantly higher in the incipient and relapsed-refractory groups of patients with DLBCL than in the effectively treated and normal control groups. IL-35 levels were elevated in the incipient and relapsed-refractory states, while its expression was lower in the effectively treated and normal controls, indicating that the measurement of IL-35 concentration may be a valuable indicator in the assessment of treatment efficacy, which is consistent with the results of the above study. Further research is required to determine the utility of IL-35 or its specific combination with other Tregs for patient diagnosis and treatment efficacy.

It has been established that IL-10 can curb the production of cytokines by T cells and exerts anti-inflammatory effects as well as immunosuppressive activity, by suppressing IL-2, interferon-gamma and granulocyte-macrophage colony stimulating factor (GM-CSF) and proliferation response of T-helper (Th) cells[13]. IL-10 has been shown to proliferate in

Table 2 Correlation analysis of interleukin (IL)-35, IL-10, transforming growth factor beta concentration

Cytokine	IL-35	IL-10	TGF-β
IL-35	1		
IL-10	0.531[b]	1	
TGF-β	0.375[a]	0.185[a]	1

[a]$P < 0.05$.

[b]$P < 0.01$. IL-35: Interleukin-35; IL-10: Interleukin-10; TGF-β: Transforming growth factor beta.

Table 3 Comparison of the percentage of CD4+, CD8+ and T-regulatory cells across the different subgroups

Group	*n*	CD4+	CD8+	Tregs
Incipient	79	32.67 ± 11.11	39.26 ± 9.06	6.32 ± 3.21
Effectively treated	45	28.63 ± 4.07	38.59 ± 9.14	5.1 ± 2.02
Relapse-refractory	34	38.01 ± 14.76	40.15 ± 9.00	7.95 ± 3.76
Control	30	26.15 ± 5.84	37.14 ± 8.14	4.11 ± 2.26
F value		9.439[c]	0.671	10.736[c]
P value		< 0.001	0.571	< 0.001
Multiple comparison		The proportion of CD4+ cells was higher in the incipient and relapsed-refractory groups than in the effectively treated and normal control groups.	/	The proportion of Tregs was higher in the incipient and relapsed-refractory groups than in the effectively treated and normal control groups.

[c]Indicates the Welch's analysis of variance.

Data presented as mean ± SD (%), unless otherwise indicated.

Tregs: T-regulatory cells.

acute myeloid leukemia cells by inhibiting cytokines, such as IL-1α, IL-1β, G-CSF, GM-CSF, IL-6, and tumor necrosis factor-alpha and boosting their production of IL-1ra[14]. Consistent with the high serum expression of IL-35, our study also demonstrated that the expression levels of serum IL-10 were significantly elevated in patients with both incipient and relapsed-refractory DLBCL compared with those in the effective treatment and normal control groups, which is consistent with the aforementioned study. More research is required to address this issue. However, it's important to note that the *in vitro* effect of IL-10 does not always correspond to its *in vivo* effect, and the mechanisms of action may vary among different disorders.

Regarding the occurrence and growth of tumors, TGF-β has a dual function as a tumor suppressor that inhibits cell proliferation and stimulates apoptosis during the development of normal and cancerous cells. However, in the late development stages of tumors, TGF-β becomes a tumor-promoting factor capable of inducing epithelial-mesenchymal transition and promoting the invasion and metastasis of tumor cells[15]. Tumor metastasis is an important cause of death in cancer patients, with up to 90% of patients with solid tumors dying from tumor metastasis.

Immune response is a complex process involving multiple cellular pathways and receptors. Whether the pathological process of DLBCL involves other immune cells, such as natural killer cells and cytokines has not been known, needs to be proven in subsequent experiments. Moreover, the study did not include patients from other institutions. Therefore, further studies are warranted in this regard.

CONCLUSION

We demonstrated elevated serum concentrations of IL-35 and IL-10 and an elevated percentage of Tregs in treatment-naïve DLBCL patients (*i.e.*, incipient group) and DLBCL patients with suboptimal outcomes (*i.e.*, relapse-refractory group), indicating their possible involvement in the pathophysiological processes of the disease and the possibility of providing a potential approach for the treatment, disease assessment, and prognosis of DLBCL.

ARTICLE HIGHLIGHTS

Research background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide, representing approximately 30%–40% of all NHL cases in different geographic regions. Although the pathogenesis of DLBCL is obscure, causes of DLBCL have attracted increasing attention; immune regulatory disorders may be one of them."

Research motivation

We aimed to explore the effect of T-regulatory cells (Tregs) interleukin (IL)-35, IL-10, and transforming growth factor-beta (TGF-β) on DLBCL, which may be helpful in the analysis of disease prognosis.

Research objectives

Expression levels of the IL-35, IL-10, and TGF-β cytokines in the serum and levels of CD4-positive (+), CD8+, and Tregs among single-nucleated cells were measured to analyze their correlation with DLBCL.

Research methods

Seventy-nine patients were included in the statistical analysis and divided into three groups according to the evaluation of clinical efficacy: incipient (new-onset and treatment-naïve), effectively treated, and relapsed-refractory. Thirty healthy individuals were included in the control group. The expression of peripheral blood T lymphocytes and their associated factors IL-35, IL-10, and TGF-β in the four groups were observed.

Research results

In contrast to the successfully treated and normal control groups, both the incipient and relapse-refractory groups exhibited greater proportions of CD4-positive (+) Tregs ($P < 0.05$), whereas the proportion of CD8+ Tregs did not differ substantially between the groups. Compared to the effectively treated and normal control groups, the incipient and relapsed-refractory groups exhibited higher serum levels of IL-35 and IL-10 ($P < 0.05$), although the differences were not statistically significant ($P > 0.05$). There was no statistically significant distinction in the expression level of TGF-β between the groups ($P > 0.05$).

Research conclusions

We demonstrated elevated serum concentrations of IL-35 and IL-10 and an elevated percentage of Tregs in treatment-naïve DLBCL patients and DLBCL patients with suboptimal outcomes, which may be closely associated with the occurrence and development of DLBCL.

Research perspectives

Our study highlights the possible pathophysiological processes of DLBCL and provides a potential approach for the treatment, disease assessment, and prognosis of DLBCL.

FOOTNOTES

Author contributions: Wu H designed and performed the research and wrote the article, Sun HC edited the article, Ouyang GF supervised the article.

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