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CD26/DPP4 levels in peripheral blood and T cells in Hashimoto's thyroiditis with normal thyroid function

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ABSTRACT

Aims: Exploring the CD26 expression in peripheral blood and T cells in Hashimoto's thyroiditis with normal thyroid function. And evaluating the association between CD26 expression and TGAb and TPOAb levels.
Methods: We collected peripheral blood and thyroid tissues from healthy controls and HT patients. Then we measured circulating CD26 level via ELISA and membrane-bound CD26 on Th and Tc cells via flow cytometry. Immunochemistry is used to evaluate CD26 expression in thyroid tissue. Moreover, we analyzed the correlation between serum CD26 and autoantibodies and CD26 on T cells.
Results: Compared with healthy controls, CD26 expression in serum and thyroid tissues were obviously lower in HT patients with normal thyroid function. And serum CD26 level was negatively related with TGAb. While no correlation was seen between membrane-bound CD26 and autoantibodies. There was no relation between serum CD26 and CD26 expression on T cells.
Conclusions: Taken together, our results show that the level of serum CD26 was associated with TGAb in HT patients with normal thyroid function.

1. Introduction

Hashimoto's thyroiditis (HT) is the most common organ-specific autoimmune disease. Although the etiology of HT has not been completely elucidated, it has been suggested that both genetic and environmental factors involved in the development of HT [1–4]. HT is recognized as an immune response which is directed at the thyroid gland leading to the gradually destruction of thyroid tissue and finally reduced biosynthesis of thyroid hormones [5]. HT is characterized by the production of thyroid autoantibodies and by thyroidal lymphocytic infiltration. Most of the patients with HT may undergo a long course with normal thyroid function.

In HT, there is an intolerance to several thyroid specific autoantigens and further the generation of autoantibodies. Among these, human thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies are recognized as the hallmark of HT and are commonly used as diagnostic indicators in clinical practice. TPO is the key enzyme responsible for the biosynthesis of the thyroid hormones. TPO is an important autoantigen in autoimmune thyroid diseases [6]. TG, synthesized and secreted by thyroid follicular epithelium, which is stored in the follicle lumens in physiological state. While in pathological state, TG is released when thyroid destruction occurs. There is evidence that autoantibodies to TPO and TG are responsible for the destruction of thyroid [7]. Moreover, previous 40 years' studies have confirmed the role of T cells and B cells in the pathogenesis of HT [8].

CD26, also known as dipeptidyl peptidase 4 (DPP4), could cleave N-terminal dipeptides from polypeptides with either proline or alanine residues in the penultimate position. CD26 is located as a soluble enzyme in body fluids or anchored in the plasma membrane of cells [9]. It has been reported that CD26 expressed on a variety of cell types, including T cells [10]. CD26 is well known for its role in glucose metabolism. DPP4 inhibitors have been developed as therapeutic agents for type 2 diabetes. Moreover, several studies have highlighted the important role of CD26 in T cell activation and immune responses. Emson and colleges [11] have shown increased expression of CD26 in patients with asthma and allergy. Results from experimental findings and preliminary clinical trials have identified potential effects in immune modulation in autoimmune diabetes [12,13]. DPP4 inhibitor MK626 in NOD mice altered the expression of the immune response-related genes in the thymus, especially those related to immunological central tolerance, which may contribute to the prevention of type 1 diabetes. Another study revealed that CD26 level on blood T cells was also associated with glucose control status in patients with type 2 diabetes [14]. The above studies suggested that CD26 may possess immune

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Table 1
Demographic characteristics of control and HT groups.

	Control	HT	*P*
N	39	71	
Gender (female %)	35 (89.7%)	67 (94.4%)	0.611
Age (year)	34.74 ± 10.65	38.74 ± 11.16	0.072
T3 (ng/ml)	1.07 ± 0.14	1.07 ± 0.22	0.875
T4 (μg/dl)	7.49 ± 1.29	7.25 ± 1.26	0.347
FT3 (pg/ml)	2.96 ± 0.39	3.02 ± 0.52	0.546
FT4 (ng/ml)	1.24 ± 0.17	1.23 ± 0.21	0.933
TSH (uIU/ml)	2.24 ± 1.22	2.92 ± 3.91	0.294
TgAb (IU/ml)	19.43 (9.99–10.01)	472.73 (106.17–458.25)	< 0.001*
TPOAb (IU/ml)	26.08 (5.05–12.72)	194.66 (26.15–261.65)	< 0.001*

HT: Hashimoto's thyroiditis; TT3, total triiodothyronine; TT4, total tetraiodothyronine; FT3, free total triiodothyronine; FT4, free total tetraiodothyronine; TSH, thyroid-stimulating hormone; TGAb, thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody. $_{*}P < 0.05$ compared between two groups.

modulation profile, offering the potential for extendibility to autoimmune diseases. Therefore, we presumed that CD26 may be associated with autoantibodies of HT with normal thyroid function.

2. Materials and methods

2.1. Study subjects

We recruited 71 outpatients with established HT in Beijing Luhe Hospital (The Affiliated Hospital of Capital Medical University) from December 2018 to April 2019. The inclusion criteria were as follows: increased TPOAb and/or TGAb, diffuse lesion in thyroid via ultrasound, normal thyroid function. The exclusion criteria were as follows: accompanied with other autoimmune diseases such as Grave's disease, pregnancy and any history of thyroid surgeries. Volunteers (n = 39) were recruited as healthy controls.

2.2. Flow cytometry

Whole-blood cells were collected using heparin sodium as an anticoagulant and measured within 8 h. After stimulated with BD Pharmingen™ Leukocyte Activation Cocktail, with BD GolgiPlug™, the tubes were then incubated in a humidified 5% CO_2 atmosphere for 5 h at 37 °C. For immune cell immunophenotypic characterization, each tube was incubated with the following antibodies for 15 min at room temperature in the dark condition: APC-CD26, APC-CY7-CD3 (BioLegend, San Diego, CA, USA) and FITC-CD8 (eBioscience Inc. San Diego, CA, USA). Then each tube was added with 100 μl BD IntraSure™ Kit (BD, San Diego, CA, USA) with gentle agitation and incubated for 5 min at room temperature in the dark condition. Next, 2 ml BD FACS™ Lysing solution was added in each tube with mixing and incubated for 10 min at room temperature in the dark condition. After centrifuging at 800 rpm for 5 min, the supernatant was discarded. Then 50 μl BD IntraSure Kit (BD, San Diego, CA, USA) was added. Each tube was stained for PE-CY7-IL-4, PE-IFN-γ (eBioscience Inc. San Diego, CA, USA) and incubated for 30 min at room temperature in the dark condition. After adding 2 ml of PBS and centrifuging at 800 rpm for 5 min, the resuspended contents were washed and then resuspended in 0.5 ml of PBS, the pellet was resuspended and used for acquisition. At least 10 000 gated events were counted in the defined lymphocyte gate. Data were acquired using a FACS CantoII and analyzed by FACSDiva software (BD, San Diego, CA, USA).

2.3. Histology

Thyroid tissues were fixed in 4% formaldehyde and embedded in paraffin. Hematoxylin and eosin (H&E) staining of thyroid sections

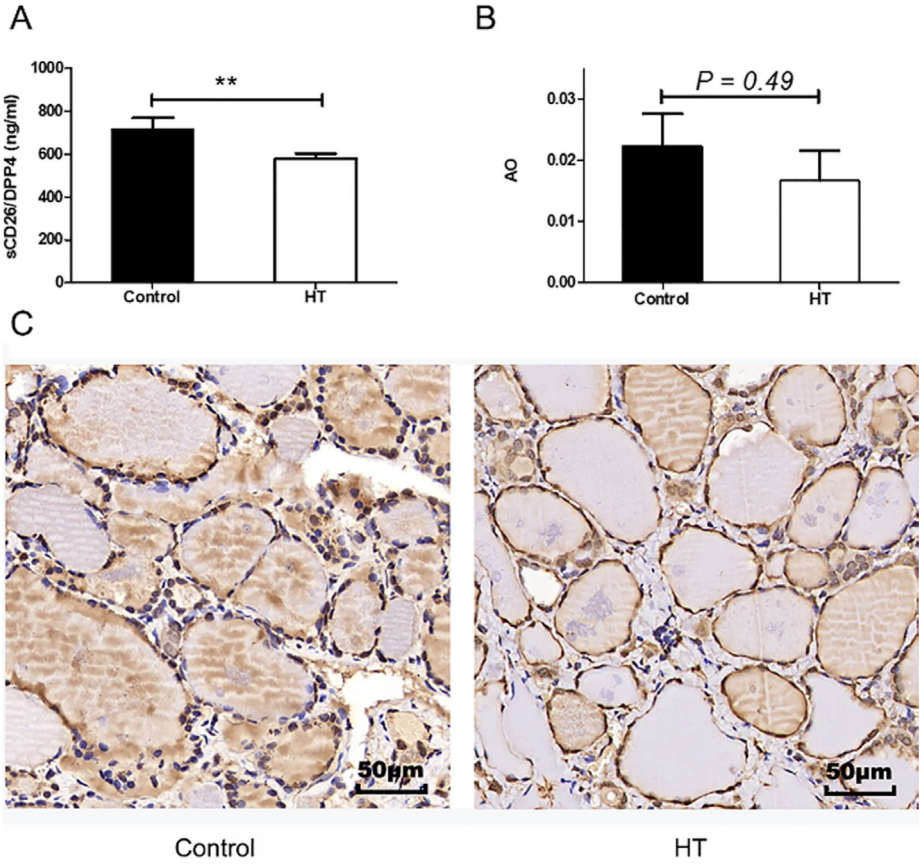

Fig. 1. The expression of sDPP4/CD26 in serum and thyroid tissues in control and HT groups. A. The serum CD26/DPP4 expression levels are decreased on HT patients than heathy controls ($P = 0.008$). B. The CD26 expression levels on thyroid tissue is slightly lowered in HT patients than heathy controls. C. CD26 staining of human thyroid tissue in heathy controls and HT patients. AO, average optical. HT, Hashimoto's thyroiditis. $^{**}P < 0.01$.

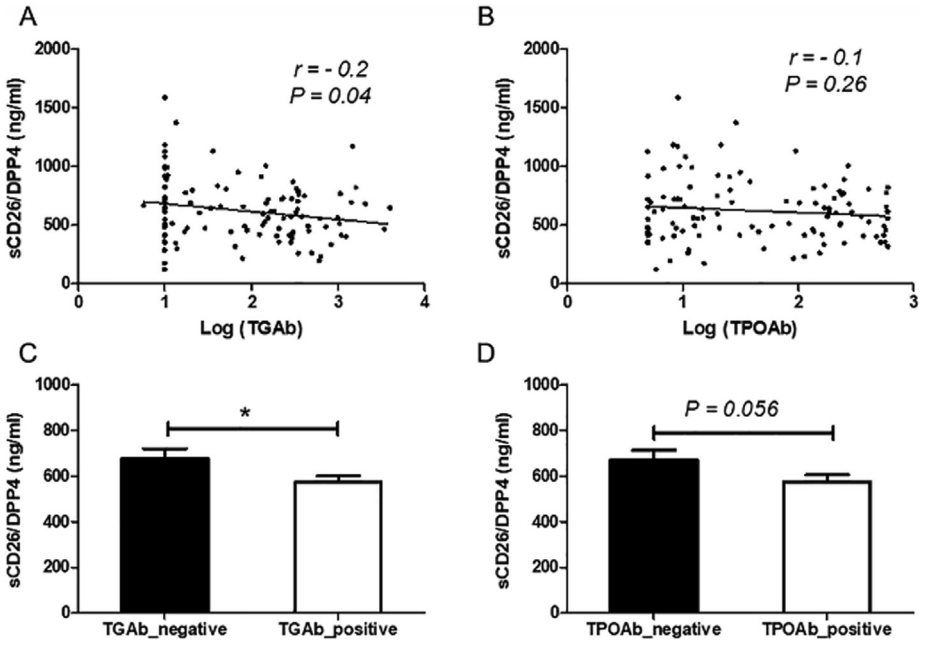

Fig. 2. The relationship between sDPP4/CD26 and TGAb and TPOAb in HT. A. The sCD26/DPP4 levels is negatively related with plasm TGAb levels. B. The sCD26/DPP4 levels is not related with plasm TPOAb. C. The sDPP4/CD26 level obviously decreased in the TGAb positive group compared with TGAb negative group (P = 0.039). D. The sDPP4/CD26 level slightly decreased in the TPOAb positive group compared with TPOAb negative group (P = 0.051).

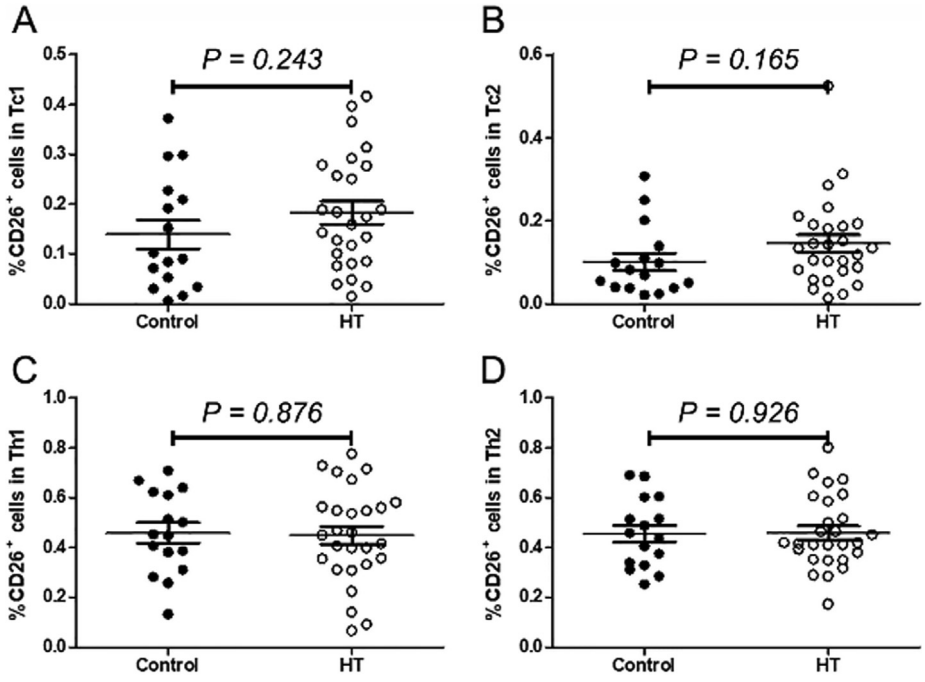

Fig. 3. The percentage of $CD26^+$ cells in the subsets of T cells. (A) Tc1 (B) Th1 (C) Th1 (D) Control, healthy controls; HT, Hashimoto's thyroiditis patients.

were performed using a standard protocol. To determine the expression of CD26, slices were incubated with the CD26 antibody (BD, San Diego, CA, USA) at 4 ℃ overnight. The results were analyzed using Image-pro plus 6.0 (Media Cybernetics, Inc., Rockville, MD, USA). The average optical (AO) method was applied: three filed (200x) was selected randomly from each slice of each group. Using Image-pro plus software to calculate the integrated optical density (IOD) and the pixel area of the tissue (AREA). Then AO = IOD/AREA, the higher AO value indicate the high CD26 expression in the thyroid tissue.

2.4. ELISA

sDPP4/CD26 was measured by a commercial human DPP4 ELISA kit (R&D, Systems, USA). The intra-assay and the interassay coefficient of variation was 5.8% and 8.6% respectively.

2.5. Statistics

The statistical analysis was performed using GrapdhPad Prism5.0. Normal distribution of data was detected using histogram or Q-Q plot. Nearly normally distributed continuous variables were presented as mean ± SD and differences were compared by student's *t* test. Nonnormally distributed continuous variables were presented as medians and quartiles and comparisons were done by Mann–Whitney *U* Test. Categorical variables were presented as number (percentages) and compared by Chi-square test. Relationships between variables were estimated using Pearson or spearman coefficient test. $P < 0.05$ were considered statistically significant.

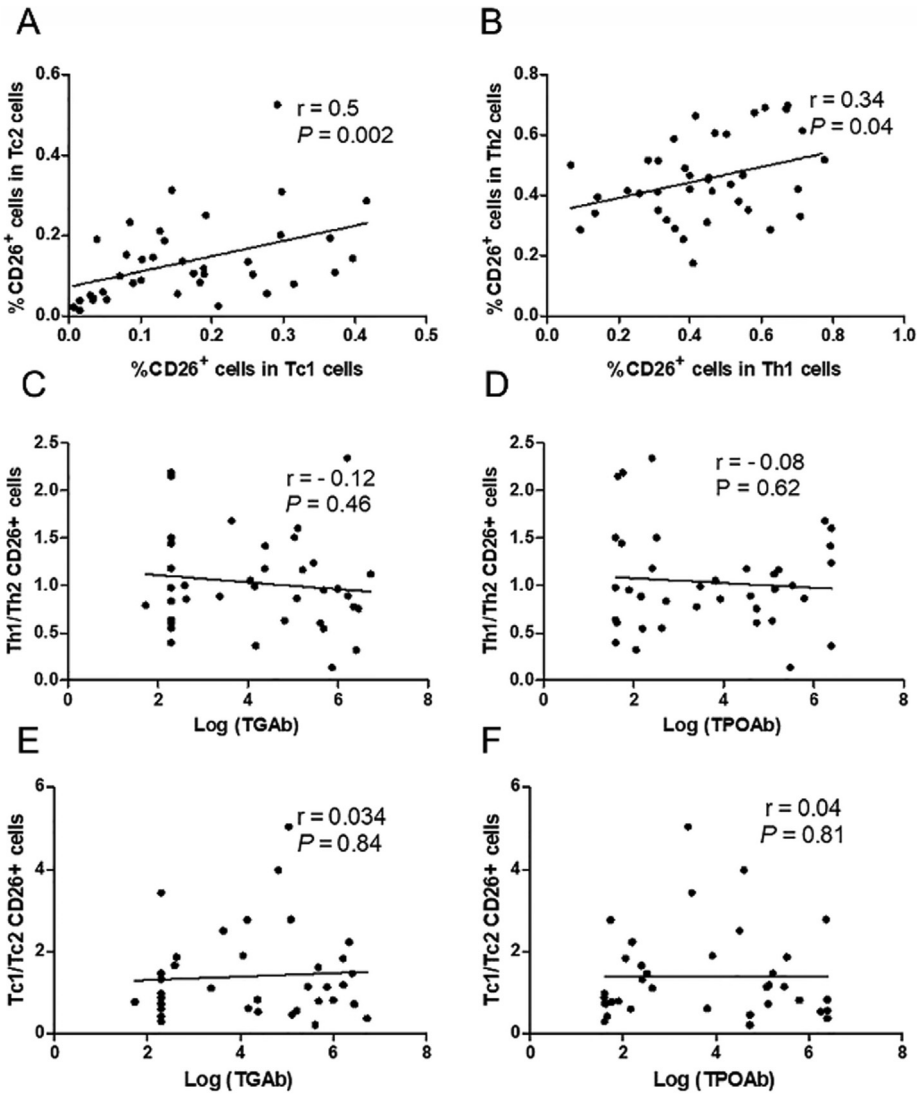

Fig. 4. The relationship between CD26 expression on T cells and TGAb and TPOAb in HT. A. Relationship between CD26/DPP4 expression on Tc1 and Tc2 cells. B. Relationship between CD26/DPP4 expression on Th1 and Th2 cells. C. Relationship between TGAb levels and the ratio of CD26/DPP4 expression on Tc1 and Tc2 cells. D. Relationship between TPOAb levels and the ratio of CD26/DPP4 expression on Tc1 and Tc2 cells. E. Relationship between TGAb levels and the ratio of CD26/DPP4 expression on Th1 and Th2 cells. F. Relationship between TPOAb levels and the ratio of CD26/DPP4 expression on Th1 and Th2 cells.

3. Results

3.1. The expression of sDPP4/CD26 in serum and thyroid tissues in healthy controls and HT patients

We collected the clinical data from 71 HT patients and 39 healthy controls. As shown in Table 1, there were no significant difference in gender, age and thyroid function between HT patients and heathy controls. However, the levels of TGAb and TPOAb were significantly higher in HT patients than heathy controls. Then we examined the serum DPP4/CD26 level in the two groups. Results showed that sDPP4/CD26 in HT group is significantly lower compared with heathy controls (717.21 ± 332.66 *vs*. 577.89 ± 209.15, $P = 0.008$) (Fig. 1A). In addition, to compare the expression of CD26 in the thyroid tissue, we also detected the expression of CD26 in the thyroid tissue of HT patients and healthy subjects. The immunohistochemical results demonstrated that the expression of CD26 in thyroid tissue is slightly decreased in patients with HT compared with the healthy controls, but with no statistical significance (Fig. 1B and C).

3.2. The relationship between sDPP4/CD26 and TGAb and TPOAb in HT

TGAb and TPOAb were known as the primary autoantibodies in HT. Therefore, we analyzed the correlation between sDPP4/CD26 and TGAb and TPOAb respectively. The data showed that sDPP4/CD26 is negatively related with TGAb ($r = -0.2$, $P = 0.04$) (Fig. 2A), but not TPOAb ($r = -0.1$, $P = 0.26$) (Fig. 2B). For further analysis, we transferred the continuous variables (TGAb, TPOAb) into categorical variables (TGAb positive and TGAb negative, TPOAb positive and TPOAb negative). Results showed that sDPP4/CD26 level obviously decreased in the TGAb positive group compared with TGAb negative group ($P = 0.039$) (Fig. 2C). Meanwhile, the trend can also be seen in the TPOAb positive group ($P = 0.056$) (Fig. 2D).

3.3. The relationship between CD26 expression on T cells and TGAb and TPOAb in HT

It is known that T cells including $CD4^+$ T cells and $CD8^+$ cells involved in the development of HT. To explore the relationship between the expression of CD26 on T cell and TGAb and TPOAb level in the peripheral blood. We measured CD26 expression on the surface of

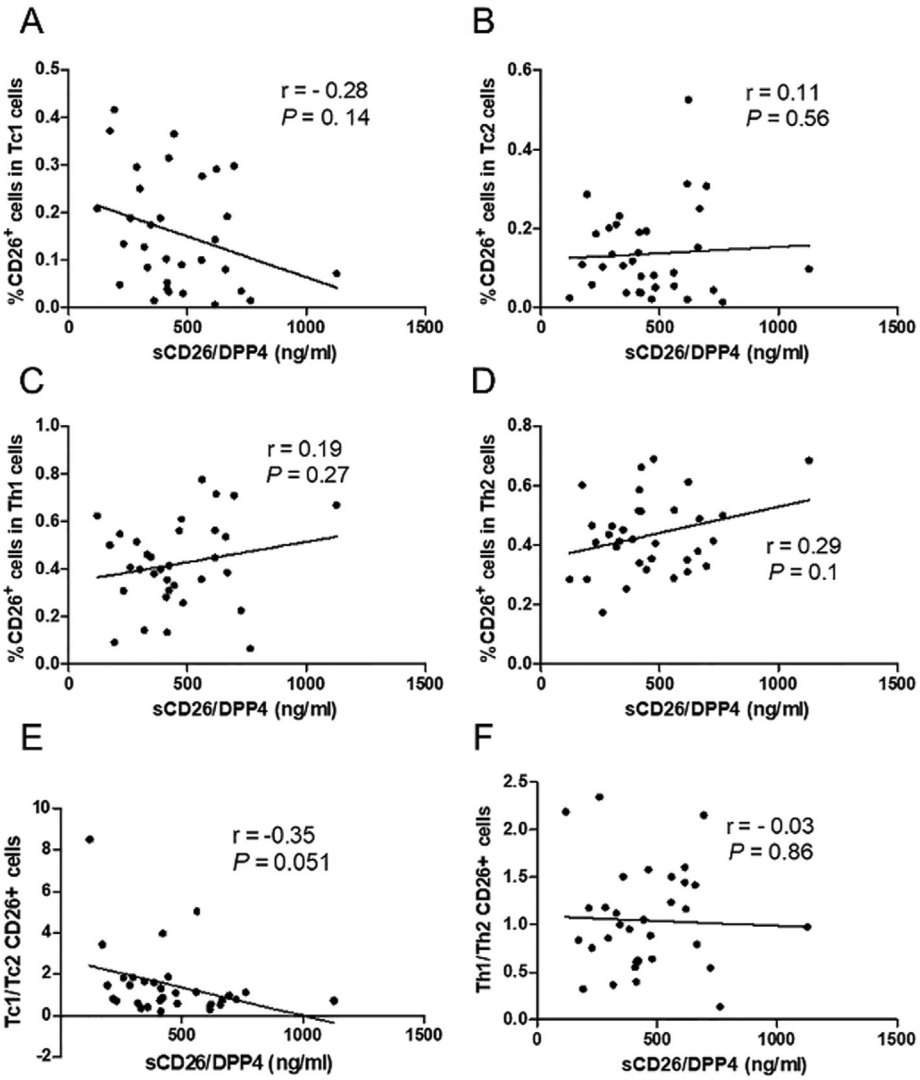

Fig. 5. The associations between serum sCD26/DPP4 levels and CD26/DPP4 expression on T cells. The relationship between CD26 expression in T cells and sDPP4/CD26. A. Relationship between and serum sCD26/DPP4 levels and CD26/DPP4 expression on Tc1 cells. B. Relationship between serum sCD26/DPP4 levels and CD26/DPP4 expression on Tc2 cells. C. Relationship between serum sCD26/DPP4 levels and CD26/DPP4 expression on Th1 cells. D. Relationship between serum sCD26/DPP4 levels and CD26/DPP4 expression on Th2 cells. E. Relationship between serum sCD26/DPP4 levels and the ratio of CD26/DPP4 expression on Tc1 and Tc2 cells. F. Relationship between and serum sCD26/DPP4 levels and the ratio of CD26/DPP4 expression on Th1 and Th2 cells.

$CD4^+$ Th1 cells, $CD4^+$ Th2 cells, $CD8^+$ Tc1 cells and $CD8^+$ Tc2 cells. The results showed that the percentages of CD26 expression on Tc1, Tc2, Th1 and Th2 cells have no difference between healthy controls and HT patients (Fig. 3). Then we analyzed the correlation among the subsets of T cells. The correlation analysis revealed that the expression of CD26 in $CD8^+$ Tc1 cells is significantly related with the expression of CD26 on $CD8^+$ Tc2 cells ($r = 0.5$, $P = 0.002$) (Fig. 4A). Moreover, the expression of CD26 on $CD4^+$ Th1 cells is significantly correlated with the expression of CD26 on $CD4^+$ Th2 cells ($r = 0.34$, $P = 0.04$) (Fig. 4B). While the expression of CD26 on $CD8^+$ Tc1cells/$CD8^+$ Tc2 cells is not significantly related with the level of TGAb and TPOAb (Fig. 4C and D). And the expression of CD26 on $CD4^+$ Th1 cells/$CD4^+$ Th2 cells was not significantly correlated with the level of TGAb and TPOAb as well (Fig. 4E and F).

3.4. The relationship between CD26 expression on T cells and sDPP4/CD26

To further explore the relationship between the expression of CD26 on $CD4^+$ and $CD8^+$ T cells and in serum (sDPP4/CD26). We performed correlation analysis and found that sDPP4/CD26 is negatively related to the expression of CD26 in $CD8^+$ Tc1 T cells, but without statistical significance ($r = -0.28$, $P = 0.14$). In addition, sDPP4/CD26 is positively related to the expression of CD26 on $CD8^+$ Tc2 T cells, $CD4^+$ Th1 T cells, $CD4^+$Th2 T cells, but without statistical significance ($r = 0.11$, $P = 0.56$, $r = 0.19$, $P = 0.27$, $r = 0.29$, $P = 0.10$, respectively). The sDPP4/CD26 is negatively related to the expression of CD26 on $CD8^+$ Tc1 cells/$CD8^+$ Tc2 cells and the expression of CD26 on $CD4^+$ Th1 cells/$CD4^+$Th2 cells ($r = -0.35$, $P = 0.051$, $r = -0.03$, $P = 0.86$, respectively) (Fig. 5).

4. Discussion

It is well known that CD26/DPP4 could regulate glucose homeostasis through enzymatic termination of incretin action. Recent researches have shown that CD26 is involved in various physiological and pathological processes of the immune system [15]. In this study, we focused on the relation between CD26 and TGAb and TPOAb in HT patients with normal thyroid function. We found that serum CD26 level was obviously lower in HT patients than healthy controls. Meanwhile, thyroid tissues in HT patients also showed reduced CD26 expression compared with healthy controls. Moreover, negative correlation was found between sCD26 and TGAb level. The similar trend can also be seen between sCD26 and TPOAb. This finding is consistent with other studies regarding autoimmune diseases, including systemic lupus erythematosus, arthritis and multiple sclerosis [16–18]. It has been reported that DPP4 activity in plasma, serum, and synovial fluid decreased in both patients with arthritis and several rat models of arthritis [19]. While rats resistant to induction of arthritis show higher plasma CD26 level [20]. It has been reported that both serum CD26 and membrane-bound CD26 have DPP-4 activity. CD26 can cleave proline,

alanine or hydroxyproline at the second position to cut polypeptides into dipeptides. CD26 is thought to be involved in a type 1 immune response. The IFN-γ induced type 1 chemokines CXCL-10 and CXCL-11 are both substrates for CD26. CD26-mediated treatment of these chemokines reduced their chemotaxis. In the current study, a decrease in the concentration of serum CD26 and a decrease in the level of membrane-bound CD26 were observed in patients with HT, which to some extent explained the increase in plasma CXCL-10 levels in patients with HT. In conclusion, a decrease in CD26 levels may exacerbate type 1 immune responses by upregulating chemokines in HT [21,22].

CD26 was originally described as a surface marker for T cells, which is specifically for a subset of $CD4^+$ cells, which respond maximally to recall antigen tetanus toxoid and induce B-cell IgG synthesis. CD26 expression on $CD4^+$ T cells correlates with Th1 responses. CD26 is also a marker for T cell activation [15]. Therefore, we examined CD26 expression on the surface of Th and Tc cells. Results indicated that there was no difference in the CD26 expression on the Th and Tc cells. Previous study also revealed that the concentration of sCD26 and membrane-bound CD26 expression on CD8+ T cells are reduced in HT patients [22]. The inconsistence may derive from the difference in thyroid function of HT patients. Yalei Liu and colleagues [22] chose HT patients with subclinical hypothyroidism, which may indicate active stage of the disease. While our study focused on HT patients with normal thyroid function. These results suggest that the change of CD26 expression in T cells may be an early marker of active phase in HT.

The lower CD26 expression indicated elevated inflammation. We next analyzed the relationship of CD26 in serum and T cells in HT patients and healthy controls. While results showed that sCD26 has no obvious association with CD26 expression on the surface in the Th1/Th2, Tc1/Tc2 cells. And there is no relationship seen between CD26 expression of Th and Tc cell and the level of TGAb and TPOAb. Recently one study has shown that different tissue derived sCD26 exerted different function. CD26 from adipocytes and hepatocytes regulate liver and adipose tissue inflammation [23]. Therefore, the source of sCD26 remains unclear.

Taken together, our results show that the level of serum CD26 are reduced in HT patients with normal thyroid function. And sCD26 is negative related with the level of TGAb. Low sCD26 level may facilitate the immune response and then increase the production of TGAb and TPOAb. While the underlying mechanism of CD26 in HT need further research to illuminate it.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Committee of Beijing Luhe Hospital. This article does not contain any studies with animals performed by any of the authors.

Declaration of Competing Interest

None.

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