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Emerging Role of Dipeptidyl Peptidase-4 in Autoimmune Disease

Jie Huang[1], Xinxin Liu[1], Yingying Wei[1], Xinlu Li[1], Shupei Gao[1], Lingli Dong[1], Xiaoquan Rao[2]* and Jixin Zhong[1]**

[1] Department of Rheumatology and Immunology, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, [2] Department of Cardiovascular Medicine, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China

Dipeptidyl-peptidase IV (DPP4), originally identified as an aminopeptidase in 1960s, is an ubiquitously expressed protease presented as either a membrane-bound or soluble form. DPP4 cleaves dipeptide off from the N-terminal of its substrates, altering the bioactivity of its substrates. Subsequent studies reveal that DPP4 is also involved in various cellular processes by directly binding to a number of ligands, including adenosine deaminase, CD45, fibronectin, plasminogen, and caveolin-1. In recent years, many novel functions of DPP4, such as promoting fibrosis and mediating virus entry, have been discovered. Due to its implication in fibrotic response and immunoregulation, increasing studies are focusing on the potential role of DPP4 in inflammatory disorders. As a moonlighting protein, DPP4 possesses multiple functions in different types of cells, including both enzymatic and non-enzymatic functions. However, most of the review articles on the role of DPP4 in autoimmune disease were focused on the association between DPP4 enzymatic inhibitors and the risk of autoimmune disease. An updated comprehensive summary of DPP4's immunoregulatory actions including both enzymatic dependent and independent functions is needed. In this article, we will review the recent advances of DPP4 in immune regulation and autoimmune rheumatic disease.

Keywords: autoimmune, autoinflammatory, DPP4, inflammation, dipeptidyl peptidase

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****Correspondence:***
Jixin Zhong
zhongjixin620@163.com
Xiaoquan Rao
xqrao@tjh.tjmu.edu.cn
Lingli Dong
tjhdongll@163.com

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INTRODUCTION

Dipeptidyl-peptidase IV (DPP4), also known as CD26, was first discovered as a protease in 1966 (1). DPP4 is mainly expressed on the cell surface, forming a homodimer. It is widely expressed on epithelial cells in various tissues (kidney, bile ducts, liver, lung and intestine), some endothelia cells, leukocyte subsets and fibroblasts (2, 3). The full length of human DPP4 is 766 amino acids (AA), including a short 6-AA cytoplasmic tail, a 22-AA transmembrane hydrophobic segment, and a 738-AA extracellular portion (2, 4, 5). In addition to the membrane-bound form, DPP4 can also be cleaved off from the cell membrane and released into plasma and other body fluids, forming a soluble form that lacks cytoplasmic domain and transmembrane domain. Since the catalytic domain is located in the extracellular portion, soluble DPP4 maintains the enzymatic activity (2).

The substrates of DPP4 have a unique feature of amino acid sequence: with alanine or proline as the preferred residue at the second amino acid. The substrates of DPP4 are categorized into incretin peptides, chemokines and cytokines, and neuropeptides. By cleaving X-Pro or X-Ala dipeptides off

from the N-terminal, DPP4 regulates the biological function of its substrates. For example, DPP4 converts glucagon-like peptide-1 (GLP-1) (7–36) and (7-37) into inactive forms GLP-1(9-36) and GLP-1(9-37), which are unable to bind GLP-1 receptor and induce insulin release from pancreatic β cells (6).

Later studies identified DPP4 as the adenosine deaminase (ADA) binding protein. By transducing costimulatory signal in T cells upon stimulation with ADA, DPP4 is considered as a T cell activation marker (7). In 2013, DPP4 was discovered as an entry receptor for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (8). By binding to spike protein on the surface of MERS-CoV, DPP4 expressed on the epithelial cells in respiratory system mediates the entry of the virus into the host cell (9–11). In addition, DPP4 had also been identified as a co-receptor for human immunodeficiency virus (12). However, later studies indicate that CCR5 is the major co-receptor for the entry of human immunodeficiency virus into $CD4^+$ T cells (13, 14) The selective expression of CCR5 on $DPP4^+$ T cell subsets may partially explain the association between HIV infection and DPP4 expression (15). A recent study identified a novel implication of DPP4 in scarring and wound healing (16). The author discovered a subpopulation of fibroblast expressing DPP4 is responsible for the bulk of connective tissue deposition in dermal scars. Inhibition of DPP4 reduced scar formation in a mouse model of wound healing. Another study reported that a mesenchymal progenitor cell population expressing DPP4 displayed a highly proliferative and multipotent phenotype and regulated the differentiation of adipocytes (17).

Autoimmune diseases are a group of chronic disorders characterized by autoimmune-mediated damage in multiple systems. Elevation of diverse inflammatory cytokines or chemokines, along with activation of multiple immune cells, could be observed in patients with autoimmune disease. In a number of autoimmune diseases, such as systemic sclerosis and IgG4-related disease, fibrosis also plays a critical role in their pathogenesis. With its involvement in immune regulation and fibrosis, DPP4 may have a pivotal implication in the development of autoimmune disease. Clinical evidence has suggested an association between the use of DPP4 enzymatic inhibitors and several autoimmune disorders, which is summarized by Zhao group and Sahoo group in 2014 and 2021 respectively (18, 19). While DPP4 has been considered a moonlighting protein due to its multifunctional features in different types of cells, an updated comprehensive summary of DPP4's immunoregulatory actions including both enzymatic dependent and independent functions is needed. This review focuses on emerging evidence of DPP4 in immune regulation and attempts to build a bridge between DPP4 and autoimmune diseases.

THE ROLE OF DPP4 IN IMMUNE SYSTEM

DPP4 is expressed in many types of immune cells, including T cells, B cells, natural killer cells (NKs), dendritic cells (DCs), and macrophages (**Table 1**) (36). The expression level of DPP4 is also associated with the activation status of immune cells. Both enzymatic dependent and independent functions of DPP4 are involved in the regulation of immune function (**Figure 1**).

T Cells

The expression of DPP4 in T cells is variable in different subpopulation and tightly regulated by the level of cell activation (37). Previous research suggested that both Th1 and Th2 express DPP4 on the surface, whereas Th1 cells express significant higher amount of DPP4 than Th2 cells (20). Flow cytometry analysis of DPP4 expression in different $CD4^+$ T helper subsets shows that the expression of DPP4 is highest in Th17 compared to Th1 and Th2 (22). On the contrary, DPP4 expression is low on Treg cells and has been regarded as a negative regulator of Treg function (38). In $CD8^+$ T cells, by providing co-stimulatory signal, DPP4 represents a specific marker of successful memory development (25, 26).

During the thymus maturation, DPP4 is considered as a maker of differential regulation of human lymphocytes activation (39). DPP4-deficient animal models show decreased number of overall lymphocytes and decreased proportion of CD4+T cells and memory T cells, while naïve T cells relatively increase (27, 40, 41).

In *in vitro* studies, inhibition of DPP4 induced immunosuppressive cytokine TGF-β, but decreased production of proinflammatory cytokines including IL-2, IL-6, and IFN-γ (41–43). There was a debate that DPP4 only exerts T cells activation function *via* its enzymatic activity (44, 45). However,

TABLE 1 | The expression and function of DPP4 in immune cells.

	Expression	DPP4 Function	References
$CD4^+$ T cells			
Th1	High expression	Co-stimulation	(20)
Th2	Relative low expression	Elevated DPP4 expression was associated with the production of Th2 cytokines	(20, 21)
Th17	High expression	Co-stimulation, correlated with Th17 cytokine production	(22, 23)
Treg	Low expression		(24)
$CD8^+$ T cells	High/negative expression	Co-stimulation	(25, 26)
B cells	Low expression	Co-stimulation, promote DNA synthesis, Ig production, and Ig isotype switching	(27, 28)
DCs	Positive expression	Modulate adenosine concentration by DPP4/ADA interaction, recruit Th1	(29, 30)
NK	Low expression	Co-stimulation, maintain cytotoxicity	(31, 32)
Macrophage	Positive expression	Regulatie M1/M2 macrophage polarization	(33, 34)
Fibroblast	Specific subpopulation	Activation marker	(16, 35)

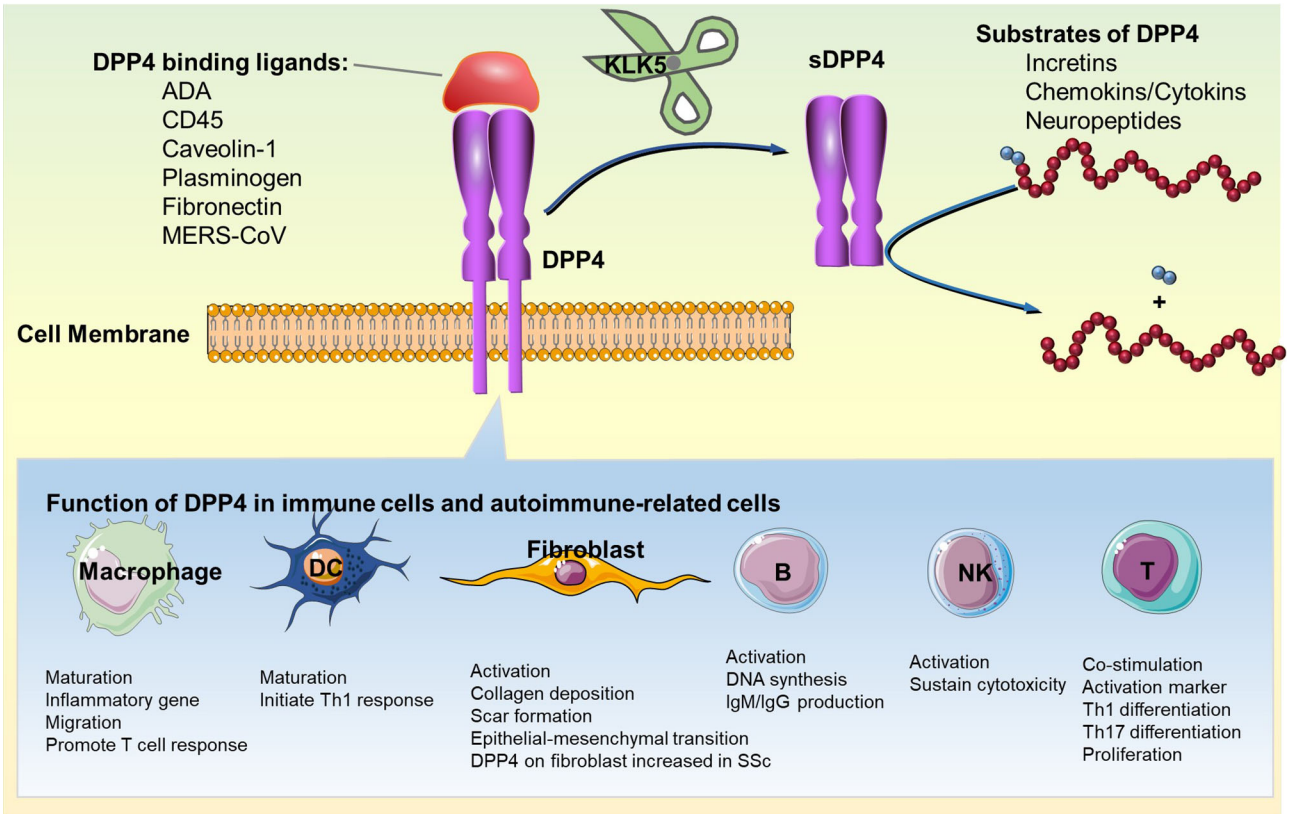

FIGURE 1 | Immunoregulatory function of DPP4: enzymatic and non-enzymatic functions of DPP4 in immune cells and fibroblast are shown. DC, dendritic cell; DPP4, dipeptidyl peptidase-4; IgG, immunoglobulin G; IgM, immunoglobulin M; KLK5, kallikrein-related peptidase 5; sDPP4, soluble DPP4; Th1, type 1 helper T cell; Th17, type 17 helper T cell.

later studies confirmed that DPP4 may also promotes T cell activation and proliferation by enzymatic independent actions. DCs, as most potent antigen-presenting cells(APCs), are pivotal in directing activation and differentiation of naïve T cells (46, 47). DPP4 and some adenosine receptors, including A_1R, $A_{2A}R$ and $A_{2B}R$, serve as binding proteins for extracellular ADA (48). Ecto-ADA anchored on DC surface through $A_{2B}R$ and DPP4 on T cells compose a ternary complex and potentiates Th1-like cell activation and high production levels of Th1 cytokines such as IFN-γ, IL-6 and TNF-α, but without affecting Th2 cytokine production (49). Another study reported that $A_{2A}R$ can also compose similar ternary complex (50). Direct interaction of DPP4 on T cell with ADA or its activating antibody results in the recruitment of CD45 in lipid raft, forming a signaling complex. The DPP4/CD45 complex then enhances the phosphorylation of downstream CD3-ζ, p56lck, and zap-70, providing co-stimulatory signal for T cell activation (51, 52). Additionally, DPP4 on T cells interacts may also directly interact with caveolin-1 on APCs. This interaction triggers CARMA1-mediated nuclear factor (NF)-κB activation and its downstream signaling, resulting in T cells proliferation in a TCR/CD3-dependent manner (53). Co-stimulatory blockade of DPP4 by DPP4 deletion or pharmacological inhibition results in a significant reduction of IL-17 and IL-21 cytokines from CD4+ T cells, suggesting a critical role of DPP4 in Th17 activation (23).

B Cells

DPP4 is expressed at a very lower level (less than 2%) in unstimulated CD20+ B cells, but significantly upregulated to around 50% through specific stimuli [including St. aureus and pokeweed mitogen(PWM)]. This result suggests a potential involvement of DPP4 in B cells activation (28). Incubation with DPP4 inhibitors suppress DNA synthesis and IgM secretion by B cells in a dose-dependent manner (28). In supporting this, DPP4 knockout mice, displayed a markedly decreased production of IgG after immunization by PWM. The decreased production of IL-4 and IL-2, delayed IFN-γ secretion in sera possibly contribute to the decreased Immunoglobulin production and impaired immunoglobulin isotype switching to IgG1, IgG2a and IgE (27). DPP4 is expressed in some B cell chronic lymphocytic leukemia cell linage and associated with the prognosis (54). In conclusion, DPP4 may serve as an activation marker for B cells, although its exact role in B cell biology is still not completely understood.

NKs

A serial of studies revealed that DPP4 might be a characteristic surface marker of NKs. In normal condition, NKs express DPP4 at a low frequency, but is dramatically increased to 30% after IL-2 stimulation (31, 55, 56). Researchers utilized peripheral blood $CD16^{+}CD56^{+}$ NK cell to confirm that DPP4 could be induced by IL-2, IL-15 or IL-12, and regarded as a potential activation marker for NK cells (57). DPP4 is able to induce protein tyrosine phosphorylation and elicit a CD16-dependent lytic response in NKs (58). In addition, DPP4 was reported to sustain NK cytotoxicity against lung cancer (6, 32).

DCs

The expression of DPP4 on DC was first detected on a restricted subpopulation in afferent lymph nodes (29).Flow cytometry analysis further suggested DPP4 was expressed at high levels on cDCs (59–61). Moreover, the expression of DPP4 on DCs was higher in visceral adipose tissue (VAT) from obese mice and humans compared with lean controls (30). During *in vitro* DCs differentiation, a significant increase in DPP4 expression was detected, suggesting a link between DPP4 expression and maturation of DCs (30). DPP4 positive DCs contribute to adaptive immunity, especially Th1-like responses. On one hand, DPP4 expressed on DC confers the ability to modify the macrophage-derived chemokines, which may attract Th1 cells (29). On the other hand, DPP4 modulates adenosine concentration and inflammation in the microenvironment of VAT by binding to ADA (30).

Macrophages

DPP4 expression is also detected on macrophages from visceral adipose tissue in both high fat diet-induced and genetically obese mice, and the expression increased with functional maturation of macrophages (30). A long-term DPP4 inhibition reduced inflammation in VAT *via* downregulating proinflammatory genes in adipose tissue macrophages, and prevented monocyte migration and actin polymerization (33). Likewise, DPP4 inhibitions by alogliptin (62) and shRNA silencing (63) suppressed macrophages infiltration and accumulation. Like in DCs, DPP4 expression on macrophage was able to promote T-cell proliferation *via* modulating adenosine concentrations in micro-environment (30).

Enzymatic Degradation of Immunoregulating Small Molecules

As discussed above, DPP4 is able to process a number of cytokines and chemokines by cleavage of N-terminal dipeptides.

Stromal cell-derived factor-1 (SDF-1), also as known as CXCL12, is a chemoattractant for T cells, hematopoietic progenitor cells, and adipose-derived regenerative cells (64–66). SDF-1 can be proteolytic cleaved by DPP4 and converted into CXCL12(3-68) (67). CXCL12(3-68) failed to induce CXCR4-mediated β-arrestin recruitment and downstream activation of IP3, Akt or ERK1/2, and thus losing its chemoattractant properties to lymphocytes. Co-administration of DPP4 inhibitor sitagliptin significantly enhanced the ability of intact SDF-1, but not CXCL12(3-68), to induce intra-articular lymphocyte infiltration (67). In addition to inactivating SDF-1, DPP4 also regulates SDF-1-mediated lymphocyte migration through direct interaction with its receptor CXCR4. DPP4 binds to CXCR4 on T lymphocytes and SDF-1 is able to induce the internalization of CXCR4/DPP4 complex. Interestingly, internalized CXCR4 is rapidly recycled back to the plasma membrane while DPP4 is clustered in intracellular vesicles, suggesting a self-regulatory mechanism of SDF-1 in reducing DPP4-dependendt inactivation (68). Other chemokines identified to be truncated by DPP4 include IP10, MIP, MIG, I-TAC, MDC, RANTES, etc. (**Table 2**).

Other cytokines degraded by DPP4 include fibroblast growth factor 2 (FGF2), IL-3, granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), IL-3, and erythropoietin (EPO) (79–81). Many interleukin family members such as IL-2/-5/-10/-13/-17/-22/-23/-27/-28 also possess potential cleavage site of DPP4 (80). However, further biochemical and biological studies are needed to identify whether the putative DPP4 truncation sites are true truncation sites for those peptides.

THE ROLE OF DPP4 IN FIBROSIS

Fibroblasts are spindle-shaped cells responsible for the synthesis of extracellular matrix and collagen in connective tissue (85, 86). Although fibroblasts are not conventional immune cells, they play an important role in immune regulation and autoimmune disease. Fibroblasts may also act as an antigen present cell to promote proliferation, activation, and recruitment of adaptive immune cells *via* both direct cell-to-cell interaction and secretion of cytokines (87, 88). The expression of DPP4 was found to at a high level in capsule fibroblasts compared to medulla fibroblasts in the thymus of mice, suggesting that DPP4 may serve as a segregate marker to distinguish different fibroblast subsets (35). Fibroblasts are center actor in fibrosis and wound healing (16, 89). SFRP2/DPP4 define a major fibroblast population in human skin (90). The expression of DPP4 allows isolation of a fibrogenic, scar forming lineage and inhibition of DPP4 reduces cutaneous scarring during wound healing (16). Another study suggested that the expression of DPP4 in the skin fibroblast was upregulated in patients with systemic sclerosis compared with that of healthy individuals. DPP4 regulates TGF-β-induced fibroblast activation in skin fibrosis and DPP4 characterizes an activated population of fibroblasts characterized by the expression of collagen and myofibroblast markers. Genetic deletion or pharmacologic inhibition of DPP4 in fibroblasts suppressed their proliferation, migration, and collagen production (91). Hui-Chun Ku et al. reported that DPP4 activated dermal fibroblasts *via* PAR2 and downstream NF-κB/SMAD signaling (92). Expression of DPP4 was increased in the thickening peritoneum of chlorhexidine gluconate-induced peritoneal fibrosis model of rats. Increased expression of DPP4 in diabetes was found to promote epithelial-mesenchymal transition and peritoneal fibrosis, which could be

TABLE 2 | Summary of DPP4 substrates.

Peptide	N-terminus	Species	Functional change after truncation	Physiological Function	References
Chemokines and cytokines					
CXCL9(Mig)	**TP**↓VVRK…	Human	Reduce activity	Lymphocyte chemotaxis	(69)
CXCL10 (IP-10)	**VP**↓LSRT	Human	Reduce activity	Lymphocyte chemotaxis	(69, 70)
CXCL11(I-TAC)	**FP**↓MFKR	Human	Reduce activity	Lymphocyte chemotaxis	(69, 71)
CXCL12(SDF-1a)	**KP**↓VSLS…	Human	Reduce activity	Lymphocyte chemotaxis	(67, 69)
CCL2(MCP-1)	**QP**↓DAV…	Human	Increase activity	Angiogenesis	(72)
CCL3(MIP-1α)	**AP**↓YGA…	Murine	Increase activity	Monocyte chemotaxis	(34)
CCL3L1(LD78β)	**AP**↓LAAD…	Human	Affinity alteration	Monocyte chemotaxis	(73, 74)
CCL5(RANTES)	**SP**↓YSSD…	Human	Reduce activity	Macrophage CSF	(75)
CCL11(Eotaxin)	**GP**↓ASV…	Human	Reduce activity	Eosinophil chemotaxis	(69, 76)
CCL22(MDC)	**GP**↓YG↓AN	Human	Reduce activity	Lymphocyte chemotaxis	(77, 78)
Cytokines					
IL-3	**AP**↓MTQ…	Human	Reduce activity	Cell proliferation	(79)
GM-CSF	**AP**↓ARS…	Human	Reduce activity	Cell proliferation	(79)
G-CSF	**AT**↓PLG…	Human	Reduce activity	Cell proliferation	(79)
EPO	**AT**↓PLG…	Human	Reduce activity	Cell proliferation	(79)
FGF2	**PA**↓LPE…	Human	loss nuclear localization signal	Inhibition *in vitro* lead to metastatic potential of prostate cancer cells	(80, 81)
Incretin hormones					
GLP-1	**HA**↓EGTFTSD-	Human	Inactivation	Postprandial insulin response	(82)
GLP-2	**HA**↓DG↓SF…	Human	Inactivation	Glucose control	(82)
GIP	**YA**↓EGTF…	Human	Inactivation	Postprandial insulin response	(82)
PACAP	**HS**↓EG↓IF…	Human	Inactivation	Neural regulation of islet	(82)
GRP	**VP**↓LP↓AG…	Human	Inactivation	Neural regulation of islet	(82)
Neuropeptides					
Neuropeptide Y	**YP**↓SKPDNPG	Human	Affinity alteration	inhibit exocrine pancreas function, feeding	(83)
Peptide YY	**YP**↓IKPEAPG	Human	Affinity alteration	Multiple function in renal, digestive system and food intake	(84)

relieved by pharmacological or genetic inactivation of DPP4 (93). Moreover, DPP4 binding to extracellular matrix proteins (such as collagen and fibronectin) and extracellular matrix degrading enzymes (such as plasminogen and streptokinase) probably contributes to cells spreading and metastasis (5, 94, 95). Streptokinase, plasminogen and its metabolite plasmin bind to cysteine-rich region of DPP4, resulting in a rapid increase of intracellular Ca^{2+} response and subsequent activation of fibroblast (5, 96). The binding of DPP4 with plasminogen also regulates the homeostasis of extracellular matrix by promoting the secretion of matrix metalloproteinases and conversion of plasminogen to plasmin (97). In addition, production of plasmin is able to degrade BP180, an autoantigen found in autoimmune skin disease bullous pemphigoid. Therefore, DPP4 may be involved in the maintaining of BP180 immunotolerance and the prevention of BP autoantibody production (98).

THE ROLE OF DPP4 IN AUTOIMMUNE DISEASE

DPP4 in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease causing pain, swelling, stiffness and loss of function of joints. Although the exact cause and pathogenesis are unclear, it's a consensus that T cell activation plays an important role in the initiation and maintaining of inflammation in RA (99). Various factors involved in T cell activation, including CD28, CD40, CTLA4, ILRA/IL2, IL-21, have been found to increase in RA (100). As an activation marker of T cells, DPP4 has received increasing attention in RA. Serum DPP4 concentration is significantly decreased in patients with RA compared to the control group (101), and this decrease is inversely correlated to disease activity (102). However, DPP4 expression on the surface of circulating lymphocytes and monocytes showed no significant differences between early RA patients and healthy controls (102, 103). Another study suggested that DPP4 expression on peripheral blood CD4+ T cells was higher in active RA compared to inactive RA and controls. However, its expression on synovial fluid T cells from RA was lower than that from osteoarthritis patients (104). The decrease of DPP4 activity also occurs in synovial fluids, fluid mononuclear cells (FMNC) and synovial membrane in RA compared with osteoarthritis (105–107). Interestingly, Anti-DPP4 autoantibodies have been observed in RA patients and may be used as a biomarker for early diagnosis of RA (108), which suggests that DPP4 may contributes to the immunopathology of RA.

SDF-1, a substrate of DPP4, is thought to play a central role in inflammatory cell recruitment *via* interacting with its receptor CXCR4. In murine model of antigen-induced arthritis, DPP4 deficiency resulted in preservation of serum active SDF-1 and enhanced infiltration of CXCR4-positive inflammatory cells in arthritic joints (109). The plasma level of DPP4 was lower than that in osteoarthritis and negatively correlated with plasma inflammation marker C-reactive protein (109). The level of

SDF-1 was inversely correlated with the number of DPP4+ T cells in synovial fluids from patients with RA (105). Since the synovial level of SDF-1 was strongly correlated with the disease activity score (DAS28 CRP) and inflammation markers (serum C-reactive protein and IL-6) (109, 110), the decrease of synovial DPP4 in RA may lead to synovial inflammation *via* SDF-1/CXCR4 axis. These results indicate a critical role of DPP4/SDF1/CXCR4 in synovial inflammation in RA.

A recent study indicates that exogenous DPP4 or overexpression of DPP4 in synovial fibroblasts reduced the production of proinflammatory cytokines such as IL-1β, IL-6 and IL-3 from fibroblasts (111). Bone erosion is a severe consequence in RA progression. In a recent study, DPP4 was found to be highly expressed in osteoclast and its expression was suppressed by an anti-resorptive agent denosumab, suggesting that osteoclast-derived DPP4 may be an important link between energy metabolism and bone remodeling (112). It is shown that the invasion of synovial fibroblasts into cartilage was enhanced by the inhibition of DPP4 in a mouse model of RA (113). However, in a streptozotocin-induced diabetic model of rat, DPP4 inhibitor was shown to attenuate the bone loss and improve mechanical bone strength, probably through reducing CTX-I-dependent bone resorption (114).

Clinical observation on patients prescribed with DPP4 inhibitors may offer critical information on role of DPP4 enzymatic activities in RA. DPP4 inhibitors-associated newly onset RA cases have been reported by several groups (115–117). However, larger-scale population studies failed to identify an association between RA and DPP4i utilization compared to other antidiabetic therapies (118–121). Future randomized controlled trials are required to investigate the exact effects of DPP4 enzymatic inhibition on the development of RA.

DPP4 in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disease with many patients presenting with a characteristic butterfly rash (erythematous rash over the cheeks and bridge of the nose). Since most patients present high titers of autoreactive antibodies and disease activity is correlated with autoantibody titers, SLE used to be considered as an adaptive immune system disorder (122).

Serum DPP4 activities were significantly decreased in mice with lupus erythematosus-like syndrome compared to healthy mice, indicating a potential involvement of DPP4 in the pathogenesis of SLE (4). Likewise, clinical evidences demonstrate lower levels of DPP4 in the serum and peripheral blood mononuclear cells of SLE patients compared to health controls (4, 123, 124). Wong et al. reported that surface expression of DPP4 on CD4+ T cell and invariant natural killer T (iNKT) lymphocytes were reduced in SLE patients, accompanied with reduced circulating iNKT and elevated Th1 response (125). DPP4 mRNA expression analysis *via* qPCR showed 3.6-fold higher in SLE group than in the healthy control group, whereas no significant correlation with disease activity (50).

Recent population-cohort studies from Taiwan and Korea showed that DPP4 inhibitors was associated with a reduced risk of SLE (126, 127). However, high-level clinical evidence on the relation between DPP4 inhibition and SLE is limited.

DPP4 in Systemic Sclerosis

Systemic Sclerosis (SSc), also known as scleroderma, is another severe autoimmune disease characterized by diffuse cutaneous and visceral fibrosis (128). Early research reported an increase in both absolute number and percentage of peripheral blood $CD4^+DPP4^+T$ in scleroderma patients, and the levels of DPP4 expression in T cells correlated with disease activity (129). Circulating soluble DPP4 was also significantly decreased in SSc patients, compared to controls (101). Compared to limited cutaneous SSc, the soluble DPP4 levels further reduced in diffuse cutaneous SSc (130), which supports the hypothesis that DPP4 activity is associated with fibrosis progress in SSc.

Myofibroblasts are main collagen-producing cells in tissue fibrosis (131). In SSc skin, myofibroblasts contribute to tissue tension and skin/joint contractures (132, 133). As discussed above, DPP4 is critical for the activation of fibroblast. DPP4-positive fibroblasts express a high level of profibrotic genes including collagen-1, collagen-3, and fibronectin (134). Additionally, stimulation with recombinant human DPP4 promotes the production of fibronectin in lung fibroblast, suggesting a role of DPP4 in fibroblast activation and tissue remodeling (135). A recent study discovered that DPP4-expressing fibroblasts are responsible for collagen deposition in dermal scars and inhibition of DPP4 reduced scar formation in a mouse model of wound healing (16). The following studies demonstrated that SFRP2/DPP4 fibroblast subpopulation is the progenitor of fibrogenic fibroblasts in SSc skin (136) and DPP4 activated NF-κB and SMAD signaling through PAR2, leading to the activation of dermal fibroblasts (92).

Utilization of DPP4 inhibitors sitagliptin and vildagliptin in murine model of bleomycin-induced skin fibrosis showed a marked anti-fibrotic effect as evidenced by ameliorated dermal thickness, hydroxyproline content, and accumulation of myofibroblasts through suppressing TGF-β-induced ERK signaling pathway (91). Vildagliptin also effectively attenuated fibrosis and inflammation in bleomycin-induced lung fibrosis (137). Although animal studies have suggested a prospective application of DPP4 inhibitors in SSc, there are limited clinical trials investigating the role of DPP4 inhibitors in patients with SSc.

DPP4 in Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a typical autoimmune-mediated digestive system disease including Crohn's disease (CD) and ulcerative colitis (UC). Although there are differences between CD and UC, they both are characterized by chronic relapsing progressive process and multi-organ involvement in later stage. The serum DPP4 level and enzymatic activity in patients with IBD were decreased significantly compared to healthy control or patients with remissive conditions, and the extent of decrease was correlated with disease activity (138–141). In addition, responders to treatments had a higher serum DPP4 level compared to nonresponders (139). DPP4 activity in the fecal was found to reduce in active UC patients, but increase in CD

patients, when compared to remitters (142). These results suggest that DPP4 activity is a potential biomarker for monitoring IBD activity and therapeutic response (143). A model of TNBS-induced colitis in DPP4$^{-/-}$ mice showed higher serum levels of neuropeptide Y (NPY), vasoactive intestinal peptide (VIP) and IL-6, which are all substrates of DPP4, compared to C57BL/6 mice. The levels of VIP and IL-6 in the colon and brain tissues were also increased in DPP4$^{-/-}$ mice during the acute inflammation phase of colitis. IL-10 in the brain was found to reduce in wild-type mice, but increase in DPP4$^{-/-}$ mice, suggesting a potential role of DPP4 in regulating neuroimmune response in colitis development (144). In dextran sulfate sodium (DSS)-induced colitis, DPP4$^{-/-}$ mice showed increased CD8+ T cells and NKT cells in the spleen, as well as increased macrophage infiltration and enhanced expression of NF-κB p65 subunit in colon mucosa (145),. Additionally, GLP-1 and GLP-2 promote the repair of injured intestinal epithelia and regulate T cell differentiation and functions, and those functions are inhibited by DPP4 enzymatic cleavage (146, 147). The protective effect of DPP4 inhibitors on IBD has been observed in animal studies. DSS-induced colitis in mice was improved by administration of DPP4 inhibitor ER-319711, as demonstrated by less colon shortening and weight loss (148). Likewise, anagliptin treatment also facilitates the restoration of intestinal mucosal damage in DSS-induced colitis in C57BL/6 mice (149). However, clinical evidence about the effect of DPP4 inhibitor on IBD is limited and inconsistent. A cross-sectional study observed an increased risk of several autoimmune diseases including Crohn's disease, Hashimoto's thyroiditis, and Psoriasis in patients on DPP4 inhibition therapy (150). Abrahami et al. also reported an association between the use of DPP4 inhibitor and increased risk of IBD (hazard ratio 1.75, 95% confidence interval 1.22 to 2.49) (151). Nevertheless, another real-world investigation of 895,747 patients on either DPP4 inhibition therapy or other anti-diabetic treatment suggested that the use of DPP4 inhibitors was not associated with increased IBD risk (152). A meta-analysis involving 16 individual studies also reported a non-significant increase in the risk of IBD after exposure to DPP4 inhibitor when using a random-effects model (Relative risk 1.52; 95% confidence interval 0.72 to 3.24). However, this finding was driven by the inclusion of a large study and further surveillance on this effect is warranted (153).

DPP4 in Autoimmune Diabetes

Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, is characterized by immune-mediated destruction of pancreatic β cells and insufficiency of insulin secretion in early ages (154). Serum DPP4 activity was found to increase in patients with T1DM and the elevation is correlated with duration of diabetes (155–157). Although DPP4i has been used as either mono-therapy or combined therapy for T2DM over a decade, there is limited evidence supporting its application in T1DM. The effect of DPP4 inhibition on lowering HbA1c in patients with T1DM was not consistent in clinical trials (158–161).

Despite inconsistent findings in clinical investigations, the role of DPP4 in T1DM progression and inflammatory process has received sufficient attention in preclinical studies. Imbalanced Th1/Th2 and Th17/Treg responses are important features of T1DM. DPP4 inhibition leads to decreased Th1 response, increase of Th2 cytokines, and restoration of Treg/Th17 imbalance (98). GLP-1, a substrate of DPP4, was reported to possess anti-inflammatory property in pancreas and adipose tissue by reducing the production of inflammatory cytokines and infiltration of immune cells (162). Therefore, the inhibition of DPP4 contribute to anti-inflammatory process in pancreatic. In NOD mice trial treated with DPP4 inhibitor MK0431, the survival of islet graft was prolonged, accompanied by a decreased migration of $CD4^+$ T cells into pancreas through a pathway involving cAMP/PKA/Rac1 activation (163). In another T1DM mouse model induced by low-dose streptozotocin, sitagliptin not only reduced blood glucose level, but also improved inflammation in pancreas by increasing $CD4^+CD25^{hi}Foxp3^+$ T cells and reducing inflammatory cells (such as $CD11b^+$ cells and $CD4^+CD26^+$ T cells) (164). Therefore, preclinical studies indicate that DPP4 inhibition may improve T1DM through mechanisms involving both incretin effect and anti-inflammatory action.

DPP4 in Other Autoimmune Diseases

In addition to diseases mentioned above, involvement of DPP4 in other autoimmune diseases are displayed in **Table 3**. However, given the lower incidence of certain autoimmune disease, limited evidences are accessible. Case reports and retrospective studies of DPP4i utilization in T2DM patients demonstrated an association between the use of DPP4i and bullous pemphigoid, a severe autoimmune skin disease (18, 173–177). Importantly, DPP4i-induced bullous pemphigoid does not remit fully after withdrawal of DPP4i, suggesting that DPP4i induces and aggravate the process of bullous pemphigoid rather than a reversible side effect of DPP4i (18). Although the exact mechanisms underlying DPP4i-associated bullous pemphigoid is currently unclear, the breakdown of immunotolerance of BP180, the major autoantigen of bullous pemphigoid, might be a key reason. As mentioned above, DPP4 is involved in the immunotolerance of BP180 by regulating the conversion of plasminogen to plasmin that is responsible for the degradation of BP180 (98). A case-control study found that salivary DPP4 activity was increased in the patients with Sjögren's syndrome (SS), and there was a positive correlation between DPP4 activity and MMP9 level (166). A serial of studies reported that DPP4 is associated with chondrocyte physiology and inhibition of DPP4 suppresses the degradation of ECM, which is considered to help the amelioration of osteoarthritis (169, 178, 179). In addition, DPP4 inhibition was also reported to improve psoriasis (172), probably by inhibiting T cell activation (171). Collectively, further animal and clinical studies are required to identify the exact role of DPP4 in the development of autoimmune diseases.

DISCUSSION

This review discusses the role of DPP4 in immune system and its role in pathogenesis of different autoimmune diseases. Apparently, the expression of DPP4 is significantly affected in different autoimmune conditions. However, DPP4 is not a

TABLE 3 | The role of DPP4 in autoimmune diseases.

	Expression	Mechanisms	Effect of DPP4 inhibitor on disease phenotype
RA	Decreased in serum (101)	Limit the recruitment of inflammatory cells (109, 110) Involved in bone erosion (114)	Inconsistent: several case reports indicate DPP4 inhibitors induce RA (117, 126), some studies reported no association or reduced risk of RA (120)
SLE	Decreased in serum (4, 123, 124)	Evidence limited	Reduce risk (126)
SSc	Increased in T cells (129)	Indication of activated fibroblast	Limited evidence in humans; Animal study shows DPP4 inhibition meliorates fibrosis *in vivo* (91, 137)
IBD	Decreased serum activity (140, 165)	Regulate neuroimmune response (145) Impair tissue recovery by inactivation of GLP-2 (147)	Biomarker for treatment response (143) DPP4i promote prognosis in animals (149) Increased IBD risks (150, 151), or no impact (152, 153)
SS	Increased in saliva (166)	Regulate expression of MMP9 (166)	Evidence limited
OA	No significant alteration (167)	Upregulate AGE-induced MMPs (168) Promote bone formation by inactivating GLP-1 (168)	Improve ECM loss (168, 169)
Psoriasis	Increased at mRNA level in lesion (170)	inhibit T cell activation (171)	Improve psoriasis severity (172)

specific marker of any autoimmune disease, as its ubiquitous expression limits the potential of DPP4 as a precise biomarker. In addition to autoimmune disease, immune cell-derived DPP4 may also other disease conditions such as type 2 diabetes. Studies have demonstrated that immune cells, especially circulating CD4+ T helper cells, are important source of plasma DPP4 activity which is responsible for postprandial glucose intolerance in patients with type 2 diabetes (180, 181). In patients with type 2 diabetes, kallikrein-related peptidase 5, an enzyme responsible for the shedding of DPP4 from cell membrane, was induced in CD4+ T cells, suggesting that immune cell-derived DPP4 is responsible for reduced incretin effect in diabetes patients (180). Experimental and clinical investigations suggest that DPP4 may play a dual role in the pathogenesis of autoimmune diseases and the inhibition of DPP4 results distinct outcome in different disease condition. A possible reason is that DPP4, as a moonlighting protein, possesses diverse functions including enzymatic degradation of various substrates and enzymatic independent interaction with many ligands. In addition, while DPP4 is widely expressed in many types of cells, DPP4 expression in different cell population may also have distinct functions. To dissect the exact role of DPP4 in autoimmune diseases, future efforts may focus on the role of DPP4 in different types of cells, the temporal and spatial characteristics of DPP4 expression (especially in different stages of disease), unrecognized ligands for DPP4, and strategies targeting the non-enzymatic activity of DPP4. Taken together, DPP4 is a promising target of autoimmune diseases although its exact mechanisms in these conditions remain elucidated.

AUTHOR CONTRIBUTIONS

JH performed literature search. JH, XXL, YW, XLL, and SG drafted the manuscript. LD, XR, and JZ revised the manuscript. All author reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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