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γδ T Cells in Peripheral Blood of Glioma Patients

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Background: Glioma is a common brain malignancy, but the effects of the γδ T cells and their subsets in peripheral blood in patients with glioma have not been reported.

Material/Methods: Flow cytometry was used to analyze the functions and expressions of δ T cells and their subsets in peripheral blood in healthy controls and patients with glioma. The Vδ2 T cells and the activation of killing function-related signaling pathway were analyzed by Western blot assay; the immunosuppressive functions of Vδ1 T cells were detected by CFSE proliferation assay; and the Vδ2 T cell killing functions were detected by killing assay.

Results: Compared with the healthy controls, the ratio of Vδ1 T cells was significantly increased and the ratio of Vδ2 T cells was significantly decreased. After *in vitro* culture and anti-TCR γδ antibody stimulation and in the presence of IL-2, in the patients with glioma, the Vδ1 T cells dominated and Vδ2 T cells were scarce. Flow cytometry staining showed that expression of immunosuppression-related molecules on the Vδ1 T cell surface was significantly increased, while the expression of killing function-related molecules and the activation of killing function-related signaling pathway in the Vδ2 T cells were significantly decreased. Functional test results showed that the immunosuppressive function of Vδ1T cells was enhanced and the killing function of Vδ1T cells was reduced.

Conclusions: The ratio and function changes of Vδ1 T cells and Vδ2 T cells are possibly associated with the pathogenesis of glioma.

MeSH Keywords: Astrocytoma • Immunosuppression • Neuroectodermal Tumors, Primitive, Peripheral

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Background

T cells are mainly divided into 2 subsets according to the expressions of TCR (T cell receptors, TCR): αβ T cells and γδ T cells [1]. γδ T cells are a group of T lymphocytes distinct from αβ T cells, and their surfaces express TCR consisting of γ chains and δ chains. γδ T cells account for a small fraction of CD antigen (cluster of differentiation, CD) 3T cells, at about 1–10% [2]. Due to the limited diversity of γδ TCR and non-restrictive MHC, γδ T cells are always regarded as innate immune cells [2]. γδ T cells can be further divided into 2 cell subsets: Vδ1 T cells (mainly distributed in epithelial related lymphoid tissue) and Vδ2 T cells (mainly distributed in peripheral blood) [3,4]. Vδ1 T cells and Vδ2 T cells have different functions. Vδ2 T cells are mainly involved in the immune surveillance of tumors and defense responses against invasion of pathogens [5–8], while Vδ1 T cells mainly have immunoregulatory functions [9].

Glioma is a common brain malignancy, accounting for about 50% of primary brain tumors [10]. Glioma refers to all neuroepithelial-derived tumors in a broad sense; and in a narrow sense, it refers to tumors derived from glial cells. At present, the etiology of glioma is still unclear, but might be correlated with tumor origin, genetic factors, biochemical environment, ionizing radiation, nitroso compounds, polluted air, unhealthy behaviors, and infections. Although surgical treatment, radiotherapy, and chemotherapy have developed rapidly in recent years, the therapeutic effect of glioma is still not ideal [11]. The pathological features of glioma are infiltrative growth of tumor, without apparent boundary with brain tissue [12]. It is difficult to achieve total resection expect for small tumors in appropriate sites in early stage. Therefore, it is urgent to find additional anti-tumor strategies to enhance the therapeutic effect of surgery and/or radiation therapy of glioma.

Immunotherapy has long been used for the treatment of cancers [13]. γδ T cells have become a popular topic of tumor immunotherapy due their unique characteristics [14,15]. It is still unclear whether immunotherapy of γδ T cells is applicable for the treatment of patients with glioma. The literature contains few studies on the change of γδ T cells in peripheral blood in patients with glioma. In the present study, we observed the ratio and function changes of γδ T cells and their subsets in peripheral blood of patients with glioma and investigated the possible role of γδ T cells and their subsets in the pathogenesis of glioma to provide a scientific basis for the application of immunotherapy of γδ T cells in patients with glioma in the future.

Material and Methods

Collection of clinical data

We collected peripheral blood samples from 30 patients undergoing glioma resection in our hospital from January 2015 to November 2016. All patients were pathologically confirmed as having glioma. Patient aged ranged from 35 to 69 years (mean, 47.32±15.93). None of the patients had received chemotherapy and radiotherapy before surgery. All included patients signed the informed consent.

Main reagents

Bovine serum albumin (BSA) was purchased from Sigma; RPMI 1640 medium and fetal bovine serum (FBS) were purchased from Gibco; PBS (phosphate buffer saline, PBS) was purchased from Hyclone; lymphocyte separation medium, PE-anti-TCR VV2 antibody, PEcy5-anti-CD3 antibody, FITC-anti-TCR Vδ1 antibody, PE-anti-TCR Vδ2 antibody, APC-anti-TNF-α antibody, APC-anti-CTLA-4 antibody, APC-anti-Foxp3 antibody, APC-anti-perforin antibody, and APC-anti-Foxp3 antibody were purchased from Biolegend; purified anti-TCR γδ antibody and purified anti-TCRVδ1 antibody for amplification were purchased from Beckman; anti-phospho-PLCγ1(Tyr783) and anti-phospho-Erk1/2 (Thr202/Tyr204) antibody were purchased from Cell Signaling Technology; anti-β-actin antibody was purchased from Sigma; naïve CD4 T cell sorting kits were purchased from Miltenyi Biotec; CFSE dye solution was purchased from Thermo; and CytoTox 96® non-radioactive cell killing detection kits were purchased from Promega.

Separation of PBMC (peripheral blood mononuclear cell, PBMC)

We collected 15 mL of peripheral venous blood from patients with glioma and healthy controls under fasting condition in the morning, then we added 15 mL of PRMI-1640 medium to a 50-mL centrifuge tube and the blood sample was added for dilution (1: 1), and 15 mL of lymphocyte separation medium was added to another 50-mL centrifuge tube. The diluted blood sample was drawn carefully using a pipette and added to separation medium to ensure that the blood was above the lymphocyte separation medium, and centrifuged it for 18 min at 800×g. After centrifugation, the albuginea layer was gently absorbed and added to a conical tube containing 15 mL of serum-free RPMI 1640 medium. After cells were mixed well, we centrifuged tubes for 10 min at 400×g; the supernatant was discarded, and the cell precipitate was re-suspended with 10 mL of serum-free RPMI 1640 medium, centrifuged for 8 min at 250×g. Then cell precipitate was re-suspended with 1 mL of RPMI-1640 complete medium containing 10% fetal bovine serum. After trypan blue staining

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and counting, the cell suspension at a concentration of 2×10^6 cells/mL was prepared.

Determination of ratio of Vδ1 T cells and Vδ2 T cells

We added 1×10^6 PBMCs obtained from the above density gradient centrifugation method to a 1.5-mL Eppendorf tube, and 1 mL of PBS washing solution containing 1% BSA was added. After mixing well, tubes were centrifuged for 8 min at 250×g, then the supernatant was discarded and the above procedure was repeated. Later, the cells were re-suspended in 0.1 ml of PBS containing 1% BSA, then the PEcy5-anti-CD3 antibody, FITC-anti-TCR Vδ1 antibody, and PE-anti-TCR Vδ2 antibody were added and incubated at 4°C in the dark for 30 min. After washing twice with PBS containing 1% BSA, cells were re-suspended in 0.1 ml of PBS for flow cytometry.

In vitro amplification of γδ T cells

Amplification was performed according to the procedures in the literature [15]. The specific procedure was: a 24-well cell culture plate was coated by anti-pan-TCRγδ mAb (10 μL of 0.05 mg/mL anti-pan-TCRγδ mAb and 500 μL of serum-free RPMI 1640 medium were added to each well and incubated at 37°C for 2 h); the prepared PBMC suspension was added to the coated wells ($3\sim5\times10^6$ cells/well) and incubated in an incubator (37°C, 5% CO_2). On Day 5, the solution was replaced for subculture; from Day 10 to Day 14, the amplified γδ T cells were collected for purity and phenotype analysis.

Amplification of Vδ1 T cells

We added 0.2 ml of RPMI-1640 medium containing 0.125 μg of anti-TCR Vδ1 monoclonal antibody to each well of a 48-well plastic culture plate, and incubated it in a saturated wet environment (37°C, 5%CO_2) for 2 h. The PBMC suspension re-suspended with complete medium (RPI-1640 + 10% FBS) was added to a 48-well plate (1.0 ml per well) coated with anti-TCR Vδ1 monoclonal antibody and cultured in a saturated wet environment (37°C, 5%CO_2). The solution was replaced or divided to wells every 1 to 3 days according to the cell growth state, cultured for 2 weeks, then the Vδ1 T cells with purity higher than 90% were sorted out by flow cytometry.

Detection of Vδ1 T cell surface molecules

We added 1×10^6 PBMCs obtained from above density gradient centrifugation method to a 1.5-mL Eppendorf tube, and 1 mL of PBS washing solution containing 1% BSA was added. After mixing well, tubes were centrifuged for 8 min at 250×g, then the supernatant was discarded and the above procedure was repeated. Cells were re-suspended in 0.1 ml of PBS containing 1% BSA, then the PEcy5-anti-CD3 antibody, FITC-anti-TCR Vδ1 antibody, and APC-anti-CTLA-4 antibody/APC-anti-Foxp3 antibody were added, and cells were incubated at 4°C in the dark for 30 min. After washing twice with PBS containing 1% BSA, cells were re-suspended in 0.1 ml of PBS for flow cytometry.

Detection of Vδ2 T cell perforin and TNF-α secretion

We added 2×10^6 Vδ2 T cells to a 48-well plate, and 100X PMA + Ion was added to the culture plate, cultured for 6 h at 37°C, then cells were collected. We added 0.5 ml of membrane rupture solution, and placed the cells in the dark for 30 min at room temperature. Cells were washed twice using penetrating fluid, then the PEcy5-anti-CD3 antibody, FITC-anti-TCR Vδ2 antibody, and APC-anti-TNF-α antibody/APC-anti-perforin antibody were added, and the cells were placed in the dark for 30 min at room temperature. Cells were washed twice using penetrating fluid, then re-suspended using 0.1 mL of PBS for testing.

Western blot analysis

The amplified Vδ2 T cells were sorted by flow cytometry to obtain Vδ2 T cells with purity greater than 90%. The total proteins of cells were extracted according to the method in the literature, and the concentration was determined. An equal amount of the extracted protein was separated by 8~10% SDS-PAGE separation gel and 5% spacer gel, and when semi-dry, it was transferred to a nitrocellulose membrane, incubated, and blocked for 2 h using TBST containing 5% BSA at room temperature. The anti-phospho-PLCγ1 (Tyr783)/anti-phospho-Erk1/2 (Thr202/Tyr204) was added and incubated at 4°C overnight. On the next day, membranes were washed 3 times with 0.1% TBST, 5 min each time, then the HRP-labeled secondary antibody was added, followed by incubation for 1 h at room temperature. After membrane washing with 0.1% TBST, the bands were dyed with Supersignal West Femto/Pico HRP-sensitive chemiluminescent substrate, and Actin was used as an internal control. All experiments were repeated at least 3 times.

Naïve CD4 T cell proliferation assay

The amplified Vδ1 T cells were sorted by flow cytometry to obtain Vδ1 T cells with purity greater than 90%. Naïve CD4 T cells were washed once with 10 ml of serum-free RPMI 1640 medium stock solution, then CFSE dye solution at a final concentration of 5 mmol/L was added, incubated 10 min in a saturated wet environment (37°C, 5% CO_2), 5 ml of pre-cooled RPMI 1640 medium containing 5% FBS (CFSE dyeing stop solution) was added to the centrifugal tube immediately, placed for 5 min on ice to stop dyeing, centrifuged 8 min at 400×g, then washed once with 10 ml RPMI 1640 medium stock solution. After cells were re-suspended in RPMI-1640 complete medium containing 10% FBS, Vδ1 T cells and the naïve CD4 T cells

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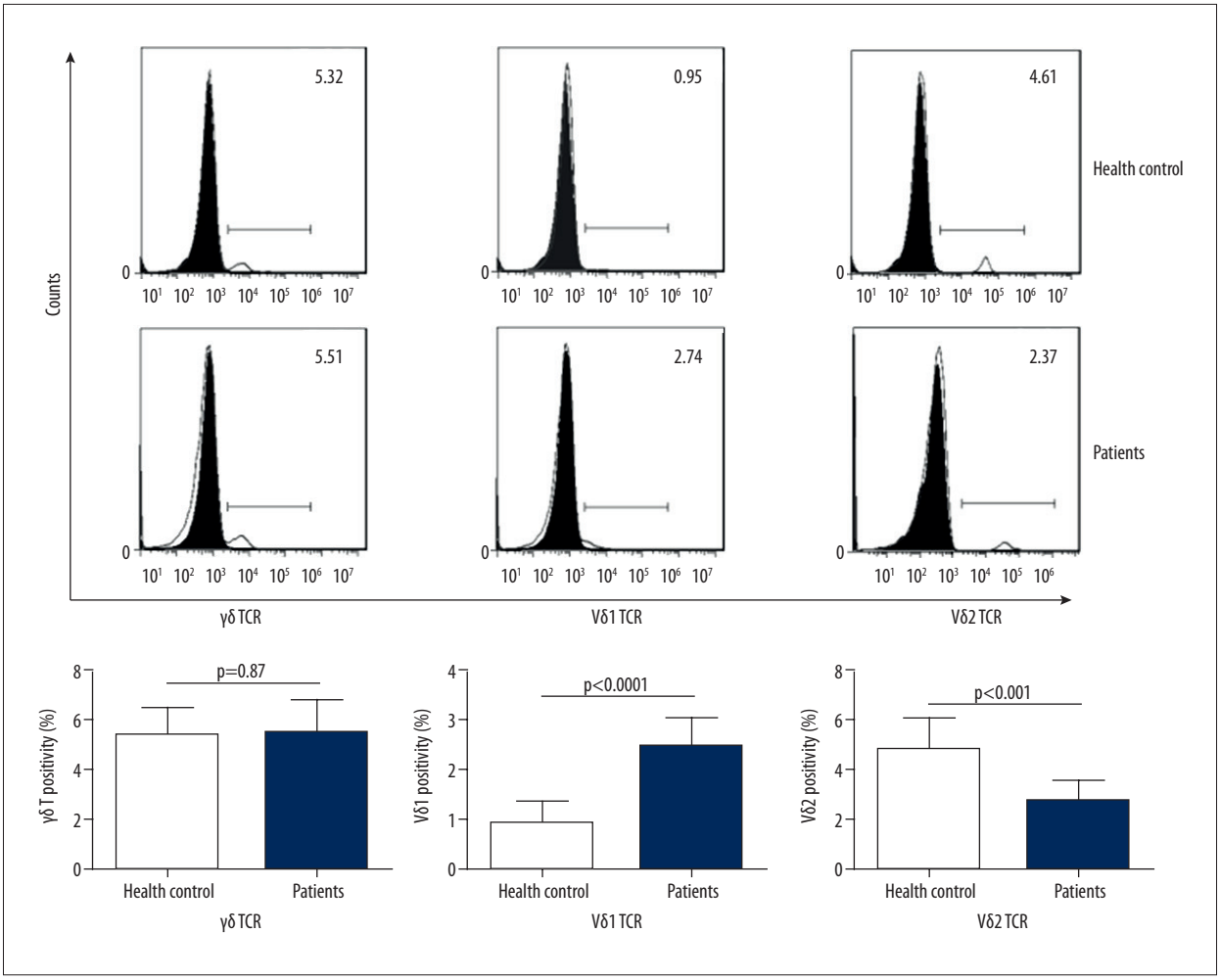

Figure 1. Detection of cell expression level by flow cytometry.

(1: 1) were added to 48-well plates coated with 1 μg/ml CD3 antibody and 2 μg/ml CD 28 antibody. After incubation for 5 days, cells were harvested for flow cytometry.

Killing function test of Vδ2 T cells

The killing function test of Vδ2 T cells was carried out according to a previously reported method [16]. SHG-44 cells and Vδ2 T cells were co-cultured at a ratio of 10: 1, 20: 1, and 30: 1. After incubation at 37°C for 6 h, 50 μl of the culture supernatant was withdrawn and then subsequent operations were performed as per the instructions of the kits.

Statistical processing

All data are expressed as mean ± standard deviations. Data analysis was performed using SPSS 16.0 statistical software. For comparison between the 2 groups, the *t* test was used. $p<0.05$ was considered a statistically significant difference.

Results

Detection of ratio of γδ T cells and their subsets in peripheral blood

The ratio of total γδ T cells in peripheral blood in healthy controls was (5.38±1.13)% and the ratio of total γδ T cells in peripheral blood in patients with glioma was (5.49±1.35)% but the difference was not statistically significant ($p>0.05$). The ratios of Vδ1 T cells in peripheral blood of healthy controls and patients with glioma were (0.91±0.42)% and (2.45±0.61)%, respectively, compared with the healthy controls, and the ratio of Vδ1 T cells in peripheral blood of patients with glioma was significantly increased ($p<0.01$). The ratios of Vδ2 T cells in peripheral blood of healthy controls and patients with glioma were (4.73±1.33)% and (2.69±0.84)%, respectively, compared with the healthy controls, and the ratio of Vδ2 T cells in peripheral blood of patients with glioma was significantly decreased ($p<0.01$) (Figure 1).

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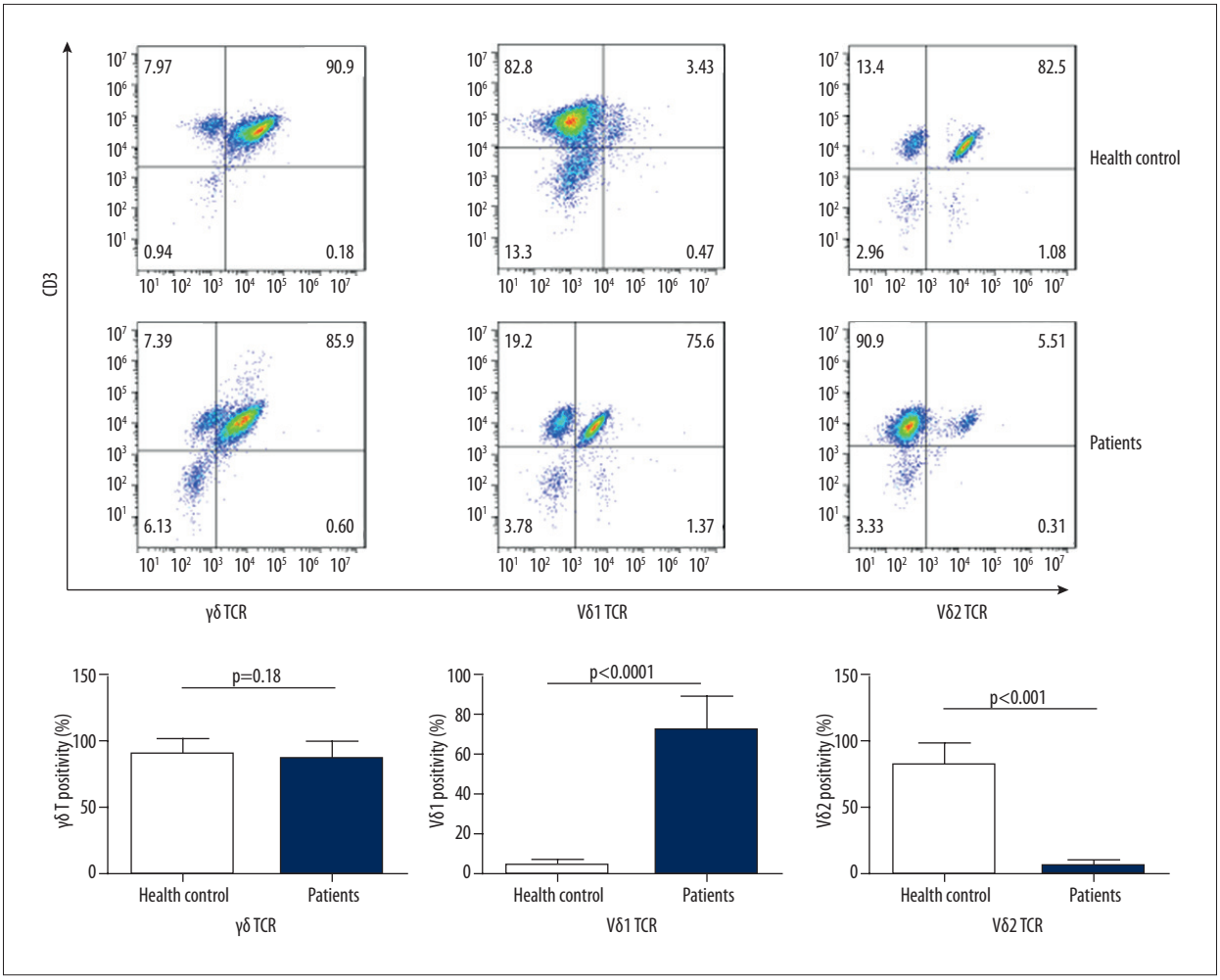

Figure 2. The ratios of γδ T cells and their subsets after amplification detected by flow cytometry.

In vitro proliferation of γδ T cell and their subsets in peripheral blood

As shown in Figure 2A, the PBMCs in healthy controls were cultured for 14 days after anti-TCR γδ antibody stimulation and in the presence of IL-2 the purity of γδ T cells could be as high as (90.13±11.42)%, of which, the ratio of Vδ2 T cells was (81.94±18.25)%, and the ratio of Vδ1 T cells was only (4.83±2.93)%. As shown in Figure 2B, after PBMCs in patients with glioma were cultured for 14 days after anti-TCR γδ antibody stimulation, and in the presence of IL-2, the purity of γδ T cells could be as high as (86.12±13.82)%, of which, the Vδ1T cells dominated, accounting for (72.94±16.94)%, while the Vδ2T cells accounted for only a small proportion, which was (6.28±3.91)%.

Detection of immunosuppression-related molecules of Vδ1 T cells

The ratio of Foxp3$^+$ Vδ1 T cells was (6.04±3.02)% in healthy controls and (22.83±5.36)% in patients with glioma compared with the healthy controls, and the ratio of Foxp3$^+$ Vδ1 T cells in patients with glioma was significantly increased (p<0.01). The ratio of CTLA-4$^+$ Vδ1 T was (1.85±0.93)% in healthy controls and (7.48±2.61)% in patients with glioma. Compared with the healthy controls, the ratio of Foxp3$^+$ Vδ1 T cells in patients with glioma was significantly increased (p<0.01) (Figure 3).

Detection of molecules and signaling pathway related to Vδ2 T cell killing function

The ratio of perforin$^+$ Vδ2 cells was (34.01±8.03)% in healthy controls and (19.42±5.26)% in patients with glioma compared with the healthy controls, and the ratio of perforin$^+$ Vδ2 cells in patients with glioma was significantly decreased (p<0.01). The ratio of TNF-α$^+$ Vδ2 T cells was (37.57±8.82)% in healthy controls and (19.73±5.23)% in patients with glioma, compared with the healthy controls, the ratio of TNF-α$^+$ Vδ2 T cells in patients with glioma was significantly decreased (p<0.01) (Figure 4A). As shown in Figure 4B, the activation of Vδ2 T cell

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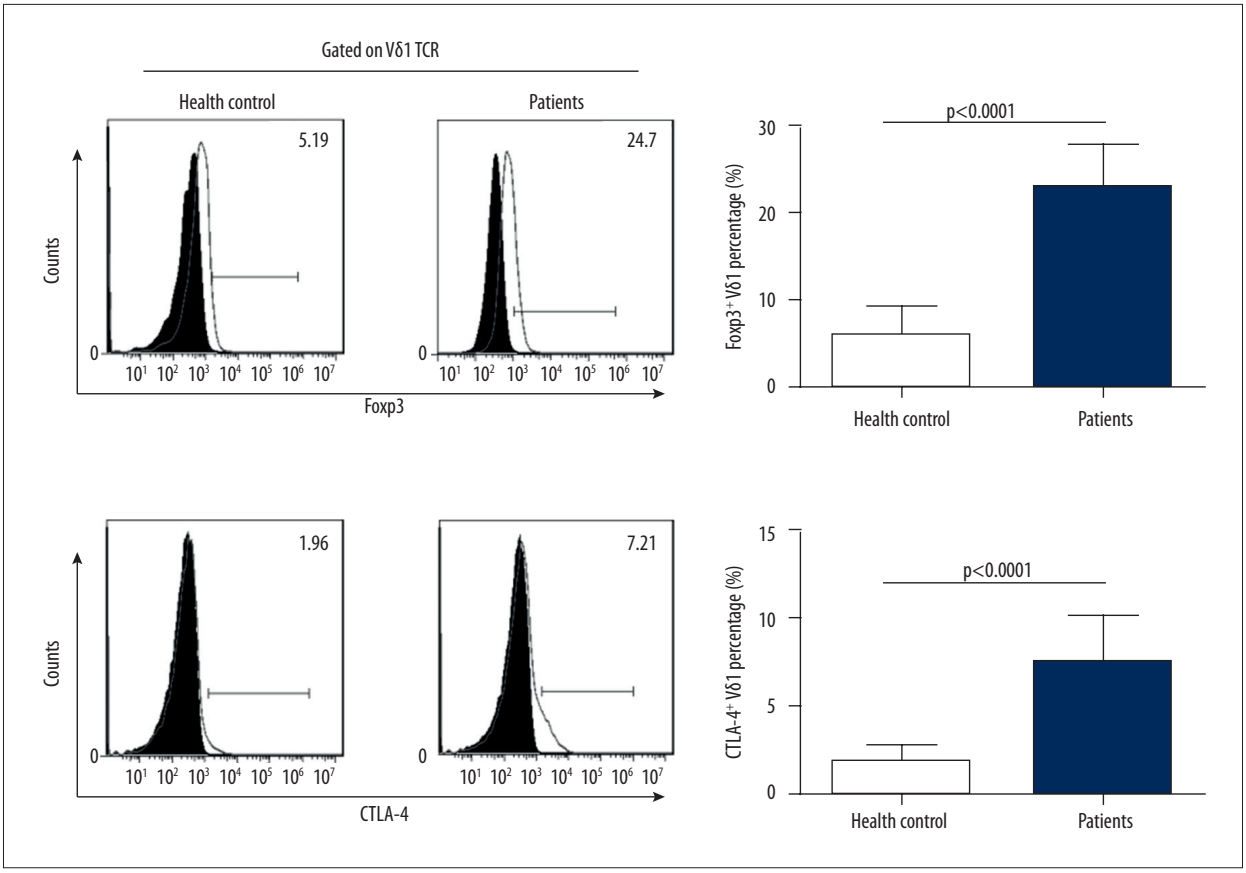

Figure 3. Detection of expression of Vδ1 T cell surface molecules by flow cytometry.

killing function-related signaling pathway in the patients with glioma was significantly lower than that in the healthy controls.

Functional test of Vδ1 T cells and Vδ2 T cells

As shown in Figure 5A, the proliferation level of Naïve CD4 T cells was (93.35±15.67)% in healthy controls, and after co-culture with Vδ1 T cells, the proliferation level of naïve CD4 T cells was (60.74±16.94)%. The proliferation level of naïve CD4 T cells was (91.63±16.35)% in patients with glioma, and after co-culture with Vδ1 T cells, the proliferation level of naïve CD4 T cells was (29.74±15.37)%. There was no significant difference in proliferation level of naïve CD4 T cells between the healthy controls and patients with glioma ($P>0.05$); however, after co-culture with Vδ1 T cells, the proliferation level of naïve CD4 T cells in patients with glioma was significantly lower than that of the healthy controls ($P<0.01$), suggesting that the immunosuppressive function of Vδ1 T cells in patients with glioma was significantly enhanced. As shown in Figure 5B, the Vδ2 T cell killing function in patients with glioma was significantly reduced compared with the healthy controls ($P<0.01$).

Discussion

Our study results show that, compared with healthy controls, the ratio of total γδ T cells in peripheral blood in patients with glioma showed no significant change. γδ T cells can be divided into 2 cell subsets: Vδ1 T cells (mainly distributed in epithelial related lymphoid tissue) and Vδ2 T cells (mainly distributed in peripheral blood) [3,4]. The results of different subsets of γδ T cells showed that the ratio of Vδ1 T cells in peripheral blood in patients with glioma was significantly increased, and the ratio of Vδ2 T cells was significantly decreased. After *in vitro* culture for 14 days after anti-TCR γδ antibody stimulation and in the presence of IL-2, the purity of γδ T cells in healthy controls and patients with glioma was over 80%; in the healthy controls, the Vδ2 T cells dominated and Vδ1 T cells were scarce, while in the patients with glioma, the Vδ1 T cells dominated and the Vδ2 T cells were scarce. The expression of immunosuppression-related molecules on the Vδ1 T cell surface in peripheral blood of patients with glioma was significantly increased and their immunosuppressive function was significantly enhanced. The expression of Vδ2 T cells and their killing function-related molecules in peripheral blood of patients with glioma was significantly decreased and the activation of Vδ2 T cells and killing function-related signaling pathway was significantly reduced,

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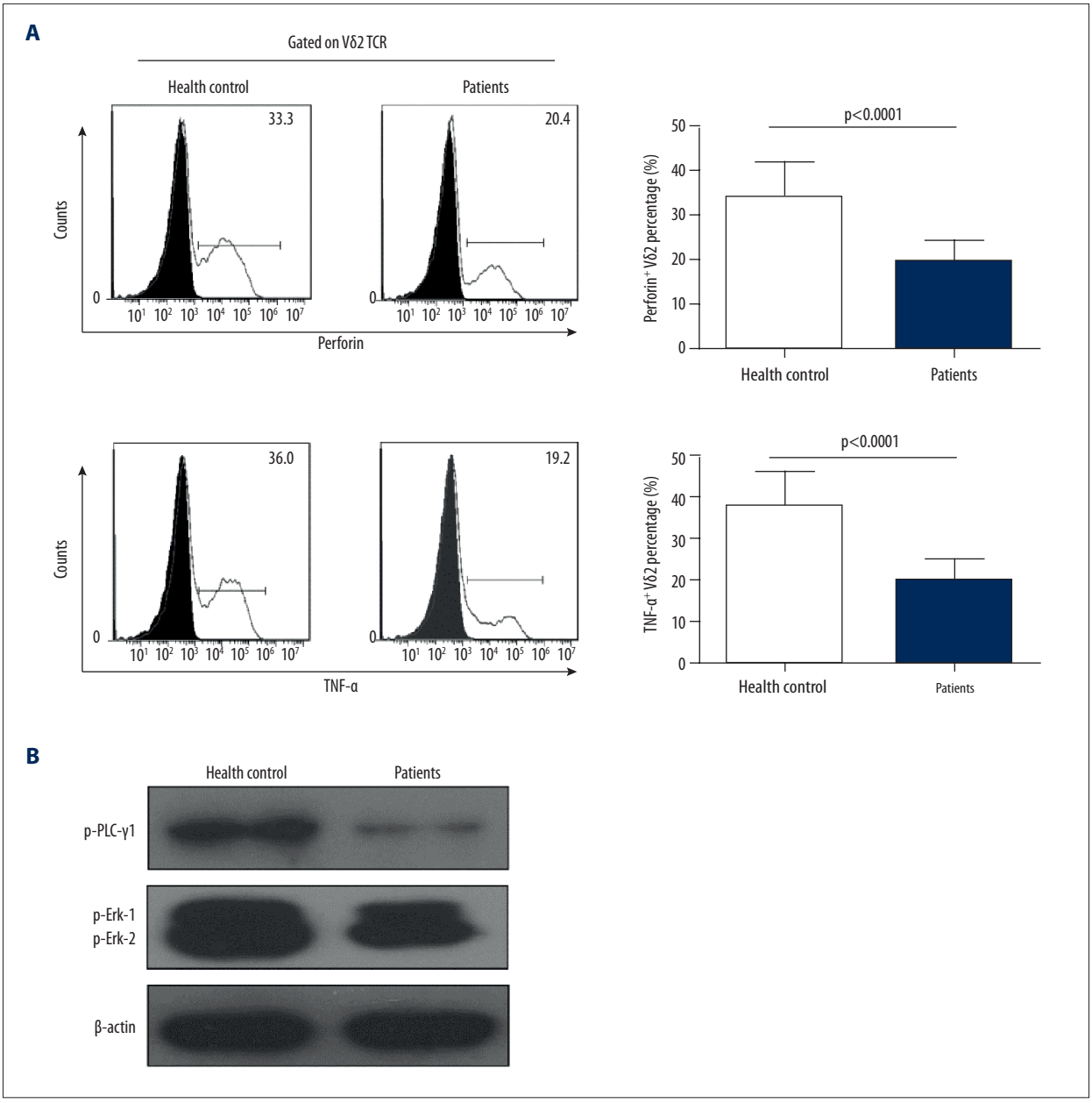

Figure 4. Detection of molecules and signaling pathway related to Vδ2 T cell killing function. (**A**) Detection of expressions of Vδ2 T perforin and TNF-α by flow cytometry; (**B**) Detection of activation of Vδ2 T cell signaling pathway by Western blot.

and the killing function of Vδ2 T cells was also significantly reduced. The above results show that the unbalanced distribution of the ratio of Vδ1T cells and Vδ2T cells in peripheral blood of patients with glioma leads to immunosuppression, allowing tumors to evade immune surveillance, thus facilitating the occurrence and progression of tumors.

The pathological features of glioma make it is difficult to cure by surgical procedures. Therefore, it is urgent to look for additional anti-tumor strategies to improve the survival of glioma patients. Adoptive immunotherapy has always been a focus in cancer treatment [13]. In adoptive immunotherapy, the sensitized lymphocytes (with specific immunity) or sensitized lymphocyte products (such as transfer factors and immune ribonucleic acid) are transfused into patients with low cellular immune function (such as cancer patients) to make them acquire anti-tumor immunity. At present, the experimental or clinical trial results of adoptive immunotherapy strategies based on natural killer (NK) cells, lymphokine-activated killer cells (LAK), and tumor-infiltrating lymphocytes (TIL) have not achieved satisfactory curative effect, mainly due to the weak antigenicity of most tumors, antigen-presenting function

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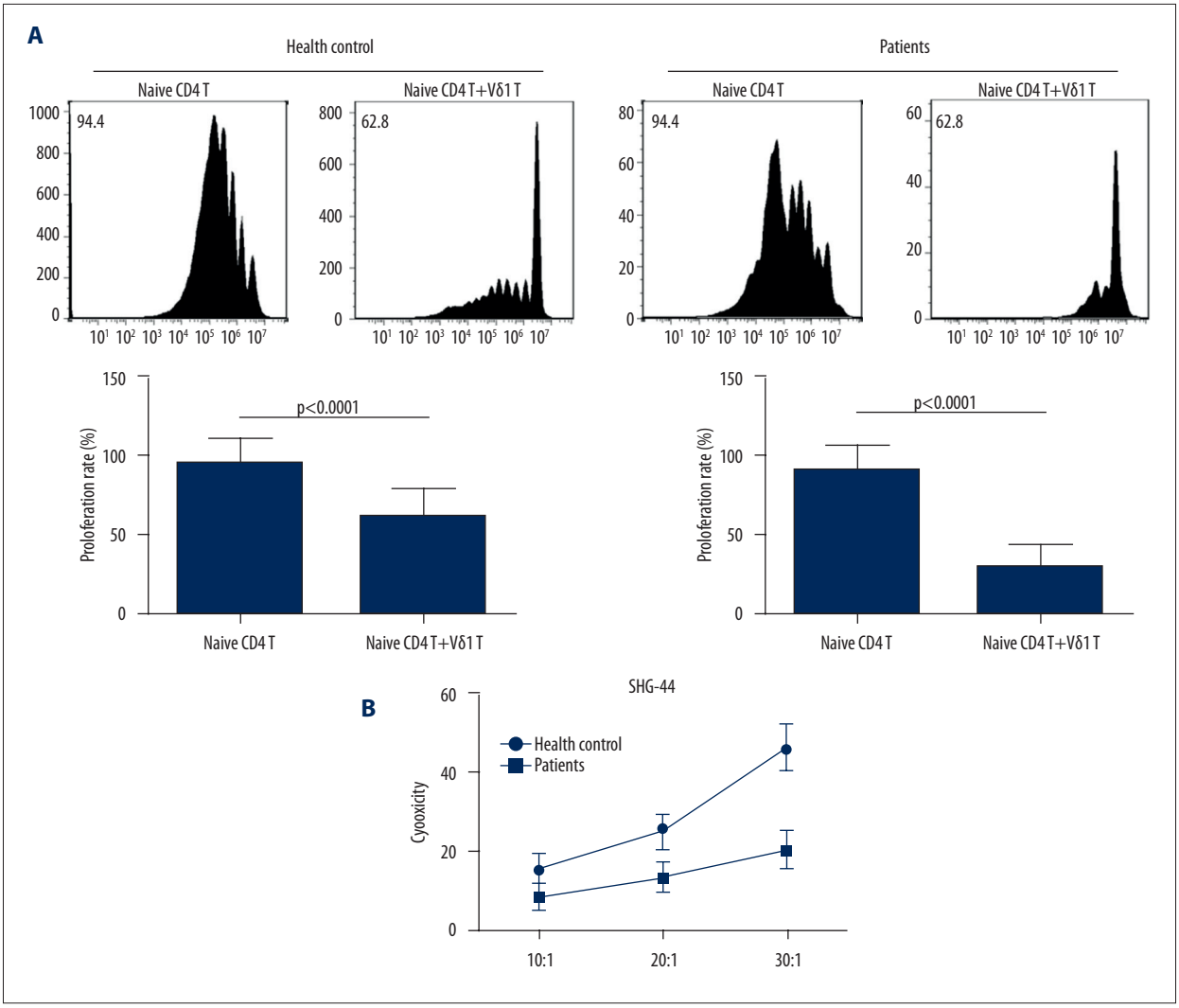

Figure 5. (**A, B**) Functional test of Vδ1 T cells and Vδ2 T cells.

defects, and the immunosuppression of patients with tumors. γδ T cells have the functional features of NK cells, cytotoxic T lymphocytes (CTL), and T helper cells (Th), and the advantage of not needing tumor antigen stimulation for *in vitro* amplification; therefore, it has become an important focus of tumor immunotherapy [14,15]. However, the 2 subsets of γδ T cells (Vδ1 T cells and Vδ2T cells) have exactly the opposite effects in the human body's anti-tumor immune responses. A variety of cancer patients can gain greatly increase effect of anti-tumor therapy by giving Vδ2 T cell adoptive therapy and zoledronic acid treatment at the appropriate time after chemotherapy [17], but Vδ1T cells mainly promote the progression of tumors by suppressing the body's immune function [18,19]. At present, there are few studies on γδ T cells and their subsets in glioma, thus it was the focus of the present study. In this study, we intended to provide a scientific basis for the use of adoptive immunotherapy of glioma through studies on γδ T cells in glioma patients.

Flow cytometry staining showed that, compared with healthy controls, the ratio of Vδ1 T cells in peripheral blood of patients with glioma was significantly increased, while the ratio of Vδ2 T cells was significantly decreased. Rong et al. [20] found that the infiltrated γδ T cells in colorectal cancer tissues are mainly Vδ1 T cells, and the ratio of Vδ2 T cells was significantly decreased. We did not analyze infiltrated γδ T cells and their subsets in tumor tissues of patients with glioma, which is a limitation of this study. We also found that, after *in vitro* amplification, Vδ1T cells dominated in patients with glioma, and Vδ2T cells only accounted for a small proportion, which was consistent with Vδ1T dominance in peripheral blood of patients with glioma. In addition, Peng et al. [19] found that Vδ1T cells also dominated after *in vitro* amplification in patients with breast cancer. As mentioned in the introduction, Vδ2T cells have tumor-killing functions, while Vδ1T cells mainly have immunosuppressive functions. Accordingly, we further investigated the immunosuppressive function of Vδ1T cells and

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the tumor-killing function of Vδ2T cells. Results revealed that the expression of immunosuppression-related molecules on the Vδ1 T cell surface in peripheral blood of patients with glioma was increased significantly and the immunosuppressive function was enhanced significantly. We found that the expressions of Vδ2 T cells and their killing function-related molecules in peripheral blood of patients with glioma were significantly decreased, the activation of Vδ2 T cells and killing function-related signaling pathway was reduced significantly, and the killing functions of Vδ2 T cells were also reduced significantly.

Conclusions

The results in this study preliminarily suggest that the unbalanced distribution of the ratio of Vδ1T cells and Vδ2T cells in peripheral blood of patients with glioma leads to immunosuppression, which may allow glioma to evade immune surveillance. Our study is the first to report on the ratio and function changes of γδ T cells and their subsets in peripheral blood of patients with glioma, which might be closely associated with the occurrence and progression of glioma. The results of this study provide a scientific basis for use of adoptive immunotherapy in patients with glioma in the future.

Conflict of interest

None.

References:

1. Haas W, Pereira P, Tonegawa S: Gamma/delta cells. Annu Rev Immunol, 1993; 11: 637–85
2. Kabelitz D, Wesch D, He W: Perspectives of gammadelta T cells in tumor immunology. Cancer Res, 2007; 67: 5–8
3. Hayday AC: gδ cells: A right time and a right place for a conserved third way of protection. Annu Rev Immunol, 2000; 18: 975–1026
4. Triebel F, Hercend T: Subpopulations of human peripheral T gamma delta lymphocytes. Immunol Today, 1989; 10: 186–88
5. Harly C, Peyrat MA, Netzer S et al: Up-regulation of cytolytic functions of human Vdelta2-gamma T lymphocytes through engagement of ILT2 expressed by tumor target cells. Blood, 2011; 117: 2864–73
6. Kabelitz D, Kalyan S, Oberg HH, Wesch D: Human Vδ2 versus non-Vδ2 γδ T cells in antitumor immunity. Oncoimmunology, 2013; 2: e23304
7. Zhao H, Xi X, Cui L, He W: CDR3δ -grafted γ9δ2T cells mediate effective antitumor reactivity. Cell Mol Immunol, 2012; 9: 147–54
8. Meraviglia S, Eberl M, Vermijlen D et al: *In vivo* manipulation of Vgamma9Vdelta2 T cells with zoledronate and low-dose interleukin-2 for immunotherapy of advanced breast cancer patients. Clin Exp Immunol, 2010; 161: 290–97
9. Kress E, Hedges JF, Jutila MA: Distinct gene expression in human Vdelta1 and Vdelta2 gammadelta T cells following non-TCR agonist stimulation. Mol Immunol, 2006; 43: 2002–11
10. Zheng H, Yang B, Xu D et al: Induction of specific T helper-9 cells to inhibit glioma cell growth. Oncotarget, 2017; 8: 4864
11. Grossman SA, Ye X, Piantadosi S et al: Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. Clin Cancer Res, 2010; 16: 2443–49
12. Lamborn KR, Yung WK, Chang SM et al: Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol, 2008; 10: 162–70
13. Kato Y, Tanaka Y, Miyagawa F et al: Targeting of tumor cells for human gammadelta T cells by nonpeptide antigens. J Immunol, 2001; 167: 5092–98
14. Bonneville M, O'Brien RL, Born WK: Gammadelta T cell effector functions: A blend of innate programming and acquired plasticity. Nat Rev Immunol, 2010; 10: 467–78
15. Yin S, Zhang J, Mao Y et al: Vav1-phospholipase C-γ1 (Vav1-PLC-γ1) pathway initiated by T cell antigen receptor (TCRγδ) activation is required to overcome inhibition by ubiquitin ligase Cbl-b during γδT cell cytotoxicity. J Biol Chem, 2013; 288: 26448–62
16. Zhou J, Kang N, Cui L et al: Anti-γδ TCR antibody-expanded γδ T cells: A better choice for the adoptive immunotherapy of lymphoid malignancies. Cell Mol Immunol, 2012; 9: 34–44
17. Mattarollo SR, Kenna T, Nieda M, Nicol AJ: Chemotherapy and zoledronate sensitize solid tumour cells to Vgamma9Vdelta2 T cell cytotoxicity. Cancer Immunol Immunother, 2007; 56: 1285–97
18. Mao Y, Yin S, Zhang J et al: A new effect of IL-4 on human γδ T cells: promoting regulatory Vδ1 T cells via IL-10 production and inhibiting function of Vδ2 T cells. Cell Mol Immunol, 2016; 13: 217–28
19. Peng G, Wang HY, Peng W et al: Tumor-infiltrating gammadelta T cells suppress T and dendritic cell function via mechanisms controlled by a unique toll-like receptor signaling pathway. Immunity, 2007; 27: 334–48
20. Rong L, Li K, Li R et al: Analysis of tumor-infiltrating gamma delta T cells in rectal cancer. World J Gastroenterol, 2016; 22: 3573–80

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