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SHORT COMMUNICATION

Soluble programmed death-1 ligand 1(sPD-L1) is significantly reduced in the serum of type 1 diabetes patients

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Introduction

Type 1 diabetes (T1D) is an autoimmune disease resulting from destruction of insulin-producing β cells mediated by T cell activation. The balance of stimulatory and inhibitory signals provided by cell surface interactions between T lymphocytes and co-stimulatory molecules is crucial for maintaining peripheral immune tolerance. Excessive expression of positive molecules or negative molecular expression defects can induce T cell immune tolerance imbalance, leading to the occurrence of autoimmune diseases. Programmed death-1 (PD-1) and its ligand PD-L1, negative co-stimulatory signal, play an important role in the development and progression of T1D [1]. Soluble programmed death-1 ligand 1 (sPD-L1), thought to be released through proteolytic cleavage of membrane PD-L1, has little research in T1D. This study aimed to explore the presence of PD-L1 in serum of type 1 diabetes patients and to investigate the influential factors of sPD-L1.

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Methods

Patients and serum samples

In this study, blood samples were collected after overnight fasting from patients at the Endocrinology Department in the second Affiliated Hospital of Soochow University, Suzhou, China between 2013 and 2017. All the T1DM patients were diagnosed with criteria of American Diabetes Association (Reference from Diabetes Care published by ADA). Samples from healthy blood donors, self-report healthy, were chosen as matched controls. Prior to commencing this study, the approval from the Ethics Review Board of the second Affiliated Hospital of Soochow University was granted.

Experiment methods

Serum and plasma were analyzed in the central laboratory of the Second Affiliated Hospital of Soochow University using routine procedures. Serum sPD-L1 concentration was quantified by enzyme-linked immunosorbent assay (ELISA). The samples were centrifuged at 1500 rpm for 10 min, and the cell-free sera were stored at − 20 °C for the ELISA assay. The levels of sPD-L1 in the sera were determined in single well using the sPD-L1 ELISA system prepared in Institute of Clinical Immunology Research Laboratory of Jiangsu Province, Suzhou, China, previously [2].

Statistical analysis

Statistical analysis was performed using the IBM SPSS statistic 22 (Chicago, IL, USA). Continuous variables were expressed as a median (range). For statistical analysis, differences in continuous variables between two independent samples were evaluated by the Mann–Whitney *U* test. Dichotomous variables were compared by the Chi-square test. Spearman's rank correlation analysis was used to evaluate

the associations between clinical variables and PD-L1 levels. The statistical software GraphPad Prism5.0 (GraphPad Software, La Jolla, CA) was used for all graph creation.

Results

sPD-L1 in type 1 diabetes and healthy controls

In this study, we recruited 176 participants divided into T1DM group and healthy control group (88 participants for each group). The clinical characteristics of the study population are summarized in Table 1.

sPD-L1 was detectable in both type 1 diabetes patients and healthy controls. Compared with healthy control group (0.3474 [0.077–1.756] ng/mL), serum levels of PD-L1 were significantly lower in type 1 diabetes patients (0.1547 [0.0714–1.0077] ng/mL) ($P < 0.002$) (Fig. 1).

However, in type 1 diabetes patients, there were no significant correlation between titers of sPD-L1 and any clinical features including fasting C-peptide, random blood glucose levels, age, duration, HbA1c, AAbs, Cr, BUN, UA, ALT, AST, TC, TG, LDL and HDL.

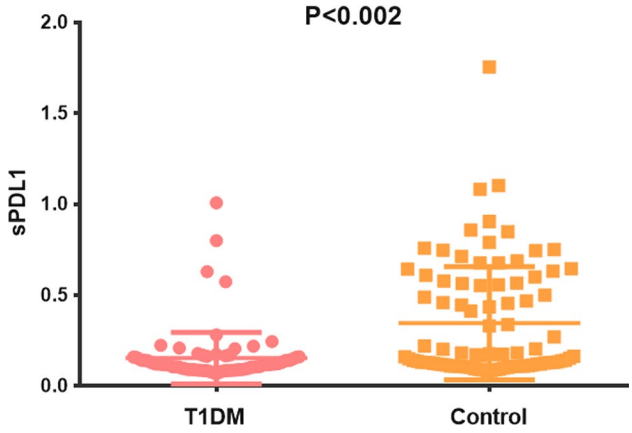

Fig. 1 Concentration of sPD-L1 is plotted for each of the 88 cases of T1DM patients and 88 cases of healthy donors. The average concentration was 0.1547 for T1DM and 0.3474 for control ($P < 0.002$)

Discussion

In the present study, serum concentration of sPD-L1 level was decreased in T1DM patients compared to controls

Table 1 Clinical features of study population

	Type 1 diabetes	Health control	*p* value[a]
Sample size, *n*	88	88	
Age, years	28 (8–53)	31 (16–59)	0.073
Gender, female (*n* %)	40 (45%)	44 (50%)	0.546
Duration, years	7 (0–39)	–	
Fasting venous blood glucose (mmol/L)	10 (1.8–28)	–	
Cr (umol/L)	56 (23–240)	–	
BUN (umol/L)	5.1 (1.4–15.2)	–	
UA (umol/L)	288 (118–727)	–	
ALT (IU/L)	17 (6–79)	–	
AST (IU/L)	18 (7–49)	–	
TC (mmol/L)	3.71 (0.33–8.77)	–	
TG (mmol/L)	1.77 (0.28–6.57)	–	
LDL (mmol/L)	2.64 (0.73–6.26)	–	
HDL (mmol/L)	1.51 (0.62–3.59)	–	
Fasting C-peptide (ng/mL)	0.43 (< 0.01–2.73)	–	
Positive anti-ICA (%)[b]	16 (31%)	–	
Positive anti-GAD (%)[b]	26 (50%)	–	
Positive anti-IAA (%)[b]	4 (8%)	–	
HbA1c (%)	8.74% (5–17.1%)	–	
PD-L1 levels (ng/mL)	0.1547 (0.0714–1.0077)	0.3474 (0.077–1.756)	<0.002

[a]*P* value is based on the statistical analysis by the Mann–Whitney *U* test or the Chi-square test assessing overall group differences

[b]Not all the patients have the antibody results, only 52 patients received an antibody screening

[c]Abbreviations: Cr for creatinine, BUN for urea, UA for uric acid, ALT for alanine aminotransferase, AST for aspartate transferase, TC for cholesterol, TG for triglycerides, LDL for low-density lipoprotein, HDL for high-density lipoprotein

($P < 0.002$). It indicated that sPD-L1 may play a protective role in the mechanism of type 1 diabetes.

Numerous studies have demonstrated that PD-1/PD-L1 signaling pathway is important in peripheral immune tolerance, tumor immunity, autoimmune diseases, and chronic infections. As an immunoregulatory molecule, PD-L1 regulates immune response by inducing apoptosis of T cell [3]. Blockading PD-1/PD-L1 interaction can lead to induction and progression of type 1 diabetes in NOD mice. In addition, the blockade of PD-1/PD-L1 on T cell may lead to T cell activation, which in turn induces an autoimmune response against pancreatic β cells and rapid destruction of β islet cells.

More than 20 cases of diabetes so far have been reported related to anti-PD-1/PD-L1 antibody treatment [4]. However, little is known about the expression of sPD-L1 in type 1 diabetes patients versus healthy people. Researches in increasing number show co-stimulatory molecules can exist in both membrane and soluble forms. sPD-L1 is released through proteolytic cleavage of membrane PD-L1, although any other source cannot be excluded. The soluble protein factors can participate in blood circulation and play a regulatory role in the immune response like cytokines. They can affect not only the adjacent cells but also the receptor on the surface of the distal cell, so as to participate in the occurrence and development of the disease.

We performed ELISA analysis and demonstrated that the titer of serum sPD-L1 level is significantly lower in type 1 diabetes patients. It is consistent with the result found by Vella et al. that T cells derived from T1D patients had decreased PD-1 expression compared to other study groups [5]. sPD-L1, a soluble co-stimulatory molecule, like the molecules on the surface of the cell membrane, bind to the receptor in the same way, mediating certain biological functions. Although the exact function of sPD-L1 still remains unclear, perhaps is same to that of its membrane bound form, which also has part of effect on T cells. Taking considering of previous studies that showed above, we assumed that pancreatic islet suffered autoimmune destructions due to the decrease of sPD-L1 in pathogenesis of T1DM.

Further studies, however, should be carried out to fetch up the limitations of our study. Firstly, the PD-L1 expression levels on T cell infiltrated in islets were not able to detect in our study. So we are unable to perform an analysis on the relationship between PD-L1 expressed on T cells infiltrated in islets of T1DM patients and serum PD-L1, which could provide further evidence to characterize the role of PD-L1 in T1DM progression. Secondly, due to the small sample size, there was no correlation found between sPD-L1 level and clinical, metabolic, immune variables so a larger population is required for validation.

In summary, in our study, sPD-L1 levels were found to be declined in participants with T1DM. sPD-L1 is regarded not only as a regulator of T cell activation but may also be a new biomarker for T1DM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008.

Human and animal rights This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent Informed consent was obtained from all patients for being included in the study.

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