International Immunopharmacology 75 (2019) 105757

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

CD26 in autoimmune diseases: The other side of "moonlight protein"

Yunjuan Zhao

Department of Endocrinology, The Second Affiliated Hospital of Guangzhou Medical University, The East Chang-Gang Road, Guangzhou, China

ARTICLE INFO

Keywords:
Dipeptidyl peptidase 4
Rheumatoid arthritis
Type 1 diabetes
Systemic lupus erythematosus
Multiple sclerosis
Inflammatory bowel disease

ABSTRACT

Dipeptidyl peptidase 4 (DPP-4) is a serine protease, which has enzymatic activity to selectively clean the N-terminal dipeptide of peptides and proteins with proline or alanine in the second position. DPP-4 inhibitor has been widely used for the treatment of type 2 diabetes by increasing the level of the glucagon-like peptide-1 and decreasing the glucose level. DPP-4, also known as lymphocyte cell surface protein CD26, plays a core role of T cell immunity. Many roles of CD26 in other immune cells have been found. As a "moonlight protein", the effect of CD26 in autoimmune diseases has attracted more and more attention. The paper reviewed the function and potential effect of CD26 in autoimmune diseases, which shows CD26 may be a new target of autoimmune diseases deserved further study.

1. Introduction

Dipeptidyl peptidase 4 (DPP-4) is a serine protease, belonging to the type II transmembrane glycoprotein family. It has enzymatic activity to selectively clean the N-terminal dipeptide of peptides and proteins with proline or alanine in the second position [1]. The soluble form of DPP-4 exists in serum, plasma, urine, semen, cerebrospinal and synovial fluid [1]. DPP-4 is also known as lymphocyte cell surface protein CD26, which is expressed on the surface of T cells, NK cells, B cells and myeloid cells and involved in T cell development and stimulation [2]. The effect of CD26 in the immune system gets more and more attention in the recent years. The change of expression and activity of CD26 in serum has been observed in several autoimmune diseases, including rheumatoid arthritis (RA), type 1 diabetes, systemic lupus erythematous (SLE) and inflammatory bowel disease (IBD) [3], which suggests it might be involved in the pathogenesis of autoimmune diseases. The complex role of CD26 in the pathogenesis of autoimmune diseases has not been elucidated until now. In this article, we review the recent research progress of CD26 in autoimmune diseases, exploring the potential effect of CD26 in the pathogenesis of autoimmune diseases.

CD26 is found on the surface of many cell types, such as lymphocytes, endothelial cells and epithelial cells. Among rat lymphocytes, about 78–85% spleen cells and 80–87% lymph node cells have CD26 expression [2]. CD26 involves in the development, maturation, differentiation and activation of T cells, and participates in immune regulation. Zhao et studied the effect of CD26 in T cell differentiation and activation in vitro [4]. He found that after antigen stimulation, the percentage of CD26 + CD4+ cells and CD26 + CD8 + T cells increases significantly and CD26 high expression is associated with the differentiation of Th1 and Th17 cells [4]. DPP-4 inhibitor suppresses the proliferation of CD4 + T and CD8 + T cells in a dose dependent manner [5]. DPP-4 inhibitors have the effect to suppress antigen-stimulated CD4 + T cell clones to produce IFN-γ, TNF-α and IL-4 in a dose-dependent manner, which suggests the regulative effect of CD26 in autoimmune diseases [6]. DPP-4 inhibitor (sitagliptin) inhibits the proliferation of phytohemagglutinin stimulated peripheral blood mononuclear cells (PBMC) from healthy volunteer, decreases CD26 expression and reduces the percentage of Th1 (CD4 + IFN-γ + T), Th2(CD4 + IL-4 + T) and Th17(CD4 + IL-17 + T), which suggests its immunosuppressive effect of T cell differentiation [7]. CD26 is considered to involve in B cell activation. After stimulation with mitogen, the expression of CD26 on human B cells increases significantly [8]. Further DPP-4 inhibitors suppress DNA synthesis in mitogenic active B cells, which confirms CD26 involves in B-cell activation [8]. CD26 deficiency leads to the number of B cells decreased in older age mouse (after 6 months) [9]. These studies suggest CD26 is involved in B cell activation as a positive regulator, oppositely, DPP-4 inhibitor or CD26 deficiency suppresses B cell activation.

The combination of CD26 and factor Xa activates inflammatory signaling in macrophages [10]. Hepatocyte-specific CD26 silence suppresses visceral adipose tissue inflammation [10], which suggests hepatocyte-specific CD26 in obesity promotes pathological adipose inflammation. DPP-4 inhibitor prevents the growth of intracranial aneurysms by inhibiting macrophage infiltration and activation [11]. Sitagliptin reduces the serum soluble CD163 (a marker for activated macrophage) in patients with type 2 diabetes [12]. Sitagliptin has the effect to decrease inflammation by regulating macrophage M1/M2 polarization in ob/ob mice [13]. DPP-4 inhibitor attenuates obesity-

E-mail address: yougukedream@163.com.

https://doi.org/10.1016/j.intimp.2019.105757
Received 22 April 2019; Received in revised form 20 June 2019; Accepted 10 July 2019
Available online 26 July 2019

related inflammation by regulating M1/M2 macrophage polarization [14]. CD26 is found to express on the surface of a restricted dendritic cells (DC) subpopulation [15]. The CD26 expression enhances during monocyte differentiation to DC [16]. Knockdown of CD26 in human DCs significantly attenuated the ability to activate T cells [16], which suggests the potential role for dendritic-expressing CD26 in adipose inflammation. CD26 is also a well-known activation marker of natural kill (NK) cells. The proportion of CD4 + NKT lymphocytes is significantly decreased in CD26$^{-/-}$ mice [17]. CD26 expresses on the surface of different kinds of immune cells and involves in their function, which suggests its role in autoimmune diseases.

2. CD26 in rheumatoid arthritis

CD26 plays a crucial role in T cell immunity, however the exact role of CD26 in RA has not been defined. Plasma CD26 is significantly decreased in patients with RA, compared with controls, and CD26 correlates negatively with inflammatory markers [18]. Serum CD26 is significantly decreased [19,20] and correlated inversely with disease activity in patients with RA [21], which suggests that CD26 not only initiates but also participates in the maintenance of RA.

In RA, CD26 activity is considered to be a contributing factor. CD26 activity in both serum and synovial fluid is significantly decreased in patients with RA, compared with osteoarthritis [22]. In another study, it shows that serum CD26 activity is decreased in patients with RA, although its levels are not elevated compared with normal control [23]. Masatoshi Kamori et al. found that CD26 activity of synovial membrane decreases in patients with RA compared with osteoarthritis [24], which suggests this peptide may play some role in immunological disorders in patients with RA. Nathalie Busso et al. found that plasma CD26 activity decreases in murine antigen-induced arthritis, which probably influents the regulation of stromal cell-derived factor-1(SDF-1)/SDF-1 receptor (CXCR4) axis [25]. Rats resistant to collagen-induced arthritis are characterized by increased CD26 activity in plasma, on the other hand, decreased CD26 activity in membrane-bound fractions of PBMCs prone to develop arthritis [26]. Regulation of CD26 activity is considered to affect signal transduction, chemokines, proliferation and recruitment of immune cells [27], which suggests that decreased CD26 activity might involve in the pathogenesis of RA [26].

Decreased plasma CD26 concentrations and activity are observed in patients with active RA compared to osteoarthritis, however, CD26 expression and activity in blood mononuclear cells show no significant difference between the RA and OA patients [28]. Compared with healthy controls, patients with RA show significantly increased percentage of CD3 + CD26+ cells [29]. CD26 expression on PB T cells is increased in patients with active RA, but not inactive RA [30]. Patients with active RA show higher percentages of peripheral blood CD26 + CD4 + T cells, compared with inactive RA and control subjects [31]. The percentage of CD4 + CD45R0 + CD26-cells is significantly decreased in patients with RA, accompanied with decreased serum CD26 activity [32].

Many studies show decreased levels of circulating DPP-4 in RA, however, the expression of CD26 on the surface of PBMC or T cells is increased. One of reasonable hypothesis is that the process of shedding CD26 from the cell surface is blocked in inflammatory response [33]. RA is considered a chronic autoimmune disease which is initiated by an antigenic peptide derived from an autoantigen or exogenous antigen. The arthritogenic peptide is presented by RA-associated MHC II molecule, which leads to the expansion of pathogenic CD4 + T cells. Collagen (especially type II collagen) is considered the most important candidate autoantigen for RA [34]. CD26 is a binding receptor for collagen [35]. From collagen recognized and binding to regulation of extracellular adenosine deaminase [36], CD26 probably plays substantial effect in the progress of RA. Except for collagen, CD26 also can bind with fibronectin [37]. Considering the effect of fibronectin in the pathogenesis of RA [38], CD26 probably involves in the pathogenesis of RA via bypass way. All the studies above points to CD26 might involve in the pathogenesis of RA and play an important role. However, the detailed mechanism is still unknown, which deserved further study.

Owing to the probable role of CD26 in RA, it implies CD26 to be a potential target to understand the pathogenesis of RA and novel treatment [26]. Anti-CD26 Igs levels are significantly increased in patients with RA compared to healthy donors [39]. High sensitivity and specificity of serum anti-CD26 levels was observed as diagnostic indicator in patients with RA, which suggests that it may involve in the pathogenesis and be a useful biomarker for early diagnosis of RA [39]. Injection of recombinant human CD26 reduces inflammation and attenuates the severity of arthritis in mice with collagen-induced arthritis [40]. RA patients have increased anti-CD26 levels compared with controls, which suggests its participation in pathogenesis and the potential as markers for diagnosis and target for treatment [39]. Some cases reported that DPP-4 inhibitor induced arthritis. The possible mechanism probably includes immunological effects, such as role of cytokines, chemokines and inflammatory cells, and genetic mechanism [41].

3. CD26 in type 1 diabetes

Increased serum CD26 activity is observed in type 1 diabetes (T1D) children [42]. Patients with latent autoimmune diabetes express higher CD26 levels compared to type 1 and type 2 diabetes, meanwhile, there is no difference of CD26 activity between type 2 diabetes and healthy controls [43]. CD26 activity elevates in patients with T1D compared with control subjects [44], which is correlated with diabetic duration [45]. Increased CD26 activity in type 1 diabetes is probably related to autoimmune process and a possible hormonal feedback mechanism [44]. Like RA [46], the correlation between CD26 expression and type 1 diabetes probably owes to the CD26 mediated T cell costimulation in autoimmune process. Serum CD26 activity increases and CD26 expression on lymphocyte decreases in patients with T1D, which indicates the potential effect of DPP-4 inhibitor in patients with T1D [44]. Serum CD26 activity is inversely correlated with plasma glucagon-like peptide (GLP)$^{17\text{-}36}$ levels in patients with T1D [47].

The potential role of CD26 in type 1 diabetes is mainly actualized by the observation of DPP-4 inhibitor treatment in experimental animal studies. Vildagliptin, a DPP-4 inhibitor, ameliorates oxidative stress and preserves islet beta-cell function in type 1 diabetic rats [48]. In alloxan-induced diabetes rat model, vildagliptin treatment induced β cell neogenesis and increased insulin secretion in a later phase of T1D [49], which suggests that DPP-4 inhibitor is capable of improving β cell function even in deterioration phase of disease. However, the detailed mechanism of β cell neogenesis is still unknown. In the non-obese diabetic mouse (a classical mouse model, which spontaneously develops T1D), DPP-4 inhibitor reduces the incidence of T1D and attenuates the insulitis, furthermore, it increases CD26 expression on CD8+ effector memory T lymphocytes from spleen and pancreatic lymph nodes in NOD mice [50]. MK626, a DPP-4 inhibitor, modifies expression of immune-related genes in the thymus of NOD mice [51]. NVP-DPP728, a DPP-4 inhibitor, reverses new on-set diabetes by attenuating insulitis, increasing CD4 + CD25 + FOXP3 + Treg cells and stimulating islet beta-cell replication in NOD mice [52]. The D41-IP, a DPP-4-based epitope vaccine prevents T1D probably by inhibition of T cell proliferation and reduction of insulitis in streptozotocin-induced diabetes mice [53]. Immunization with a DPP-4 based multi-epitope vaccine induces the streptozotocin treated mice to produce specific anti-CD26 antibody, induces splenic T cell proliferation and decreases diabetic and insulitis incidence [53]. DPP-4 inhibitor exerts anti-inflammation effect via inhibiting macrophages infiltration and down-regulating inflammatory molecules in a rat model of T1D [54].

Recently few clinical studies pay attention to the effect of DPP-4 inhibitors on T1D. Sitagliptin (a DPP-4 inhibitor) treatment preserves β cell function in patients with autoimmune diabetes, which is probably due to the immune regulatory effect of DPP-4 inhibitor [55]. DPP-4

inhibitor has been demonstrated to preserve β cell function in patients with latent autoimmune diabetes, possibly owing to its immune modulatory effect [56].

These studies indicate that CD26 involves in the pathogenesis of T1D, and DPP-4 inhibitor may be a potential drug to protect β cell function by immunoregulation.

4. CD26 in systemic lupus erythematosus

In the New Zealand Black mouse, an animal model of SLE. CD26 activity in plasma and spleen is decreased, compared with the control mice [19]. Likewise, decreased serum CD26 activity was observed in patients with SLE compared with controls, which indicates the potential effect of CD26 in the pathogenesis of SLE [19,57]. PTY Wong et al. found that there is no significant difference of plasma soluble CD26 between SLE patients with control subjects, however, decreased cell surface expression of CD26 on iNKT cells in SLE patients was observed, compared with controls [58]. In this study, no difference of plasma soluble CD26 between SLE and control is probably due to the narrow distribution of disease activity and small number of active patients. However, in another study, Valizadeh M et al. found that CD26 gene expression of peripheral blood cells increases significantly in SLE patient compared with the healthy controls, which is not related to the disease activity [59]. In this study, the CD26 mRNA was tested using peripheral blood cells, however, other studies tested the plasma levels and activity of CD26, which probably explained the difference of CD26 expression. Until now, the studies of CD26 in SLE are limited in the expression of CD26 in patients with SLE. There is no relatively mechanism study in vivo or in vitro. It is still unclear that the effect of CD26 in the pathogenesis of SLE, which deserved further study.

5. CD26 in multiple sclerosis

Multiple sclerosis (MS) is a T-cell mediated autoimmune disease, determined by genetic and environmental factors. Plasma DPP-4 concentration and activity is significantly decreased in MS patients compared with healthy control, inversely, the frequency of CD8 + $CD26^{hi}$T cells is increased in MS patients [60].

CD26 plays a pivotal role in autoreactive T cell activation. Gene deletion of CD26 downregulates Th1 immune responses in $CD26^{-/-}$ mice [61]. Th1 and Th17 lymphocytes involvement in the pathogenesis of MS has been certified by numerous sources. Inhibition of CD26 and CD13(APN) increases TGF-β1 production and modulates T cell function and autoimmunity in central nervous system, which suggests its potential therapeutic effect in MS [62]. PETIR-001, a dual inhibitor of DPP-4 and aminopeptide N, has the effect to delay and ameliorate EAE in SJL/J mice, which suggests its therapeutic effect on CNS inflammation [63]. DPP-4 inhibitor decreases the clinical symptoms of adoptive transfer EAE and increases the concentration of TGF-β1 in plasma and spinal cord tissue [64]. DPP-4 inhibitor increases TGF-β secretion and suppresses TNF-α secretion and autoreactive T cell proliferation in autoimmune encephalomyelitis [64]. Many studies showed the protective effect of DPP-4 inhibitor in MS models, possibly due to increase TGF-β secretion. However, the detailed effect of CD26 in the pathogenesis of MS is still unclear, which deserves further study.

6. CD26 in inflammatory bowel disease

The patients with Crohn's disease (CD) and ulcerative colitis have significantly lower serum DPP-4 activity compared to healthy control, which correlates inversely with disease severity [65]. Serum CD26 levels decreases in patients with CD, compared with controls, besides, CD26 levels are relevant to the severity of CD [66]. It indicates DPP-4 to be a potential target for the treatment of IBD [67].

The effect of CD26 in inflammatory events of IBD is still unknown. Lara Baticic et al. found that CD26 deficiency affects the immune response during the process of colitis development in $CD26^{-/-}$ mice [68]. Increased percentage of splenic CD8 + T cells is observed in the acute phase of dextran sulfate sodium-induced colitis, accompanied with increased expression of NF-κB p65 subunit in the colon in CD26-deficient mice [69], which suggests CD26 deficiency involves in immunophenotypic changes during the development of colitis. Compared with healthy mice, colonic CD26 activity is decreased in dextran sulfate sodium-induced colitis in C57BL/6 mice [70]. CD26 deficiency significantly increases infiltration of macrophages in the colonic mucosa in dextran sulfate sodium –induced CD26-/- mice [71].

DPP-4 inhibitor treatment alleviates disease activity, decreases histological score and increases the Ki67-positive rate and insulin-like growth factor-1 gene expression in experimental murine colitis [71]. DPP-4 inhibitors alleviate neutrophil infiltration and maintain regulatory T-cells population in dextran sulfate sodium colitis, which proposes its potential therapeutic effect in IBD [72].

7. CD26 in other autoimmune diseases

In a population-based study, the rate of Hashimoto's thyroiditis is significantly higher in patients received DPP-4 inhibitors treatment than diabetic control subjects [73]. Compared with healthy people, the HT patients have lower plasma sCD26 concentration, accompanied with lower CD26 expression on the surface of CD8 + T cells [74]. Administration of the DPP-4 inhibitor remarkably suppresses cardiac fibrosis and reduces inflammatory cytokine gene expression in experiment autoimmune myocarditis mice [75]. Thus the agents present in DPP-4 inhibitors may be useful to treat and/or prevent clinical myocarditis.

Selective decrease of CD26 expression was found in patient with HIV-1 infection [76]. CD26 is considered as a key adhesion molecule for HIV peptide binding [77], which suggests the key role of CD26 in the pathogenesis of AIDS. CD26 is also considered to be involved in tumor immunity, acute graft-versus-host disease and other immune-mediated disorders.

8. Conclusion

CD26 exists on the surface of many immune cells and involves in their functions, such as T cells, B cells, macrophages and dendritic cells (Table 1). Except its enzyme activity, CD26 involves in the pathogenesis of many autoimmune diseases. Serum CD26 is significantly decreased in RA, SLE, MS and IBD, however, increased serum CD26 expression and activity is observed in T1D, likewise, CD26 expresses differently in immune cells in autoimmune diseases, which suggests CD26 acts in different ways in different autoimmune diseases (Table 1).

The effect of DPP-4 inhibitors in autoimmune diseases has two sides, on one side, they have the effect to block T cell proliferation and inhibit cytokine production; on the other side, they were found to trigger inflammatory arthritis, inflammatory bowel disease (Table 1) and bullous pemphigoid.

As a multiple function protein, CD26 plays an important role in immune response and autoimmunity. Natural substrates of CD26 are involved in the process of immunomodulation. Targeting CD26 probably has many therapeutic potentials. Thus, we need to pay attention to the complex role of CD26, known as “moonlight protein”, in autoimmune diseases, which deserves our further research.

Author contribution

Yunjuan Zhao wrote and revised the manuscript.

Funding details

This work was supported by National Natural Science Foundation of China [Grant No. 81700728], Natural Science Doctoral Initial Funding of Guangdong Province [Grant: Guangdong Science Project Financial

Table 1
CD26 expression and effect on different cell types in different autoimmune diseases.

	CD26 expression		The effect of DPP-4 inhibitor/anti-CD26
	Immune cells	Serum DPP-4 level and activity	
Rheumatoid arthritis	CD3 + T: CD3 + CD26 + T increasing [29] CD4 + T: CD4 + CD45R0 + CD26-T decreased [32] CD4 + CD26 + T increasing [31]	Serum DPP-4 level decrease [18] [21] DPP-4 activity decreased [19][20][22] [23] [24][28]	Anti-CD26 increased [39] DPP-4 inhibitor induces arthritis [41]
Type 1 diabetes	CD26 on lymphocytes decreased [44]	DPP-4 level activity increases [42] [45,44]	DPP-4 inhibitor alleviates T1D [48] [50] [56] DPP-4 inhibitor increases CD26 expression on CD8 + T [50] DPP-4 inhibitor increases CD4 + CD25 + Foxp3 + Tregs [52] Vildagliptin increases β-cell neogenesis in a rat model of T1D [49] Sitagliptin treatment decreases insulin doses and alleviates diseases in a patient with T1D [78] Combined DPP-4 inhibitor with anti-CD3 antibody alleviates T1D in NOD mice [79] DPP-4 inhibitor increases islet neogenesis and β-cell survival in a type 1 diabetic rat model [80]
Systemic lupus erythematosus	CD26 expression on PB increasing [59] CD26 expression on iNKT cell decreased [58]	Serum sCD26 levels were decreased [81] DPP-4 activity decreased [19] [81] [57]	
Multiple sclerosis	CD8 + $CD26^{high}$ T cell increased [60]	DPP-4 level and activity decreased [60]	Gene deletion of CD26 downregulates Th1 immunity [61] DPP-4 inhibitor alleviates EAE [63] [64]
Inflammatory bowel diseases		CD26 activity decreases [70] [65] CD26 level decreased [66] Tissue and plasma DPP-4 was decreased [67]	CD26 deficiency increases CD8 + T cells [69] CD26 deficiency increases macrophage infiltration [70] DPP-4 inhibitor alleviates disease activity

No. (2017)105], Science and Technology Projects of Guangzhou [Grant No. 201707010365], 2017 Medical and Health Technology Projects of Guangzhou [Grant No. 0024288A10814040], 2016 Municipal college project of Guangzhou [Grant No. 1201630638].

Declaration of Competing Interest

The author declares that this review was conducted in the absence of any financial relationships that could be construed as a potential conflict of interest.

References

[1] A.-M. Lambeir, C. Durinx, S. Scharpé, I.D. Meester, Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV, Crit. Rev. Clin. Lab. Sci. 40 (2003) 209–294, https://doi.org/10.1080/713609354.
[2] M.D. Gorrell, J. Wickson, G.W. McCaughan, Expression of the rat CD26 Antigen (dipeptidyl peptidase IV) on subpopulations of rat lymphocytes, Cell. Immunol. 134 (1991) 205–215, https://doi.org/10.1016/0008-8749(91)90343-A.
[3] C. Klemann, L. Wagner, M. Stephan, S. von Hörsten, Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system, Clin. Exp. Immunol. 185 (2016) 1–21, https://doi.org/10.1111/cei.12781.
[4] X. Zhao, Investigation on the role of CD26 in Th1 and Th17 cell differentiation and allogeneic graft rejection, https://refubium.fu-berlin.de/handle/fub188/6721, (2018) , Accessed date: 13 July 2019.
[5] N. Kitagawa, M. Hamaguchi, S. Majima, T. Fukuda, T. Kimura, Y. Hashimoto, M. Tanaka, M. Yamazaki, N. Nakamura, M. Fukui, Dipeptidyl peptidase-4 inhibitors have adverse effects for the proliferation of human T cells, J. Clin. Biochem. Nutr. (2018) 17–64, https://doi.org/10.3164/jcbn.17-64.
[6] D. Reinhold, B. Hemmer, B. Gran, A. Steinbrecher, S. Brocke, T. Kähne, S. Wrenger, I. Born, J. Faust, K. Neubert, R. Martin, S. Ansorge, Dipeptidyl peptidase IV (CD26): role in T cell activation and autoimmune disease, Adv. Exp. Med. Biol. 477 (2000) 155–160, https://doi.org/10.1007/0-306-46826-3_17.
[7] M.M. Pinheiro, C.L. Stoppa, C.J. Valduga, C.E. Okuyama, R. Gorjão, R.M.S. Pereira, S.N. Diniz, Sitagliptin inhibit human lymphocytes proliferation and Th1/Th17 differentiation in vitro, Eur. J. Pharm. Sci. 100 (2017) 17–24, https://doi.org/10.1016/j.ejps.2016.12.040.
[8] F. Bühling, U. Junker, D. Reinhold, K. Neubert, L. Jäger, S. Ansorge, Functional role of CD26 on human B lymphocytes, Immunol. Lett. 45 (1995) 47–51, https://doi.org/10.1016/0165-2478(94)00230-O.
[9] C. Klemann, J. Schade, R. Pabst, S. Leitner, J. Stiller, S.V. Hörsten, M. Stephan, CD26/dipeptidyl peptidase 4-deficiency alters thymic emigration patterns and leukocyte subsets in F344-rats age-dependently, Clin. Exp. Immunol. 155 (2009) 357–365, https://doi.org/10.1111/j.1365-2249.2008.03839.x.
[10] D.S. Ghorpade, L. Ozcan, Z. Zheng, S.M. Nicoloro, Y. Shen, E. Chen, M. Blüher, M.P. Czech, I. Tabas, Hepatocyte-secreted DPP4 in obesity promotes adipose inflammation and insulin resistance, Nature 555 (2018) 673–677, https://doi.org/10.1038/nature26138.
[11] T. Ikedo, M. Minami, H. Kataoka, K. Hayashi, M. Nagata, R. Fujikawa, S. Higuchi, M. Yasui, T. Aoki, M. Fukuda, M. Yokode, S. Miyamoto, Dipeptidyl peptidase-4 inhibitor anagliptin prevents intracranial aneurysm growth by suppressing macrophage infiltration and activation, J. Am. Heart Assoc. 6 (2017), https://doi.org/10.1161/JAHA.116.004777.
[12] A. Hattori, M. Takemoto, H. Tokuyama, M. Koshizaka, K. Yokote, Sitagliptin but not alpha glucosidase inhibitor reduced the serum soluble CD163, a marker for activated macrophage, in individuals with type 2 diabetes mellitus, Diabetes Res. Clin. Pract. 126 (2017) 138–143, https://doi.org/10.1016/j.diabres.2017.02.010.
[13] W. Zheng, J. Zhou, S. Song, W. Kong, W. Xia, L. Chen, T. Zeng, Dipeptidyl-peptidase 4 inhibitor sitagliptin ameliorates hepatic insulin resistance by modulating inflammation and autophagy in ob/ob mice, Int. J. Endocrinol. 2018 (2018) 8309723, , https://doi.org/10.1155/2018/8309723.
[14] F. Zhuge, Y. Ni, M. Nagashimada, N. Nagata, L. Xu, N. Mukaida, S. Kaneko, T. Ota, DPP-4 inhibition by linagliptin attenuates obesity-related inflammation and insulin resistance by regulating M1/M2 macrophage polarization, Diabetes (2016) db160317, https://doi.org/10.2337/db16-0317.
[15] D.R. Gliddon, C.J. Howard, CD26 is expressed on a restricted subpopulation of dendritic cells in vivo, Eur. J. Immunol. 32 (2002) 1472–1481, https://doi.org/10.1002/1521-4141(200205)32:5<1472::AID-IMMU1472>3.0.CO;2-Q.
[16] J. Zhong, X. Rao, J. Deiuliis, Z. Braunstein, V. Narula, J. Hazey, D. Mikami, B. Needleman, A.R. Satoskar, S. Rajagopalan, A potential role for dendritic cell/macrophage-expressing DPP4 in obesity-induced visceral inflammation, Diabetes 62 (2013) 149–157, https://doi.org/10.2337/db12-0230.
[17] S. Yan, D. Marguet, J. Dobers, W. Reutter, H. Fan, Deficiency of CD26 results in a change of cytokine and immunoglobulin secretion after stimulation by pokeweed mitogen, Eur. J. Immunol. 33 (2003) 1519–1527, https://doi.org/10.1002/eji.200323469.
[18] P. Sinnathurai, W. Lau, A. de R. Vieira, W.W. Bachovchin, H. Englert, G. Howe, D. Spencer, N. Manolios, M.D. Gorrell, Circulating fibroblast activation protein and dipeptidyl peptidase 4 in rheumatoid arthritis and systemic sclerosis, Int. J. Rheum. Dis. (2016), https://doi.org/10.1111/1756-185X.13031.
[19] M. Hagihara, M. Ohhashi, T. Nagatsu, Activities of dipeptidyl peptidase II and dipeptidyl peptidase IV in mice with lupus erythematosus-like syndrome and in patients with lupus erythematosus and rheumatoid arthritis, Clin. Chem. 33 (1987) 1463–1465 http://clinchem.aaccjnls.org/content/33/8/1463 , Accessed date: 21 October 2018.
[20] M. Grujic, I.Z. Matic, M.D. Crnogorac, A.D. Velickovic, B. Kolundzija, O.J. Cordero, Z. Juranic, S. Prodanovic, M. Zlatanovic, D. Babic, N. Damjanov, Activity and expression of dipeptidyl peptidase IV on peripheral blood mononuclear cells in patients with early steroid and disease modifying antirheumatic drugs naïve

rheumatoid arthritis, Clin. Chem. Lab. Med. 55 (2016) 73–81, https://doi.org/10.1515/cclm-2015-1279.
[21] O.J. Cordero, F.J. Salgado, A. Mera-Varela, M. Nogueira, Serum interleukin-12, interleukin-15, soluble CD26, and adenosine deaminase in patients with rheumatoid arthritis, Rheumatol. Int. 21 (2001) 69–74, https://doi.org/10.1007/s002960100134.
[22] S. Buljevic, D. Detel, L.B. Pucar, R. Mihelic, T. Madarevic, B. Sestan, J. Varljen, Levels of dipeptidyl peptidase IV/CD26 substrates neuropeptide Y and vasoactive intestinal peptide in rheumatoid arthritis patients, Rheumatol. Int. 33 (2013) 2867–2874, https://doi.org/10.1007/s00296-013-2823-z.
[23] M. Cuchacovich, H. Gatica, S.V. Pizzo, M. Gonzalez-Gronow, Characterization of human serum dipeptidyl peptidase IV (CD26) and analysis of its autoantibodies in patients with rheumatoid arthritis and other autoimmune diseases, Clin. Exp. Rheumatol. 19 (2001) 673–680.
[24] M. Kamori, M. Hagihara, T. Nagatsu, H. Iwata, T. Miura, Activities of dipeptidyl peptidase II, dipeptidyl peptidase IV, prolyl endopeptidase, and collagenase-like peptidase in synovial membrane from patients with rheumatoid arthritis and osteoarthritis, Biochem. Med. Metab. Biol. 45 (1991) 154–160, https://doi.org/10.1016/0885-4505(91)90016-E.
[25] N. Busso, N. Wagtmann, C. Herling, V. Chobaz-Péclat, A. Bischof-Delaloye, A. So, E. Grouzmann, Circulating CD26 Is Negatively Associated with Inflammation in Human and Experimental Arthritis, Am. J. Pathol 166 (2005) 433–442, https://doi.org/10.1016/S0002-9440(10)62266-3.
[26] S.C. Yamasaki, S. Murari-do-Nascimento, P.F. Silveira, Neutral aminopeptidase and dipeptidyl peptidase IV in the development of collagen II-induced arthritis, Regul. Pept. 173 (2012) 47–54, https://doi.org/10.1016/j.regpep.2011.09.004.
[27] A. Sedo, J.S. Duke-Cohan, E. Balaziova, L.R. Sedova, Dipeptidyl peptidase IV activity and/or structure homologs: contributing factors in the pathogenesis of rheumatoid arthritis? Arthritis Res. Ther. 7 (2005) 253, https://doi.org/10.1186/ar1852.
[28] L. Sromova, P. Busek, L. Sedova, A. Sedo, Intraindividual changes of dipeptidyl peptidase-IV in peripheral blood of patients with rheumatoid arthritis are associated with the disease activity, BMC Musculoskelet. Disord. 16 (2015) 244, , https://doi.org/10.1186/s12891-015-0707-y.
[29] A. Mizokami, K. Eguchi, A. Kawakami, H. Ida, Y. Kawabe, T. Tsukada, T. Aoyagi, K. Maeda, C. Morimoto, S. Nagataki, Increased population of high fluorescence 1F7 (CD26) antigen on T cells in synovial fluid of patients with rheumatoid arthritis, J. Rheumatol. 23 (1996) 2022–2026 http://europepmc.org/abstract/med/8970035 , Accessed date: 21 October 2018.
[30] R. Gerli, C. Muscat, A. Bertotto, O. Bistoni, E. Agea, R. Tognellini, G. Fiorucci, M. Cesarotti, S. Bombardieri, CD26 surface molecule involvement in T cell activation and lymphokine synthesis in rheumatoid and other inflammatory synovitis, Clin. Immunol. Immunopathol. 80 (1996) 31–37, https://doi.org/10.1006/clin.1996.0091.
[31] C. Muscat, A. Bertotto, E. Agea, O. Bistoni, R. Ercolani, R. Tognellini, F. Spinozzi, M. Cesarotti, R. Gerli, Expression and functional role of 1F7 (CD26) antigen on peripheral blood and synovial fluid T cells in rheumatoid arthritis patients, Clin. Exp. Immunol. 98 (1994) 252–256, https://doi.org/10.1111/j.1365-2249.1994.tb06134.x.
[32] O.J. Cordero, R. Varela-Calviño, T. López-González, C. Calviño-Sampedro, J.E. Viñuela, C. Mouriño, Í. Hernández-Rodríguez, M. Rodríguez-López, B.A. de la Iglesia, J.M. Pego, CD26 expression on T helper populations and sCD26 serum levels in patients with rheumatoid arthritis, PLoS One 10 (2015) e0131992, , https://doi.org/10.1371/journal.pone.0131992.
[33] O.J. Cordero, F.J. Salgado, M. Nogueira, On the origin of serum CD26 and its altered concentration in cancer patients, Cancer Immunol. Immunother. 58 (2009) 1723–1747, https://doi.org/10.1007/s00262-009-0728-1.
[34] D.E. Trentham, R.A. Dynesius-Trentham, E.J. Orav, D. Combitchi, C. Lorenzo, K.L. Sewell, D.A. Hafler, H.L. Weiner, Effects of oral administration of type II collagen on rheumatoid arthritis, Science 261 (1993) 1727–1730, https://doi.org/10.1126/science.8378772.
[35] K. Loster, K. Zeilinger, D. Schuppan, W. Reutter, The cysteine-rich region of dipeptidyl peptidase IV (CD 26) is the collagen binding site, Biochem. Biophys. Res. Commun. 217 (1995) 341–348, https://doi.org/10.1006/bbrc.1995.2782.
[36] J. Kameoka, T. Tanaka, Y. Nojima, S.F. Schlossman, C. Morimoto, Direct association of adenosine deaminase with a T cell activation antigen, CD26, Science 261 (1993) 466–469, https://doi.org/10.1126/science.8101391.
[37] H.-C. Cheng, M. Abdel-Ghany, B.U. Pauli, A novel consensus motif in fibronectin mediates dipeptidyl peptidase IV adhesion and metastasis, J. Biol. Chem. 278 (2003) 24600–24607, https://doi.org/10.1074/jbc.M303424200.
[38] X. Chang, R. Yamada, A. Suzuki, Y. Kochi, T. Sawada, K. Yamamoto, Citrullination of fibronectin in rheumatoid arthritis synovial tissue, Rheumatology (Oxford) 44 (2005) 1374–1382, https://doi.org/10.1093/rheumatology/kei023.
[39] O.J. Cordero, R. Varela-Calviño, T. López-González, M. Grujic, Z. Juranic, C. Mouriño, Í. Hernández-Rodríguez, M. Rodríguez-López, B.A. de la Iglesia, J.M. Pego-Reigosa, Anti-CD26 autoantibodies are involved in rheumatoid arthritis and show potential clinical interest, Clin. Biochem. 50 (2017) 903–910, https://doi.org/10.1016/j.clinbiochem.2017.06.001.
[40] S.E. Herlihy, M.L. Brown, D. Pilling, B.R. Weeks, L.K. Myers, R.H. Gomer, Role of the neutrophil chemorepellent soluble dipeptidyl peptidase IV in decreasing inflammation in a murine model of arthritis, Arthritis Rheum. 67 (2015) 2634–2638, https://doi.org/10.1002/art.39250.
[41] A. Mascolo, C. Rafaniello, L. Sportiello, M. Sessa, D. Cimmaruta, F. Rossi, A. Capuano, Dipeptidyl peptidase (DPP)-4 inhibitor-induced arthritis/arthralgia: a review of clinical cases, Drug Saf. 39 (2016) 401–407, https://doi.org/10.1007/s40264-016-0399-8.
[42] A. Iwabuchi, T. Kamoda, M. Saito, H. Nozue, I. Izumi, T. Hirano, R. Sumazaki, Serum dipeptidyl peptidase 4 activity in children with type 1 diabetes mellitus, J. Pediatr. Endocrinol. Metab. 26 (2013) 1093–1097, https://doi.org/10.1515/jpem-2013-0122.
[43] L. Duvnjak, K. Blaslov, M. Vučić Lovrenčić, J. Knežević Ćuća, Persons with latent autoimmune diabetes in adults express higher dipeptidyl peptidase-4 activity compared to persons with type 2 and type 1 diabetes, Diabetes Res. Clin. Pract. 121 (2016) 119–126, https://doi.org/10.1016/j.diabres.2016.09.013.
[44] T. Varga, A. Somogyi, G. Barna, B. Wichmann, G. Nagy, K. Rácz, L. Selmeci, G. Firneisz, Higher serum DPP-4 enzyme activity and decreased lymphocyte CD26 expression in type 1 diabetes, Pathol. Oncol. Res. 17 (2011) 925, https://doi.org/10.1007/s12253-011-9404-9.
[45] S. Osawa, D. Kawamori, N. Katakami, M. Takahara, F. Sakamoto, T. Katsura, T. Yasuda, H. Kaneto, M. Matsuhisa, T. Matsuoka, I. Shimomura, Significant elevation of serum dipeptidyl peptidase-4 activity in young-adult type 1 diabetes, Diabetes Res. Clin. Pract. 113 (2016) 135–142, https://doi.org/10.1016/j.diabres.2015.12.022.
[46] K. Ohnuma, H. Inoue, M. Uchiyama, T. Yamochi, O. Hosono, N.H. Dang, C. Morimoto, T-cell activation via CD26 and caveolin-1 in rheumatoid synovium, Mod. Rheumatol. 16 (2006) 3–13, https://doi.org/10.3109/s10165-005-0452-4.
[47] A. Zóka, G. Barna, O. Hadarits, Z. Al-Aissa, B. Wichmann, G. Műzes, A. Somogyi, G. Firneisz, Altered crosstalk in the dipeptidyl peptidase-4-incretin-immune system in type 1 diabetes: a hypothesis generating pilot study, Hum. Immunol. 76 (2015) 667–672, https://doi.org/10.1016/j.humimm.2015.09.018.
[48] D. de L. Ávila, G.R. de Araújo, M. Silva, P.H. de A. Miranda, M.F. Diniz, M.L. Pedrosa, M.E. Silva, W.G. de Lima, D.C. Costa, Vildagliptin ameliorates oxidative stress and pancreatic beta cell destruction in type 1 diabetic rats, Arch. Med. Res. 44 (2013) 194–202, https://doi.org/10.1016/j.arcmed.2013.03.004.
[49] P.H. de Amorim Miranda, O.M. Monteiro, J.V. Rossoni, M.E. Silva, W.G. de Lima, D.C. Costa, Vildagliptin induces β-cell neogenesis and improves the lipid profile in a later phase of type 1 diabetes, Curr. Pharm. Biotechnol. 16 (2015) 60–65.
[50] N. Alonso, M.T. Julián, J. Carrascal, R. Colobran, I. Pujol-Autonell, S. Rodriguez-Fernández, A. Teniente, M.A. Fernández, A. Miñarro, M.C.R. de Villa, M. Vives-Pi, M. Puig-Domingo, Type 1 diabetes prevention in NOD mice by targeting DPPIV/CD26 is associated with changes in CD8+T effector memory subset, PLoS One 10 (2015) e0142186, , https://doi.org/10.1371/journal.pone.0142186.
[51] M.T. Julián, N. Alonso, R. Colobran, A. Sánchez, A. Miñarro, I. Pujol-Autonell, J. Carrascal, S. Rodríguez-Fernández, R.M. Ampudia, M. Vives-Pi, M. Puig-Domingo, CD26/DPPIV inhibition alters the expression of immune response-related genes in the thymi of NOD mice, Mol. Cell. Endocrinol. 426 (2016) 101–112, https://doi.org/10.1016/j.mce.2016.02.014.
[52] L. Tian, J. Gao, J. Hao, Y. Zhang, H. Yi, T.D. O'Brien, R. Sorenson, J. Luo, Z. Guo, Reversal of new-onset diabetes through modulating inflammation and stimulating β-cell replication in nonobese diabetic mice by a dipeptidyl peptidase IV inhibitor, Endocrinology. 151 (2010) 3049–3060, https://doi.org/10.1210/en.2010-0068.
[53] Z. Li, J. Fang, R. Jiao, X. Wei, Y. Ma, X. Liu, P. Cheng, T. Li, A novel multi-epitope vaccine based on Dipeptidyl Peptidase 4 prevents streptozotocin-induced diabetes by producing anti-DPP4 antibody and immunomodulatory effect in C57BL/6J mice, Biomed. Pharmacother. 89 (2017) 1467–1475, https://doi.org/10.1016/j.biopha.2017.01.089.
[54] R. Kodera, K. Shikata, T. Takatsuka, K. Oda, S. Miyamoto, N. Kajitani, D. Hirota, T. Ono, H.K. Usui, H. Makino, Dipeptidyl peptidase-4 inhibitor ameliorates early renal injury through its anti-inflammatory action in a rat model of type 1 diabetes, Biochem. Biophys. Res. Commun. 443 (2014) 828–833, https://doi.org/10.1016/j.bbrc.2013.12.049.
[55] T. Awata, A. Shimada, T. Maruyama, Y. Oikawa, N. Yasukawa, S. Kurihara, Y. Miyashita, M. Hatano, Y. Ikegami, M. Matsuda, M. Niwa, Y. Kazama, S. Tanaka, T. Kobayashi, Possible Long-term efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for slowly progressive type 1 diabetes (SPIDDM) in the stage of non-insulin-dependency: an open-label randomized controlled pilot trial (SPAN-S), Diabetes Ther. 8 (2017) 1123–1134, https://doi.org/10.1007/s13300-017-0299-7.
[56] Y. Zhao, L. Yang, Y. Xiang, L. Liu, G. Huang, Z. Long, X. Li, R.D. Leslie, X. Wang, Z. Zhou, Dipeptidyl peptidase 4 inhibitor sitagliptin maintains β-cell function in patients with recent-onset latent autoimmune diabetes in adults: one year prospective study, J. Clin. Endocrinol. Metab. 99 (2014) E876–E880, https://doi.org/10.1210/jc.2013-3633.
[57] M. Stancíková, Z. Lojda, J. Lukác, M. Ruzicková, Dipeptidyl peptidase IV in patients with systemic lupus erythematosus, Clin. Exp. Rheumatol. 10 (1992) 381–385 http://europepmc.org/abstract/med/1356680 , Accessed date: 20 June 2019.
[58] P.T.Y. Wong, C.K. Wong, L.S. Tam, E.K. Li, D.P. Chen, C.W.K. Lam, Decreased expression of T lymphocyte co-stimulatory molecule CD26 on invariant natural killer T cells in systemic lupus erythematosus, Immunol. Investig. 38 (2009) 350–364, https://doi.org/10.1080/08820130902770003.
[59] M. Valizadeh, A. Ahmadzadeh, M. Behzadi, F. Yeganeh, CD26 mRNA expression in systemic lupus erythematosus, Rheumatol. Res. 3 (2018) 77–82, https://doi.org/10.22631/rr.2018.69997.1045.
[60] M. Tejera-Alhambra, A. Casrouge, C. de Andrés, R. Ramos-Medina, B. Alonso, J. Vega, M.L. Albert, S. Sánchez-Ramón, Low DPP4 expression and activity in multiple sclerosis, Clin. Immunol. 150 (2014) 170–183, https://doi.org/10.1016/j.clim.2013.11.011.
[61] V. Preller, A. Gerber, S. Wrenger, M. Togni, D. Marguet, J. Tadje, U. Lendeckel, C. Röcken, J. Faust, K. Neubert, B. Schraven, R. Martin, S. Ansorge, S. Brocke, D. Reinhold, TGF-β1-mediated control of central nervous system inflammation and autoimmunity through the inhibitory receptor CD26, J. Immunol. 178 (2007) 4632–4640, https://doi.org/10.4049/jimmunol.178.7.4632.
[62] D. Reinhold, A. Biton, S. Pieper, U. Lendeckel, J. Faust, K. Neubert, U. Bank,

M. Täger, S. Ansorge, S. Brocke, Dipeptidyl peptidase IV (DP IV, CD26) and aminopeptidase N (APN, CD13) as regulators of T cell function and targets of immunotherapy in CNS inflammation, Int. Immunopharmacol. 6 (2006) 1935–1942, https://doi.org/10.1016/j.intimp.2006.07.023.

[63] D. Reinhold, U. Bank, D. Entz, A. Goihl, D. Stoye, S. Wrenger, S. Brocke, A. Thielitz, S. Stefin, K. Nordhoff, A. Heimburg, M. Täger, S. Ansorge, PETIR-001, a dual inhibitor of dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN), ameliorates experimental autoimmune encephalomyelitis in SJL/J mice, Biol. Chem. 392 (2011) 233–237, https://doi.org/10.1515/bc.2011.024.

[64] A. Steinbrecher, D. Reinhold, L. Quigley, A. Gado, N. Tresser, L. Izikson, I. Born, J. Faust, K. Neubert, R. Martin, S. Ansorge, S. Brocke, Targeting dipeptidyl peptidase IV (CD26) suppresses autoimmune encephalomyelitis and up-regulates TGF-β1 secretion in vivo, J. Immunol. 166 (2001) 2041–2048, https://doi.org/10.4049/jimmunol.166.3.2041.

[65] J. Varljen, B. Mijandrušić Sinčić, L. Batičić, N. Varljen, D. Detel, A. Lekić, Clinical relevance of the serum dipeptidyl peptidase IV (DPP IV/CD26) activity in adult patients with Crohn's disease and ulcerative colitis, Croat. Chem. Acta 78 (2005) 427–432 https://hrcak.srce.hr/index.php?show=clanak&id_clanak_jezik=53 , Accessed date: 24 October 2018.

[66] D.O. Magro, P.G. Kotze, C.A.R. Martinez, M.G. Camargo, D. Guadagnini, A.R. Calixto, A.C.J. Vasques, M. de L.S. Ayrizono, B. Geloneze, J.C. Pareja, M.J. Saad, C.S.R. Coy, Changes in serum levels of lipopolysaccharides and CD26 in patients with Crohn's disease, Intest. Res. 15 (2017) 352–357, https://doi.org/10.5217/ir.2017.15.3.352.

[67] G.W. Moran, C. O'Neill, P. Padfield, J.T. McLaughlin, Dipeptidyl peptidase-4 expression is reduced in Crohn's disease, Regul. Pept. 177 (2012) 40–45, https://doi.org/10.1016/j.regpep.2012.04.006.

[68] L. Baticic, D. Detel, N. Kucic, S. Buljevic, E.P. Pugel, J. Varljen, Neuroimmunomodulative properties of dipeptidyl peptidase IV/CD26 in a TNBS-induced model of colitis in mice, J. Cell. Biochem. 112 (2011) 3322–3333, https://doi.org/10.1002/jcb.23261.

[69] D. Detel, S. Buljevic, L.B. Pucar, N. Kucic, E.P. Pugel, J. Varljen, Influence of CD26/dipeptidyl peptidase IV deficiency on immunophenotypic changes during colitis development and resolution, J. Physiol. Biochem. 72 (2016) 405–419, https://doi.org/10.1007/s13105-016-0491-7.

[70] D. Detel, E.P. Pugel, L.B. Pucar, S. Buljevic, J. Varljen, Development and resolution of colitis in mice with target deletion of dipeptidyl peptidase IV, Exp. Physiol. 97 (2011) 486–496, https://doi.org/10.1113/expphysiol.2011.061143.

[71] S. Mimura, T. Ando, K. Ishiguro, O. Maeda, O. Watanabe, M. Ujihara, Y. Hirayama, K. Morise, K. Maeda, M. Matsushita, K. Funasaka, M. Nakamura, R. Miyahara, N. Ozaki, H. Goto, Dipeptidyl peptidase-4 inhibitor anagliptin facilitates restoration of dextran sulfate sodium-induced colitis, Scand. J. Gastroenterol. 48 (2013) 1152–1159, https://doi.org/10.3109/00365521.2013.832366.

[72] R. Yazbeck, M.L. Sulda, G.S. Howarth, A. Bleich, K. Raber, S. von Hörsten, J.J. Holst, C.A. Abbott, Dipeptidyl peptidase expression during experimental colitis in mice, Inflamm. Bowel Dis. 16 (2010) 1340–1351, https://doi.org/10.1002/ibd.21241.

[73] K. Kridin, K. Amber, M. Khamaisi, D. Comaneshter, E. Batat, A.D. Cohen, Is there an association between dipeptidyl peptidase-4 inhibitors and autoimmune disease? A population-based study, Immunol. Res. 66 (2018) 425–430, https://doi.org/10.1007/s12026-018-9005-8.

[74] Y. Liu, Y. Li, Y. Gong, N. Yu, Y. Zhang, R. You, C. Qu, G. Lu, Y. Huang, Y. Gao, Y. Gao, X. Guo, CD26 expression is down-regulated on CD8+ T cells in patients with Hashimoto's thyroiditis, Int. Immunopharmacol. 54 (2018) 280–285, https://doi.org/10.1016/j.intimp.2017.11.024.

[75] H. Hirakawa, H. Zempo, M. Ogawa, R. Watanabe, J.-I. Suzuki, H. Akazawa, I. Komuro, M. Isobe, A DPP-4 inhibitor suppresses fibrosis and inflammation on experimental autoimmune myocarditis in mice, PLoS One 10 (2015), https://doi.org/10.1371/journal.pone.0119360.

[76] M.V. Blazquez, J.A. Madueño, R. Gonzalez, R. Jurado, W.W. Bachovchin, J. Peña, E. Muñoz, Selective decrease of CD26 expression in T cells from HIV-1-infected individuals, J. Immunol. 149 (1992) 3073–3077 https://www.jimmunol.org/content/149/9/3073 , Accessed date: 20 June 2019.

[77] R.E. Smith, J.W. Talhouk, E.E. Brown, S.E. Edgar, The significance of hypersialylation of dipeptidyl peptidase IV (CD26) in the inhibition of its activity by tat and other cationic peptides. CD26: a subverted adhesion molecule for HIV peptide binding, AIDS Res. Hum. Retrovir. 14 (1998) 851–868, https://doi.org/10.1089/aid.1998.14.851.

[78] M.M. Lima-Martínez, E. Guerra-Alcalá, M. Contreras, J. Nastasi, J.A. Noble, C. Polychronakos, One year remission of type 1 diabetes mellitus in a patient treated with sitagliptin, Endocrinol. Diabetes Metab. Case Rep. 2014 (2014), https://doi.org/10.1530/EDM-14-0072.

[79] L. Ding, C.A. Gysemans, G. Stangé, Y. Heremans, Y. Yuchi, T. Takiishi, H. Korf, M. Chintinne, R.D. Carr, H. Heimberg, D. Pipeleers, C. Mathieu, Combining MK626, a novel DPP-4 inhibitor, and low-dose monoclonal CD3 antibody for stable remission of new-onset diabetes in mice, PLoS One 9 (2014) e107935, , https://doi.org/10.1371/journal.pone.0107935.

[80] J.A. Pospisilik, J. Martin, T. Doty, J.A. Ehses, N. Pamir, F.C. Lynn, S. Piteau, H.-U. Demuth, C.H.S. McIntosh, R.A. Pederson, Dipeptidyl peptidase IV inhibitor treatment stimulates beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats, Diabetes 52 (2003) 741–750.

[81] H. Kobayashi, O. Hosono, T. Mimori, H. Kawasaki, N.H. Dang, H. Tanaka, C. Morimoto, Reduction of serum soluble CD26/dipeptidyl peptidase IV enzyme activity and its correlation with disease activity in systemic lupus erythematosus, J. Rheumatol. 29 (2002) 1858–1866 http://www.jrheum.org/content/29/9/1858 , Accessed date: 25 October 2018.