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Effects of regulatory B-cells on intracranial aneurysms by mediating IL-1β/IL-1R pathways

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Abstract

The purpose of this study was to explore the effects of regulatory B-cells (Breg) on intracranial aneurysms by mediating IL-1β/IL-1R pathways. The study involved 60 patients undergoing angiography in a hospital from January to June 2022, divided into two groups: 30 with intracranial aneurysms (observation group) and 30 without (control group). Researchers extracted peripheral blood mononuclear cells (PBMC) to analyze the proportion of CD19+CD24hiCD38hiB cells using flow cytometry. These cells, along with T-cells and regulatory T-cells (Treg), were isolated through magnetic bead cell sorting. Following co-culture, the proliferation of T-cells and their related secretory factors were assessed. Additionally, Breg cells, treated with an IL-1R receptor blocker or IL-1R expression adenovirus, were studied to evaluate the levels of IL-10 and TGF-β. In the study, the observation group showed lower levels of CD19+CD24hiCD38hiB cells, IL-10, and TGF-β in PBMC than the control group ($P<0.05$). T-cell proportions were similar in both groups pre and post co-culture ($P>0.05$). Post co-culture, IFN-γ decreased while IL-4 increased in both groups. The observation group had higher IFN-γ and lower IL-4 than the control group ($P<0.05$). TNF-α in CD8+T cells, and granzyme B and perforin mRNA levels decreased post co-culture but were higher in the observation group ($P<0.05$). IL-10 and TGF-β in Treg cells increased in both groups post co-culture but were lower in the observation group ($P<0.05$). The observation group also had fewer CD19+IL-1R+IL-10+B cells ($P<0.05$). After IL-1R blocker addition, IL-10 and TGF-β in the supernatant decreased in the observation group ($P<0.05$). Following transfection, IL-1 and TGF-β levels increased compared to the blank group ($P<0.05$). The function of peripheral blood CD19+CD24hiCD38hiB cells is impaired in patients with intracranial aneurysms, which may be related to IL-1β/IL-1R pathways disorder.

Keywords: Intracranial aneurysm; Regulatory B-cell; T-cell; IL-1β/IL-1R signaling pathway.

1. Introduction

Intracranial aneurysm is a local abnormal bulge of an internal cerebral artery, which usually forms in a weak area of the arterial wall. The bulging is similar to a small air bubble or cyst, usually appearing in the artery bifurcation, these areas of blood vessel walls are more likely to be damaged due to blood flow impact. Intracranial aneurysm ranks third in the incidence of cerebrovascular diseases, next to cerebral thrombosis (cerebral infarction) and cerebral hemorrhage caused by hypertension. Intracranial aneurysms may be asymptomatic for a long time, but its fracture risk has become a serious medical problem. Rupture of the tumor can lead to subarachnoid hemorrhage, a life-threatening condition because blood leaks into the space between the brain and the meninges. Symptoms of a ruptured tumor may include severe headache, vision problems, loss of consciousness, nausea, and vomiting [1]. Any age, is more focused on 40 ~ 60 years old females [2]. At present, the specific etiology of intracranial aneurysms is not completely clear, but it is generally believed that it is closely related to a variety of factors. The main risk factors include hypertension, cerebral arteriosclerosis and vasculitis. High blood pressure can damage the blood vessel wall for a long time, thus increasing the risk of aneurysm. Cerebral arteriosclerosis, that is, the thickening and hardening of the arterial wall, will weaken the structural integrity of the blood vessels and provide the conditions for the formation of aneurysms. In addition, vasculitis, the inflammatory reaction of the vessel wall, may also lead to thinning of the vessel wall, increasing the likelihood of aneurysm development. Despite these potential risk factors, the mechanism of intracranial aneurysm formation still needs to be further studied and explored [3]. Recent studies have shown that immune cells play an important role in the development of intracranial aneurysms, but most of them focus on T-cells [4]. B-cells as a

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key member in the body of the adaptive immune response, including regulatory B-cells (Breg) a unique and function immunosuppressive function of B-cells, may through the interaction between cells regulate their reactive T-cells, and regulatory T-cells, macrophages, antigen-presenting cells, natural killer cells, etc. [5]. It has been reported that a large number of macrophages gather around intracranial aneurysm lesions and secrete a large amount of IL-1β to promote inflammatory response [6]. Research has shown that Breg cells express IL-1R when IL-1R after receiving the IL-1 beta, activates Breg cells plays a role as an anti-inflammatory, and balance the body's immune [7]. Therefore, it is speculated that IL-1β/IL-1R signaling pathway may be involved in the pathogenesis and progression of intracranranial aneurysms by regulating Breg cells. This study will research this and analyze the relationship between Breg cells and intracranial aneurysms, so as to further clarify the pathogenesis of such diseases and lay a theoretical foundation for the development of a new generation of anti-tumor immune drugs.

2. Materials and Methods

2.1. Study design

A total of 60 subjects who underwent angiography in our hospital from January 22 to June 2022 were selected, of which 30 cases were confirmed to have intracranial aneurysms as the observation group, and the other 30 cases without intracranial aneurysms as the control group. Exclusion criteria: frequent use of anti-inflammatory drugs and/or other inflammatory diseases; Concurrent infection; It is accompanied by autoimmune diseases, diabetes, cardiovascular diseases, tumors and other serious diseases. The age of the control group ranged from 53 to 78 years, with an average age of 66.72±7.61 years. 19 cases (11 male and female. The observation group of 52 ~ 78 years old, average age (67.15 + 7.85); There were 13 males and 17 females. There was no significant difference in basic data between the two groups (P>0.05), which was balanced and comparable.

2.2. Extraction of peripheral blood mononuclear cells (PBMC)

Peripheral venous blood (10 mL) was collected and placed in an anticoagulant tube, centrifuged at 3000 r/m for 10 min to separate plasma, then the separated plasma was added to the upper layer of Ficoll solution, centrifuged at 1500 r/m for 30 min, and the middle layer was PBMC, which was stored in the refrigerator at -80℃.

2.3. The subtype of B reg cells was determined by flow cytometry

Flow antibodies against CD24, CD38 and CD19 were added, respectively, and then incubated at room temperature in A dark place for 15 min. Membrane breaker A solution, cleaved erythrocyte solution and membrane breaker B solution were added in sequence, followed by fluorescent antibody, incubated in a dark place for 15 min, centrifuged at 1500 r/m for 5 min to remove the supernatant, and then the cells were resuspended in PSB. The proportion of CD19+CD24hiCD38hiB cells was detected by flow cytometry.

2.4. Magnetic bead cell sorting

The supernatant was centrifuged at 1200 r/m for 10 min, diluted with glacial acetic acid, followed by the addition of biotin-antibody mixture and incubation on ice for 10 min, followed by the addition of biotin-antibody mixture and incubation on ice for 10 min followed by centrifugation at 1200 r/m for 10 min. After washing three times, the piston of the MS column was removed, and the collected liquid was T-cells, CD4+T cells, CD8+T cells, Treg cells and CD19+CD24hiCD38hiB cells. The purity of sorted cells was verified by flow cytometry.

2.5. Cell co-culture

Purified CD4+T cells, CD8+T cells and Treg cells were activated by the addition of CD3 and CD28 antibodies and then co-cultured with CD19+CD24hiCD38hiB cells for 72 hours. T-cells were labeled with 3[H] -thymidine after co-culture, and the proliferation of T-cells was detected by flow cytometry. After co-culture with other cells, CD4+T cells, CD8+T cells and Treg cells were separated by magnetic beads, and the expression of related secreted factors was detected.

2.6. ELISA was used to detect the expression of related secreted factors

CD19+CD24hiCD38hiB cells, CD4+T cells, CD8+T cells and Treg cells before and after co-culture were isolated. The levels of IL-10 and TGF-β in Breg cells and IFN-γ and IL-4 in CD4+T cells were detected according to the instructions of the ELISA kit. The expression of TNF-α in CD8+T cells and IL-10 and TGF-β in Treg cells were detected.

2.7. The mRNA levels of granzyme B and perforin were detected by real-time fluorescence quantitative PCR

CD8+T cells were isolated and co-cultured. TRIzol reagent was added to isolate and co-culture CD8+T cells. Total RNA was extracted, and cDNA template strand was synthesized by reverse transcription. After 38 cycles of 95℃ for 60 s, 95℃ for 5 s, and 58℃ for 30s, the relative expression levels of granzyme B and perforin mRNA were calculated by 2-ΔΔCt.

2.8. Regulation of the IL-1β/IL-1R signaling pathway in Breg cells

The PMBC of the subjects were added with IL-10, CD19 and IL-1R antibodies, and the proportion of CD19+IL-1R+IL-10+B cells was detected by flow cytometry. CD19+CD24hiCD38hiB cells were isolated and stimulated with PMA followed by IL-1R receptor blocker. The expression of IL-10 and TGF-β in the supernatant was detected by ELISA. CD19+CD24hiCD38hiB cells isolated from PMBC of the observation group were transfected with IL-1R expressing adenovirus as the transfection group, and blank adenovirus was transfected as the blank group. After stimulation with PMA, the expression of IL-10 and TGF-β in the supernatant was detected.

2.9. Statistical analysis

Statistic Package for Social Science (SPSS) 26.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. The measurement data were expressed as mean ± standard deviation (±s) and t-test was used. Count data were expressed as rate (%) and χ^2 test was used. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of CD19+CD24hiCD38hiB cells and cytokine levels in PBMC between the two groups

In the comparison of the levels of CD19+CD24hiCD38hiB cells and cytokines in PBMC of the two groups, the flow graph is shown in Figure 1, which shows that the mononuclear cells are rounded out to remove the debris cell residue, the effective cells are rounded out, and then the CD19+ gate is set, the B-cells are rounded out, and the CD19+B cells are used as the gate. CD19+CD24hiCD38hiB cells were circled. Compared with the control group, the proportion of CD19+CD24hiCD38hiB cells in PBMC, IL-10 and TGF-β in the observation group was significantly decreased ($P < 0.05$). Refer to Table 1.

3.2. Effect of CD19+CD24hiCD38hiB cells on T-cell proliferation

There was no significant difference in the proportion of T-cells between the two groups before and after co-culture ($P > 0.05$). Refer to Table 2.

3.3. Effect of Breg cells on CD4+T cell function

Before co-culture, there was no significant difference in the levels of IFN-γ and IL-4 in CD4+T cells between the two groups ($P > 0.05$). After co-culture, the IFN-γ in CD4+T cells of the two groups was lower than that before co-culture, and the IL-4 was higher than that before co-culture, but the IFN-γ in the observation group was higher than that in the control group, and the IL-4 was lower than that in the control group ($P < 0.05$). Refer to Table 3.

3.4. Effect of Breg cells on CD8+T cell function

Before co-culture, there were no significant differences in TNF-α content, granzyme B and perforin mRNA levels of CD8+T cells between the two groups ($P > 0.05$). After co-culture, the TNF-α content and mRNA levels of granzyme B and perforin in CD8+T cells in the two groups were lower than those before co-culture, but the TNF-α, granzyme B and perforin mRNA in the observation group were higher than those in the control group after co-culture ($P < 0.05$). Refer to Table 4.

3.5. Effect of Breg cells on Treg cell function

Before co-culture, there was no significant difference in the content of IL-10 and TGF-β in Treg cells between the two groups ($P > 0.05$). After co-culture, two groups of

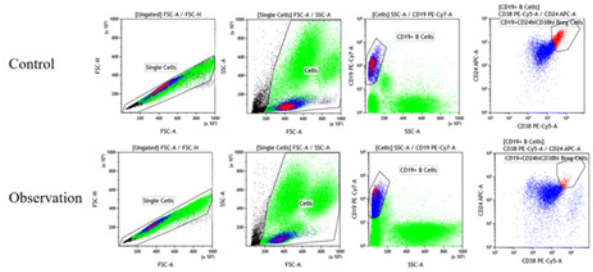

Fig. 1. Comparison of CD19+CD24hiCD38hiB cell levels in PBMC between the two groups.

Table 1. Comparison of CD19+CD24hiCD38hiB cells and cytokine levels in PBMC between the two groups (n=30).

Index	Control	Observation	*t*	*P*
$CD19^{+}CD24^{hi}CD38^{hi}$Bcell (%)	18.65±2.34	5.32±0.91	29.080	<0.001
IL-10 (pg/mL)	1.25±0.14	0.84±0.09	13.493	<0.001
TGF-β (ng/mL)	0.91±0.10	0.58±0.08	14.114	<0.001

Table 2. Effect of Breg cells on T-cell proliferation (n=30).

Index	Time	Control	Observation	*t*	*P*
Tcell (%)	Before co-culture	52.34±5.88	53.55±6.25	0.345	0.737
	After co-culture	54.57±5.16	55.62±5.43	0.768	0.446

Table 3. Effects of Breg cells on CD4+T cell function (n=30).

Index	Time	Control	Observation	*t*	*P*
IFN-γ (ng/mL)	Before co-culture	22.34±3.88	23.55±3.25	1.309	0.196
	After co-culture	10.57±2.16*	16.62±2.43*	10.192	<0.001
IL-4 (pg/mL)	Before co-culture	48.62±6.24	50.17±6.85	0.916	0.363
	After co-culture	59.32±7.21*	54.45±7.04*	2.647	0.010

Compared with that before co-culture, *$P < 0.05$.

Table 4. Effect of Bregcell on CD8+Tcell function (n=30).

Index	Time	Control	Observation	*t*	*P*
TNF-α (ng/mL)	Before co-culture	39.54±4.27	38.69±4.03	0.793	0.431
	After co-culture	17.26±2.85	26.48±3.27	11.642	<0.001
Granzyme B mRNA	Before co-culture	3.27±0.28	3.19±0.25	1.167	0.248
	After co-culture	1.63±0.21	2.45±0.23	14.421	<0.001
Perforin mRNA	Before co-culture	2.99±0.26	3.05±0.31	0.812	0.420
	After co-culture	1.54±0.20	2.66±0.27	18.257	<0.001

Compared with that before co-culture, *$P < 0.05$.

Table 5. Effects of Breg cells on Treg cell function (n=30).

Index	Time	Control	*t*	*P*
IL-10 (pg/mL)	Before co-culture	11.32±2.15	0.277	0.783
	After co-culture	30.48±3.22	9.770	<0.001
TGF-β (ng/mL)	Before co-culture	1.05±0.18	1.819	0.074
	After co-culture	2.24±0.22	11.117	<0.001

IL-10 Treg cells and TGF - beta content is higher than that of Before co-culture, but the observation group after co-cultivation IL-10 and TGF - beta is lower than the control group ($P < 0.05$). As shown in table 5.

3.6. Regulation of the IL-1β/IL-1R signaling pathway in Breg cells

Compared with the control group and observation group PBMC CD19 + IL-1 r + IL-10 + B-cells of significantly lower than [(20.75 + 2.88) % than (3.28 + 0.61) %, $P < 0.05$). Compared with before adding, After adding IL-1R receptor blocker, the levels of IL-10[(1.55±0.20) pg/mL vs. (0.60±0.11) pg/mL] and TGF-β [(1.37±0.18) pg/mL vs. (0.74±0.14) pg/mL] in the supernatant of the observation group were significantly decreased ($P < 0.05$). Compared with the blank group, transfection group that IL-10 supernatant fluid [(1.58 + 0.19) pg/mL (2.49 + 0.25) pg/mL] and TGF - beta content [(1.42 + 0.21) pg/mL (2.25 + 0.26) pg/mL] increased significantly ($P < 0.05$). Refer to Figure 2.

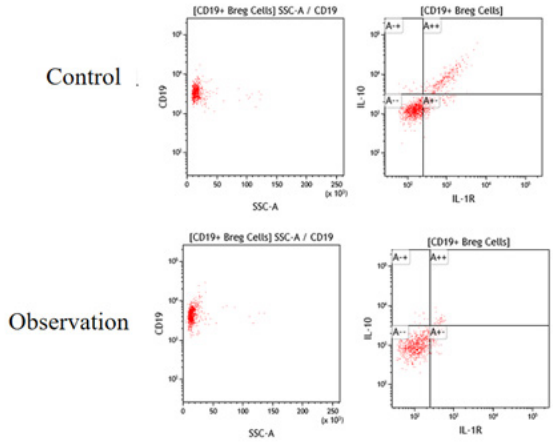

Fig. 1. Comparison of CD19+IL-1R+IL-10+B cell levels in PBMC between the two groups.

4. Discussion

Immune inflammatory cells can release a variety of active substances, such as proteolytic enzymes, which cause the degradation of the aneurysm wall, media and collagen components of intracranial saccular aneurysms, thereby weakening the rigidity and elasticity of the aneurysm wall, leading to the thinning and even rupture of the aneurysm [8]. At present, the origin and development of Breg cells haven't been researched clearly but found in a variety of inflammatory diseases of Breg distribution of abnormal cells [9,10]. However, the specific relationship between Breg cells and intracranial aneurysms remains unclear.

At present, it is believed that the phenotype of Breg cells is different among different species, and CD19+CD24hiCD38hiB cells are the phenotype found in human body [11]. This study found that the proportion of CD19+CD24hiCD38hiB cells in PBMC of the observation group was significantly lower than that of the control group, and its secretion factors IL-10 and TGF-β were also significantly lower than that of the control group. The results indicate that the number and function of CD19+CD24hiCD38hiB cells are abnormal in intracranial aneurysms. Previous studies [12,13] reported that Breg cells can induce the differentiation of CD4+T cells and Treg cells, inhibit the differentiation of cytotoxic CD8+T cells, and maintain the homeostasis of natural killer T-cells. QuBiHui etc. [14-16] the study found that peripheral blood CD19 + CD24hiCD38hiB cell function in patients with abdominal aortic aneurysm is insufficient, the CD4 + T-cell secretion of IFN - gamma enhancement, to participate in the occurrence of abdominal aortic aneurysm development. In this study, CD19+CD24hiCD38hiB cells have no significant effect on the proliferation of T-cells, but they can regulate the function of CD4+T cells, CD8+T cells and Treg cells, as shown by the decrease of IFN-γ and the increase of IL-4 in CD4+T cells. The content of TNF-α and the mRNA levels of granzyme B and perforin in CD8+T cells were decreased, and the content of IL-10 and TGF-β in Treg cells was increased. However, the above regulatory ability in the observation group was lower than that in the control group, suggesting that the negative immune regulatory ability of patients with intracranial aneurysms was reduced due to the dysfunction of CD19+CD24hiCD38hiB cells. Accelerate the inflammatory response.

IL-1β is a potent pro-inflammatory factor, which plays an important role in inflammatory diseases, especially cardiovascular diseases, by regulating the expression of integrin in leukocytes and endothelial cells to initiate and control inflammatory responses [16]. IL-1β can bind to IL-1R and trigger signals through the adaptor protein MyD88 to induce matrix metabolic disorders and vascular dysfunction. Will recruit immune cells, the aortic wall and gather around the white blood cells to produce inflammation, intensifying formation of the aneurysm [17]. Studies have shown that IL-1β can activate Breg cells to inhibit inflammatory response by binding to IL-1R on the surface of Breg cells [18-20]. In this study, the proportion of CD19+IL-1R+IL-10+B cells in PBMC of the observation group was significantly lower than that of the control group, and the contents of IL-10 and TGF-β in the supernatant of the observation group were further reduced after adding IL-1R receptor blocker. Overexpression of IL-1R promoted the secretion of IL-10 and TGF-β in CD19+CD24hiCD38hiB cells in vitro. The above results suggest that the dysfunction of CD19+CD24hiCD38hiB cells in patients with intracranial aneurysms may be related to the decrease of IL-1R on the cell surface and the blockage of IL-1β/IL-1R signaling pathway.

In conclusion, the lack of function of CD19+CD24hiCD38hiB cells in peripheral blood of patients with intracranial aneurysms may be related to the

dysfunction of IL-1β/IL-1R pathway. This study provides an in-depth analysis of the role of CD19+CD24hiCD38hiB cells in the internal aneurysm from the aspects of quantity, function and regulatory mechanism, which provides a theoretical basis for the pathogenesis of such diseases and also contributes to the development of a new generation of anti-tumor immune drugs. However, there are other phenotypes of Breg cells in the human body, and the relationship between Breg cells and intracranial aneurysms remains to be explored.

Conflict of interests
The author has no conflicts with any step of the article preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate
This study was approved by the ethics committee.

Informed consent
Signed written informed consent was obtained from the patients and/or guardians.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions
Chanhong Shi, Fang Tian: Conceptualization, methodology, writing original draft preparation. Xuewei Yang, Jinhui Song, Dongwang Qi: Investigation, software, statistical analysis. Jianwei Li: Reviewing and editing, funding acquisition, supervision. All authors read and approved the final manuscript.

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