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Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions

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ABSTRACT

Dipeptidyl peptidase 4 (DPP4) inhibitors (DPP4is) are oral anti-diabetic drugs (OADs) for the treatment of type 2 diabetes mellitus (T2DM) through inhibiting the degradation of incretin peptides. Numerous investigations have been focused on the effects of DPP4is on glucose homeostasis. However, there are limited evidences demonstrating their Potential modulatory functions in the immune system. DPP4, originally known as the lymphocyte cell surface protein CD26, is widely expressed in many types of immune cells including CD4(+) and CD8(+) T cells, B cells, NK cells, dendritic cells, and macrophages; and regulate the functions of these cells. In addition, DPP4 is capable of modulating plenty of cytokines, chemokines and peptide hormones. Accordingly, DPP4/CD26 is speculated to be involved in various immune/inflammatory diseases and DPP4is may become a new drug class applied in these diseases. This review focuses on the regulatory effects of DPP4is on immune functions and their possible underlying mechanisms. Further clinical studies will be necessitated to fully evaluate the administration of DPP4is in diabetic patients with or without immune diseases.

Contents

1. Introduction

Dipeptidyl peptidase 4 (DPP4) is a transmembrane glycoprotein with a molecular mass of 220–240 kDa, originally known as T cell surface marker cluster of differentiation 26 (CD26) (Kameoka, Tanaka, Nojima, Schlossman, & Morimoto, 1993; Ohnuma, Dang, & Morimoto, 2008). Human DPP4/CD26 consists of a short 6 amino acid intracellular domain, a transmembrane region, and an extracellular domain which possesses dipeptidyl peptidase activity and selectively cleaves off the N-terminal dipeptides from peptides with proline, alanine or, to a lesser extent, serine at the penultimate position.

Abbreviations: AT, Adipose tissue; BP, Bullous pemphigoid; CVD, Cardiovascular disease; CCL, C-C motif chemokine ligand; CXCL, Chemokine (C-X-C motif) ligand; CPRD, Clinical Practice Research Datalink; CD26, Cluster of differentiation 26; CSF, Colony-stimulating factor; CD, Crohn's disease; CXCR4, CXC chemokine receptor 4; DC, Dendritic cell; DPP4, Dipeptidyl peptidase 4; DPP4is, DPP4 inhibitors; EPC, Endothelial progenitor cell; EPO, Erythropoietin; FGF2, Fibroblast growth factor 2; G-CSF, Granulocyte-CSF; GM-CSF, Granulocyte-macrophage-CSF; GLP-1, Glucagon like peptide-1; GIP, Glucose dependent insulinotropic peptide; HCC, Hepatocellular carcinoma; HFD, High fat diet; IBD, Inflammatory bowel disease; IFN-γ, Interferon gamma; IL, Interleukin; LADA, Latent autoimmune diabetes in adults; MI, Myocardial infarction; NK, Natural killer; NOD, Non-obese diabetic; OADs, Oral antidiabetic drugs; PCa, Prostate cancer; Treg, Regulatory T; RA, Rheumatoid arthritis; RASF, RA synovial fibroblast; SGLT2, Sodium glucose cotransporter 2; SGLT2i, SGLT2 inhibitor; sDPP4, Soluble DPP4; STZ, Streptozotocin; SDF-1, Stromal cell-derived factor-1; Th, T helper; TLR2, Toll-like receptor 2; TGF-β, Transforming growth factor-β; TNF-α, Tumor necrosis factor-α; T2DM, Type 2 diabetes mellitus; UC, Ulcerative colitis.

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DPP4/CD26 is widely expressed in different organs, including kidney, gastrointestinal tract, liver and bone marrow, as well as on the surface of various cell types such as stromal, stem, epithelial, endothelial, and immune cells (Thul et al., 2017; Waumans, Baerts, Kehoe, Lambeir, & De Meester, 2015). Moreover, it also exists as a soluble form (sDPP4/CD26) in body fluids (Varin et al., 2019), which is composed of the extracellular amino acids, and shows significant DPP4 activity (Casrouge et al., 2018; Durinx et al., 2000).

It is known that the gut-derived incretins glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) are essential for preservation of glucose homeostasis (Ahren & Hughes, 2005; Baggio & Drucker, 2007), while DPP4 rapidly degrades circulating GLP-1 and GIP. Over a decade, DPP4 inhibitors (DPP4is), which are commonly called gliptins, work as valuable oral antidiabetic drugs (OADs) in the treatment of type 2 diabetes mellitus (T2DM) through extending the half-life of native incretins (Marguet et al., 2000; Mari et al., 2005). After the first DPP4i, sitagliptin, has been approved by the Food and Drug Administration (FDA) for adults with T2DM in 2006, numerous gliptins, are generated, including saxagliptin, alogliptin, vildagliptin, linagliptin, teneligliptin, trelagliptin, and omarigliptin.

Investigations from over the past 2 decades have demonstrated that DPP4 may have broad biological functions beyond glucose metabolism as evidenced by its various substrates and widespread expression. Specifically, DPP4 cleaves a large number of cytokines, chemokines and peptide hormones involved in the regulation of immune system (Broxmeyer et al., 2012; Proost et al., 1999). It is also capable of modulating lymphocyte function in many aspects, especially in T cell activation and signal transduction. Accordingly, it is assumed that DPP4is have immune regulatory functions and potential therapeutic uses in the treatment of autoimmune and inflammatory diseases.

However, there are limited studies and clinical evidences demonstrating their immune modulatory functions and precise mechanism underlying this process. This review focuses on these functions of DPP4/CD26 and its inhibitors, which may provide some new clues for the clinical application of gliptins.

2. Effect of DPP4/CD26 on the immune system

CD26 may exert its effect on the immune system through two mechanisms. On the one hand, its enzymatic function results in a decomposition of targeted substrates into inactive and active fragments and exerts a direct effect on the immune response. On the other hand, CD26 acts as a potent costimulatory molecule in the process of T cell signal transduction (Ohnuma et al., 2008).

DPP4 exerts these non-catalytic functions via binding with caveolin-1, fibronectin, adenosine deaminase (ADA), and CXC chemokine receptor 4 (CXCR4) (Cheng, Abdel-Ghany, & Pauli, 2003; Herrera et al., 2001; Ohnuma et al., 2007; Ohnuma et al., 2008). The best-known signal transduction is the interaction between DPP-4 and ADA. The ADA is an enzyme that catalyzes the hydrolytic deamination of adenosine to inosine (Martin, Huguet, Centelles, & Franco, 1995). It has long been known that high concentrations of adenosine inhibit the proliferation of T lymphocytes (Green & Chan, 1973). Only the ADA bound to CD26 is functional and could counteract the inhihitory effect of extracellular adenosine. Accordingly, CD26/ADA/adenosine pathway is considered as an essential model in T-cell activation. Beyond that, the CD4(+) T cells, capable of transendothelial migration in vitro, appear to highly express CD26, indicating a potential function of CD26 in T cell migration (Brezinschek, Lipsky, Galea, Vita, & Oppenheimer-Marks, 1995).

Besides T lymphocytes, CD26 is identified to be expressed in B cells, natural killer (NK) cells, dendritic cells (DCs) and macrophages as well (Table 1). However, the immune regulatory function of DPP4/CD26 in these cells remains poorly characterized.

2.1. CD4(+) and CD8(+) T cells

It has been previously demonstrated that higher expression of CD26 on cell surface of CD4(+) T cells is correlated with their T helper type 1 (Th1)-like phenotype, whereas the lower expression of CD26 is associated with their Th2-like phenotype (Willheim et al., 1997). Furthermore, high CD26 surface expression is also correlated with the production of Th1-type cytokines (Reinhold et al., 1997; Willheim et al., 1997).

DCs are the most potent antigen-presenting cells (APC) specialized in the initiation of immune responses by directing the activation and differentiation of naïve T lymphocytes. Pacheco et al. reported that, in a deaminase activity-independent way, ADA interacts with CD26 on the T cell surface. The complex subsequently anchors to DC surface by an ADA-anchoring protein and then triggers costimulation, leading to an augmented T-cell activation with a Th1 pattern and a marked increase in the production of Th1 proimmflamatory cytokines including interferon gamma (IFN-γ), tumor necrosis factor (TNF)-α, and interleukin (IL)-6 (Pacheco et al., 2005). On the contrast, CD26 knockout in mice leads to a reduction in Th1 immune responses (Preller et al., 2007) but an up-regulation of Th2-type cytokines, such as IL-4, IL-5, and IL-13 (Yan, Gessner, Dietel, Schmiedek, & Fan, 2012). These findings further confirm the importance of CD26 in the proliferation and function of Th1 and Th2 cells.

IL-17-producing CD4(+) T cells (Th17 cells), the proliferation of which is regulated by IL-6, IL-23, and transforming growth factor (TGF)-β, play an important role in the pathogenesis of autoimmune inflammation; while regulatory T (Treg) lymphocytes exert their immunosuppressive effect by means of direct cell-to-cell interaction or through secretion of cytokines such as TGF-β and IL-10 (Shao, Yu, & Shen, 2018).

It has been found that expression of enzymatically active CD26/DPP4 is higher in human Th17 cells than in Th1, Th2, or Tregs cells (Bengsch et al., 2012). Phenotypic analysis has revealed that CD26(++)CD4(+) T cells contain more than 90% of Th17 cells (Bengsch et al., 2012). CD26 knockout results in a significant reduction of the Th17 cytokines such as IL-17 and IL-21 in mice with lung transplantation (Yamada et al., 2016). The author assumed that the modulation of Th17 cells by CD26 is via the costimulatory effects on signaling lymphocytic activation (Yamada et al., 2016). However, further investigation on downstream signaling was not performed. IL-6 is important for T cell proliferation and Th17 cells show an IL6-dependent increase (Wang et al., 2018; Winer et al., 2009). We have described that CD26 is correlated with augmented Th1 activation along with a marked increase of Th1 cytokines including IL-6. Pinheiro et al. found that sitagliptin treatment could completely abolish IL-6 expression by peripheral blood mononuclear cells (PBMCs) with the stimulation of phytohemagglutinin (PHA) from healthy volunteers and inhibit Th1/Th17 differentiation in vitro (Pinheiro et al., 2017). Thus, we assume that IL-6 may also be involved in CD26-mediated Th17 proliferation.

On the contrary, CD26 expression is lower on the membranes of Treg cells (Mandapathil et al., 2010), which has been characterized as a negative selection marker for human Tregs (Garcia Santana, Tung, & Gulnik, 2014). Based on CD39/CD26 marker, analysis of human natural regulatory T cells (nTregs) has identified five different cell subsets, representing a distinct stage of maturation respectively (Schiavon et al., 2019). In addition, DPP4i significantly increases the Treg expansion in non-obese diabetic (NOD) mice (Tian et al., 2010), indicating that DPP4/CD26 inhibition may be responsible for the proliferation of Treg lymphocytes. Martinez-Navio identified that ADA promotes an augmented generation of CD4(+)CD25(high)Foxp3(+) Tregs by a mechanism that seems to be mainly dependent on its enzymatic activity (Martinez-Navio et al., 2011). Accordingly, CD26/ADA/adenosine is considered to exert an important regulatory role in the generation of Tregs.

It has been previously demonstrated that both CD8(+)CD26(high) and CD8(+)CD26(−) cells represent activated cell phenotypes and

Table 1
Expression and function of DPP4/CD26 on immune cells.

Immune cells	Expression	Function	Reference
Th1 cell	High expression	CD26 is correlated with the production of Th1 cytokines	(Preller et al., 2007; Reinhold et al., 1997; Willheim et al., 1997)
Th2 cell	Low expression	DPP4 inhibition leads to up-regulation of Th2 cytokines	(Willheim et al., 1997; Yan et al., 2012)
Th17 cell	Highest CD26 expression in CD4(+) T cell	CD26 is correlated with the production of Th17 cytokines	(Bengsch et al., 2012; Yamada et al., 2016)
Treg cell	Negative/low expression	DPP4 inhibition leads to up-regulation of Tregs	(Garcia Santana et al., 2014; Mandapathil et al., 2010; Schiavon et al., 2019; Tian et al., 2010)
CD8(+) T cell	High/negative expression	CD26 mediates co-stimulation of CD8(+) T cells	(Hatano et al., 2013; Ibegbu et al., 2009)
B cell	Low expression	CD26 is correlated with B cell activation	(Buhling et al., 1995; Klemann et al., 2009; Morimoto et al., 1989; Yan et al., 2003)
NK cell	Low expression	CD26 is correlated with the proliferation and cytotoxicity of NK cells	(Buhling et al., 1994; Shingu et al., 2003; Yan et al., 2003)
DC	Positive expression	CD26 together with ADA stimulates T-cell proliferation	(Gliddon & Howard, 2002; Zhong et al., 2013)
Macrophage	Positive expression	DPP4 regulates M1/M2 macrophage polarization	(Shah et al., 2011; Zhuge et al., 2016)

Note: ADA, adenosine deaminase; DC, dendritic cell; DPP4, Dipeptidyl peptidase 4; NK cell, natural killer cell; Th1 cell, T helper type 1 cell; Th2 cell, T helper type 2 cell; Th17 cell, IL-17-producing cell; Treg cell, regulatory T cell.

may offer a characteristic marker of successful memory development (Hatano, Ohnuma, Yamamoto, Dang, & Morimoto, 2013; Ibegbu et al., 2009). CD28 is one of the molecules expressed in T cells, which provides co-stimulatory signals for T cell activation (Gamble et al., 2018). Interestingly, CD26-mediated co-stimulation of CD8(+) T cells results in greater cytotoxic effect than that induced by CD28 co-stimulation pathway (Hatano et al., 2013). The modulation of CD26 on CD8(+) T lymphocytes may use costimulatory transduction mediated by early growth response 2 (EGR2) and IL-10 (Hatano et al., 2015; Pinheiro et al., 2017).

2.2. B cells, and NK cells

In addition to its effects on CD4(+) and CD8(+) T cells, CD26 also contributes to the modulation of maturation, proliferation, and immunoglobulin isotype switching of B cells (Buhling et al., 1995; Morimoto et al., 1989). Less than 5% of freshly isolated CD20(+) B cells express the CD26 antigen in the peripheral blood of healthy donors and common variable immunodeficiency (CVID) patients. Upon activation by pokeweed mitogen, the fraction of CD26(+) human B cells can increase to around 50% (Buhling et al., 1995), suggesting an involvement of CD26 in B-cell activation. Specific suppression of DPP4 activity reduces the B cell activation in a dose-dependent manner (Buhling et al., 1995). DPP4 inhibitor could suppress the enzymatic activity and thereby trigger certain signal transduction pathways leading to a decrease in DNA synthesis of B cells (Buhling et al., 1995). Howbeit, the authors failed to identified the detailed molecular mechanisms.

One of the most important functions of B lymphocytes is the secretion of immunoglobulins (Igs). A significant change of Ig secretion by B cells in CD26-deficient mice was identified, which may be triggered by a change of different cytokines including IFN-γ, IL-4, and IL-2, (Yan, Marguet, Dobers, Reutter, & Fan, 2003); while no difference of Ig secretion was observed in another study (Vora et al., 2009). As published by Morimoto, CD26 was found to be expressed on the CD4 memory/helper (CD45RO + CD29+) population, which can respond to recall antigens and induce B-cell IgG synthesis (Morimoto et al., 1989). Buhling et al. measured the IgM concentrations from highly purified B cells with different inhibitor concentrations and found a dose-dependent decrease of IgM secretion (Buhling et al., 1995). Based on these findings, CD26 mediated B-cell Ig secretion may either through T cell-dependent B-cell responses or direct effects on B cells.

Buhling et al. showed that freshly isolated human NK cells express only low amounts of CD26 (Buhling et al., 1994). Furthermore, the authors identified that specific DPP4 inhibitors suppress DNA synthesis and cell cycle progression, thus concluding that CD26 is involved in the modulation of NK cell proliferation. DPP4/CD26 may also be involved in the natural cytotoxicity of NK cells, which is verified by the observation that NK cell cytotoxicity against tumour (MADB106) cells is diminished in a DPP4/CD26-deficient F344 rat sub-strain, a model of lung metastasis (Shingu et al., 2003). One of the underlying mechanisms is that tumor target cells can directly adhere to NK cells via CD26. In addition, NK cells can exert their cytotoxicity via secretory lysosomes. Interestingly, DPP4/CD26 has been found on the membrane of secretory lysosomes in NK cells by mean of proteomic analysis (Casey, Meade, & Hewitt, 2007). Whether CD26 on secretory lysosomes could also mediate NK cell cytotoxicity is remained to be identified.

2.3. Dcs and macrophages

The first description of DPP4/CD26 expression on DCs was reported by Gliddon and colleagues from bovine afferent lymph and lymph nodes (Gliddon & Howard, 2002). Both obese humans and rodents demonstrated increased DPP4/CD26 expression on DCs from visceral adipose tissue (AT) (Zhong et al., 2013). It is considered that CD26 expression by DC confers the ability to modify macrophage-derived chemokine (MDC) so that it may not stimulate Th2 polarized cells but attract and induce responses in Th1 polarized cells (Gliddon & Howard, 2002). Furthermore, the CD26-ADA complex on DCs is capable of stimulating T cell proliferation via adenosine degradation in mixed lymphocyte reaction (MLR) assays using T-cell/DC cocultures (Zhong et al., 2013). These findings disclose a novel mechanism for the paracrine regulation of inflammation in AT by DPP4.

DPP4/CD26 expression on macrophages from visceral AT was also identified in both high fat diet (HFD)-induced (C57BL/6) and genetically obese (ob/ob) mice (Zhong et al., 2013). Long-term DPP4 inhibition by alogliptin decreases visceral AT macrophage content (CD11b(+), CD11c(+), Ly6C(hi)) in a ApoE (−/−) mouse model (Shah et al., 2011). Similarly, Ikedo et al. identified that alogliptin inhibits the accumulation of macrophages in intracranial aneurysms in SD rats and they verified that such effect is independent of GLP-1 (Ikedo et al., 2017). Silencing expression of DPP4 by shRNA targeting hepatocytes in HFD induced obese mice also suppresses macrophage inflammation of visceral AT (Ghorpade et al., 2018). Furthermore, Zhong and colleague reported that macrophage-expressing DPP4 binds ADA, resulting in T-cell proliferation via modulation of adenosine concentrations and then the development of adipose inflammation (Zhong et al., 2013). All these findings disclose the significant role of DPP4/CD26 on macrophage proliferation and function.

Additionally, it is found that DPP4/CD26 is predominantly expressed in M1-polarized macrophages in white AT of HFD induced obese mice (Zhuge et al., 2016), indicating its effect on the regulation of M1/M2 Macrophage Polarization. Macrophage inflammatory protein-1α (MIP-1α), also known as C-C motif chemokine ligand (CCL) 3, is a chemokine and DPP4 substrate. It has been reported that cleavage by DPP4 converts MIP-1α into a most efficient chemoattractant (Proost et al., 2000). DPP4i linagliptin fails to induce M2 macrophage polarization and exert insulin-sensitizing effects in MIP-1α$^{-/-}$ mice (Zhuge et al., 2016), suggesting that DPP4 regulates M1/M2 polarization may be mediated by MIP-1α.

2.4. Cytokines, chemokines, and peptide hormones

Although DPP4 is responsible for proteolytic cleavage of a wide range of substrates, most of DPP4-related researches have been focused on the incretin hormones GLP-1 or GIP for T2DM treatment (Ahren & Hughes, 2005; Baggio & Drucker, 2007; Unniappan et al., 2006). In addition to incretins, cytokines (Broxmeyer et al., 2012; O'Leary et al., 2017; Wesley, McGroarty, & Homoyouni, 2005), chemokines (Barreira da Silva et al., 2015; De La Luz Sierra et al., 2004; Hollande et al., 2019; Janssens et al., 2017; Oravecz et al., 1997; Proost et al., 1999; Proost et al., 2001; Qin et al., 2018), and some neuropeptides (Frerker et al., 2007; Guieu et al., 2006) have been identified as its substrates (Table 2), thereby, allowing DPP4 to regulate immune responses.

Plenty of chemokines and cytokines have been recognized as DPP4 targets. Among them, chemokine (C-X-C motif) ligand 12 (CXCL12, also known as stromal cell-derived factor-1, SDF-1) is the most popular one. It is a chemokine which can attract various progenitor cells, stem cells, leukocytes, neurons, angioblast/endothelial cells, and tumor cells. Thus it is involved in plenty of processes such as angiogenesis, hematopoiesis, and tissue repair (e.g., myocardial infarction (MI) and ischeamic stroke) (Bromage, Davidson, & Yellon, 2014; Kubota et al., 2016; Yang et al., 2018; Zhang et al., 2017). CXCL12/SDF-1 acts through the G protein-coupled CXCR4. Proteolytic cleavage of CXCL12 by DPP4 generates CXCL12(3–68) and results in a reduced CXCR4 affinity and a loss of its calcium-dependent signaling and chemotactic properties (De La Luz Sierra et al., 2004; Janssens et al., 2017).

In addition, DPP4 plays a more general role in regulating the activities of cytokines. DPP4 has been identified to truncate cytokines such as fibroblast growth factor 2 (FGF2), IL-3, granulocyte-macrophage (GM)-colony-stimulating factor (CSF), granulocyte (G)-CSF and erythropoietin (EPO), thus, resultantly decrease their activity and function (Broxmeyer et al., 2012; O'Leary et al., 2017; Wesley et al., 2005). Besides, there are a plenty of cytokines with the potential truncation site of DPP4 including IL-1, −2, −5, −6, −8, and − 10 (Ou, O'Leary, & Broxmeyer, 2013). However, whether these cytokines have true DPP4 truncation sites needs to be specifically determined via mass spectrometry and comparable analysis. Biological assays in vitro and in vivo will be necessary to determine if the functional activity of truncated molecules differs from the full-length form of the protein.

Furthermore, some cytokines regulated by DPP4 may be via complicated interactions between factors/immune cells rather than direct truncation. For example, ADA-DPP4 interaction acts as co-stimulatory signals during T cell receptor signaling, resulting in enhanced secretion of IFNγ and TNF-α (De Meester et al., 1994; Kameoka et al., 1993). Likewise, Steinbrecher et al. suggested that DPP4 suppression may stimulate TGF-β secretion from activated T cells, hence, have an anti-inflammatory effect in a mice model of experimental autoimmune encephalomyelitis (EAE) (Steinbrecher et al., 2001).

Taken together, these cytokines, chemokines, and peptide hormones mentioned in Table 2 are not meant to cover all identified factors but rather to describe that there are a wide variety of biologically molecules that may be truncated or regulated by DPP4/CD26.

Table 2
Known/potential factors truncated/regulated by DPP4/CD26.

Substrate	Reference
Chemokines	
CCL2 (MCP-1)	(Qin et al., 2018)
CCL3 (MIP-1α)	(Zhuge et al., 2016)
CCL5 (RANTES)	(Oravecz et al., 1997)
CCL11 (Eotaxin)	(Hollande et al., 2019)
CCL22 (MDC)	(Gliddon & Howard, 2002; Proost et al., 1999)
CXCL10 (IP-10)	(Barreira da Silva et al., 2015; Proost et al., 2001)
CXCL11 (I-TAC)	(Proost et al., 2001)
CXCL12 (SDF-1)	(De La Luz Sierra et al., 2004; Janssens et al., 2017)
Mig	(Proost et al., 2001)
Cytokines	
IL-3	(Broxmeyer et al., 2012; O'Leary et al., 2017)
GM-CSF	(Broxmeyer et al., 2012)
G-CSF	(Broxmeyer et al., 2012)
Erythropoietin	(Broxmeyer et al., 2012)
FGF2	(Wesley et al., 2005)
IL-1*	(Ou et al., 2013)
IL-2*	(Ou et al., 2013)
IL-5*	(Ou et al., 2013)
IL-6*	(Ou et al., 2013)
IL-8*	(Ou et al., 2013)
IL-10*	(Ou et al., 2013)
TGF-β#	(Steinbrecher et al., 2001)
IFNγ#	(De Meester et al., 1994; Kameoka et al., 1993)
TNF-α#	(De Meester et al., 1994; Kameoka et al., 1993)
Incretin hormones	
Gastric inhibitory peptide (GIP)	(Ahren & Hughes, 2005)
Gastrin-releasing peptide (GRP)	(Ahren & Hughes, 2005)
GLP-1	(Baggio & Drucker, 2007)
GLP-2	(Baggio & Drucker, 2007)
Peptide YY(1–36)	(Unniappan et al., 2006)
Neuropeptides	
NPY	(Frerker et al., 2007)
Substance P	(Guieu et al., 2006)

CCL, C-C motif chemokine ligand; CXCL, Chemokine (C-X-C motif) ligand; FGF2, fibroblast growth factor 2; G-CSF, Granulocyte-CSF; GIP, Gastric inhibitory peptide; GLP, hormones glucagon like peptide; GM-CSF, Granulocyte-macrophage-colony-stimulating factor; GRP, Gastrin-releasing peptid; IL, interleukin; IFNγ, interferon gamma; IP-10, IFN-gamma-inducible protein-10; I-TAC, IFN-inducible T-cell alpha-chemoattractant; MCP-1, monocyte chemotactic protein 1; MDC, macrophage-derived chemokine; Mig, monokine induced by IFN-gamma; MIP-1α, Macrophage inflammatory protein-1α; NPY, neuropeptideY; SDF-1, stromal cell-derived factor-1; RANTES, regulated on activation in normal T-cell expressed and secreted; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

* Potential truncation by DPP4/CD26.

\# Regulation rather than truncation by DPP4/CD26.

3. Effects and underlying mechanisms of DPP4/CD26 inhibition on immunotherapy

DPP4is have been linked to the diseases as summarized in Table 3, including but not limited to autoimmune diabetes, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), allograft rejection, tumor, cardiovascular disease (CVD), asthma, infectious diseases and bullous pemphigoid (BP). However, the effect of DPP4is on these diseases is controversial.

3.1. DPP4/CD26 inhibition on autoimmune diseases

3.1.1. DPP4/CD26 inhibition on autoimmune diabetes

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by the destruction of pancreatic β cells and inadequate insulin secretion (Roep & Tree, 2014). Under this circumstance, even slight preservation of residual β cell mass may result in significant benefits in clinic (Palmer et al., 2004). Unfortunately, there are no immunomodulatory drugs that have been reported to induce/assist the disease

Table 3
Effect of DPP4 inhibition in autoimmune/inflammatory diseases.

	Effect of DPP4 inhibition	Reference
Autoimmune diabetes	HbA1c reduction in T1DM patients	(Ellis et al., 2011; Farngren et al., 2012)
	No treatment efficacy in T1DM/LADA patients	(Garg et al., 2013; Hari Kumar et al., 2013; Zhao et al., 2014)
	β cell preservation in LADA patients	(Johansen et al., 2014; Zhao et al., 2014)
	No effect of β cell preservation in T1DM/LADA patients	(Griffin et al., 2014; Hari Kumar et al., 2013)
	β cell preservation in animal model	(Conarello et al., 2003; Jelsing et al., 2012; Kim et al., 2012; Kim et al., 2008; Pospisilik et al., 2003; Suarez-Pinzon et al., 2009; Takeda et al., 2012; Tian et al., 2010)
IBD	Increased risk in T2DM patients	(Abrahami et al., 2018; Kridin et al., 2018; Wang et al., 2019)
	Improved colitis in animal model	(Ban et al., 2011; Salaga et al., 2017; Salaga et al., 2018)
RA	Decreased risk in T2DM patients	(Kim et al., 2015; Seong et al., 2019)
	No association in T2DM patients	(Douros et al., 2018)
	Increased disease severity in animal model	(Busso et al., 2005; Ospelt et al., 2010)
Allograft rejection	Rejection suppression in animal models of islet, lung, skin transplantation	(Jung et al., 2006; Kim et al., 2009; Zhai et al., 2007; Zhao et al., 2019)
Cancer	No association in T2DM patients	(Barnett et al., 2012; Green et al., 2015; Leiter, et al., 2015; Mita, et al., 2016)
	Tumor suppression in vitro/in animal models of HCC, breast cancer, melanoma, CML, and multiple myeloma	(Barreira da Silva et al., 2015; Herrmann et al., 2014; Hollande et al., 2019; Nishida et al., 2018; Qin et al., 2018)
	Tumor development in vitro/in animal models of PCa, lung cancer, and CRC	(Russo et al., 2018; Shingu et al., 2003; Wesley et al., 2005; Xie et al., 2017)
CVD	Cardiovascular safety in T2DM patients	(Aroor et al., 2018; Green et al., 2015;Scirica et al., 2013; White et al., 2013)
	Increased risk in HF in T2DM patients	(Scirica et al., 2013; White et al., 2013)
	Cardioprotection in animal model	(Bostick et al., 2014; Hocher et al., 2013; Kubota et al., 2016; Mulvihill et al., 2016; Shah et al., 2011; Connelly et al., 2013; Zhang et al., 2010)
	No effect or impairment of cardiac function in animal model	(Mulvihill et al., 2016; Yin et al., 2011)
Asthma	Increased airway inflammation in animal model	(Yan et al., 2012)
	Decreased airway inflammation in animal model	(Schmiedl et al., 2010)
Infectious diseases	Increased risk of nasopharyngitis and urinary tract infection but no association of upper respiratory tract infections in T2DM patients	(Amori et al., 2007; Gamble et al., 2018)
	Potential adverse effect on MERS patients	(Inn et al., 2018; Raj et al., 2013)
	Potential therapeutic effect on HCV patients	(Decalf et al., 2016; Riva et al., 2014)
	No effect on HIV patients	(Dube et al., 2019; Goodwin et al., 2013)
BP	Increased risk in T2DM patients	(Aouidad et al., 2013; Arai et al., 2018; Bene, et al., 2016; Benzaquen et al., 2018; Douros et al., 2019; Garcia et al., 2016; Kridin & Bergman, 2018; Lee et al., 2019; Plaquevent, et al., 2019; Varpuluoma et al., 2018)

Note: BP, bullous pemphigoid; CML, chronic myeloid leukemia; CRC, colorectal cancer; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; LADA, Latent autoimmune diabetes in adults; MERS, Middle East respiratory syndrome; Pca, prostate cancer; RA, rheumatoid arthritis; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

remission. Currently, DPP4is are widely applied as valuable mono- or combination therapeutic OADs for T2DM. However, only a portion of clinical studies have indicated potential efficacy regarding glycemic control and β cell preservation in T1DM.

Autoimmune diabetes is characterized by an increased Th1 immune response and a decreased Th2 response. In addition, the imbalance of Th17/Treg is also involved in the pathogenic process (Shao et al., 2012). It has been described in Table 1 that DPP4 inhibition down-regulates Th1-like phenotype, up-regulates Th2-type cytokines, stimulates the proliferation of Tregs, and decreases IL-17 production. Thus, DPP4is are supposed to have the potential to treat autoimmune diabetes. In preclinical trials, inhibition of DPP4 activity has been shown to enhance islet neogenesis and β cell survival, and reverse/delay the onset of diabetes in either streptozotocin (STZ)-induced animal model of T1DM (Conarello et al., 2003; Pospisilik et al., 2003; Takeda et al., 2012) or NOD mouse model of autoimmune diabetes (Jelsing, Vrang, van Witteloostuijn, Mark, & Klein, 2012; Tian et al., 2010). A combination therapy of DPP4i and proton pump inhibitor (PPI) increases circulating levels of GLP-1 and gastrin in acutely diabetic NOD mice, resulting in the restoration of pancreatic insulin content, insulin secretion and normoglycaemia (Suarez-Pinzon, Cembrowski, & Rabinovitch, 2009). Treatment of STZ-induced T1DM mice with DPP4i MK0431 before and after islet transplantation prolongs the survival of islet grafts (Kim et al., 2008). Differently, Kim et al. reported that β cell mass is enhanced in NOD mice by the combination of Toll-like receptor 2 (TLR2) agonist and DPP4i, but not by DPP4i or TLR2 agonist alone (Kim et al., 2012).

Most of the previous animal studies considered that β cell preservation by DPP4is is attributed to an increase in GLP-1 (Conarello et al., 2003; Kim et al., 2008; Pospisilik et al., 2003; Suarez-Pinzon et al., 2009; Takeda et al., 2012). Dysfunctional Tregs are thought to be a hallmark of T1DM (Geach, 2016). Preclinical data from Tian and colleagues demonstrated that up-regulation of Tregs by DPP4 inhibition is associated with the remission of NOD mice (Tian et al., 2010). It is possible that DPP4 suppression results in the changes of chemokines in diabetic NOD mice and thus promotes the migration of Tregs to pancreas (Fig. 1A).

Due to these significant results from animal experiments, numerous clinical studies are conducted to investigate the therapeutic effect of DPP4is in patients with T1DM. Four placebo-controlled studies investigated the efficacy of sitagliptin/vildagliptin treatment in T1DM (Ellis et al., 2011; Farngren, Persson, Schweizer, Foley, & Ahren, 2012; Garg et al., 2013; Hari Kumar, Shaikh, & Prusty, 2013). Two studies showed significant HbA1c reduction of −0.27 and − 0.34% after DPP4is treatment for 8 or 4 weeks, respectively (Ellis et al., 2011; Farngren et al., 2012), while the other two studies didn't show any treatment-related differences (Garg et al., 2013; Hari Kumar et al., 2013). A meta-analysis from Wang et al. revealed that the additional use of DPP4is results in a greater decrease in HbA1c levels compared to insulin monotherapy, although it is not significant (Wang, Long, et al., 2018).

Additionally, some trials investigated the effect of gliptins on β cell preservation. In individuals with newly diagnosed T1DM, sitagliptin treatment for one year failed to result in any significant difference of c-peptide secretion between groups (Hari Kumar et al., 2013). Likewise, Griffin and colleagues randomly assigned T1DM participants to receive a combined therapy of oral sitagliptin and a PPI lansoprazole or matched placebo for 12 months; however, the difference of c-peptide between groups is not significant (Griffin, Thompson, Gottschalk, Kyllo, & Rabinovitch, 2014). These two trials estimated that gliptins are incapable of preserving β cell mass in autoimmune diabetes. Latent autoimmune diabetes in adults (LADA) is a special subtype of T1DM. Interestingly, a one-year prospective study conducted in LADA patients demonstrated that a combined treatment of sitagliptin to these patients who receive insulin provides significant improvements in the parameters of islet function (Zhao et al., 2014). Similarly, another DPP4i, linagliptin, contributes to a progressive increase in c-peptide levels in patients with LADA during a 2-year study (Johansen et al., 2014).

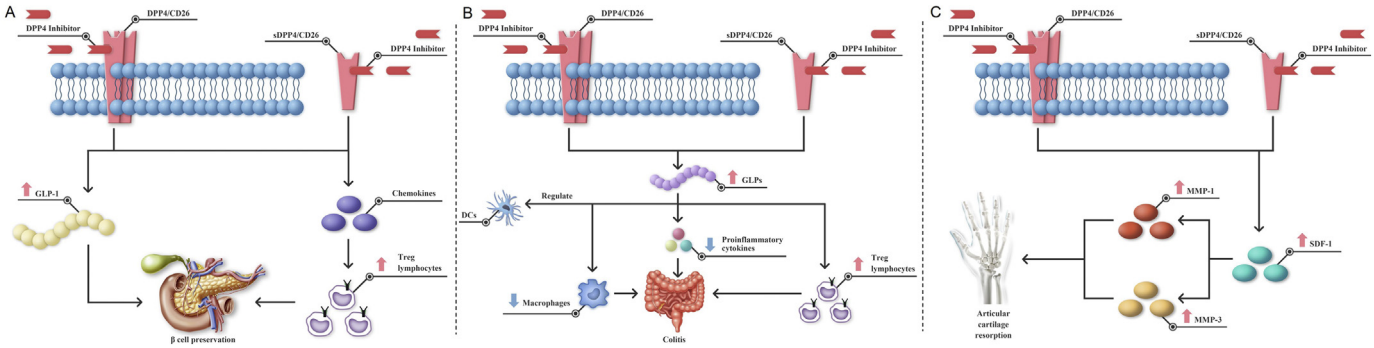

Fig. 1. The underlying mechanisms of DPP4 inhibition in autoimmune diabetes (A), inflammatory bowel disease (B), rheumatoid arthritis (C).

Taken together, these existing studies fail to strongly support the clinical application of DPP4is in either glucose control or β cell preservation in T1DM patients. The contrary conclusions obtained from the above clinic trials may be attributed to different baseline characteristics of the included patients (such as c-peptide levels, HbA1c, and disease duration), distinct follow-up lengths, different sample size, and other variables. Another point worth noting is that, DPP4 suppression alone may not be able to completely prevent autoimmune attack against β cells under overt T1DM condition. Thus, additional immunological measures will probably be necessary for TIDM treatment in order to attenuate the established autoimmunity.

Besides, traditional animal models of T1DM are unlikely to provide accurate predictions for clinical success in human studies because of the substantial genetic variation and the environment that is not present in laboratory rodents. Future researches should shift towards studies in human beings with consistent baseline characteristics of participants. In addition, larger sample size, longer follow-up duration, and the monitoring of immune parameters (such as T cells, B cells, and cytokines) should be taken in consideration.

3.1.2. DPP4/CD26 inhibition on IBD

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is an autoimmune digestive system disease characterized by chronic, remittent or progressive inflammation in the gastrointestinal tract (Abbott, Yazbeck, Geier, Demuth, & Howarth, 2006). Recent researches disclose a potential association of DPP4 inhibition with the risk of IBD in T2DM.

Duan and Zatorski reviewed the studies about the role of GLPs and DPP4is in IBD (Duan, Rao, Braunstein, Toomey, & Zhong, 2017; Zatorski, Salaga, & Fichna, 2019). It is considered that T lymphocytes such as Tregs, macrophages, DCs, and proinflammatory cytokines may be involved in DPP4i-GLPs mediated gut immunity. Preclinical studies on animal models about the underlying mechanisms are limited with only 3 studies included (Ban et al., 2011; Salaga et al., 2017; Salaga et al., 2018). Administration of DPP4 inhibitor EMDB-1 (Salaga et al., 2017; Salaga et al., 2018) or ER-319711 (Ban et al., 2011) could markedly attenuate colitis in mouse models of experimental colitis, which may be mediated by GLP-2 (Fig. 1B). The downstream signals of DPP4i-GLPs remain unclear, which need to be further explored.

Real-world evidences present an opposite conclusion to animal studies. A study of 283 T2DM patients treated with gliptins revealed that the prevalence of CD is significantly higher in patients with DPP4i treatment than in controls (Kridin et al., 2018). A retrospective cohort study using the United Kingdom Clinical Practice Research Datalink (CPRD) found that new use of DPP4is over a median duration of 1.6 years is associated with an increased risk of IBD (hazard ratio 1.75) compared to other antidiabetic medications (Abrahami et al., 2018). In addition, hazard ratios gradually increase along with longer durations of DPP4is usage, which reach a peak after three to four years (Abrahami et al., 2018). Wang demonstrated a weak-to-moderate signal of IBD associated with DPP4i use through the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) database (Wang et al., 2019).

Li et al. performed a meta-analysis of randomized controlled trials (RCTs) and no association between DPP4i and IBD was found. Howbeit, sub-analysis identified that DPP4i OADs may reduce CD risk but increase UC risk (Li et al., 2019). Of note, this analysis may have been underpowered to detect such an association due to the limited number of included trials/events and the statistical imprecision. Thus, we suggest that the association between DPP4is and IBD should be noted by physicians. It should be cautious when treating diabetic patients with IBD.

3.1.3. DPP4/CD26 inhibition on RA

RA is a chronic, systemic inflammatory disease with unknown etiology and is characterized by progressive destruction of articular cartilage and erosion of the underlying bone (Speiser, Ho, & Verdeil, 2016).

Altered DPP4 activity was first noted in mice with RA in 1989 (Gotoh, Hagihara, Nagatsu, Iwata, & Miura, 1989). To gain insights into the pathophysiological role of CD26 in arthritis, Busso et al. explored DPP4 expression in experimental mice model of arthritis, murine antigen-induced arthritis (AIA), and found a reduced plasma DPP4 activity in those mice models (Busso et al., 2005). Secretion of CXCL12/SDF-1, the substrate of DPP4, by RA synovial fibroblasts (RASFs) is crucially involved in the inflammatory process by recruitment of CXCR4-expressing T cells and monocytes from the periphery into the rheumatoid synovium (Seki, Selby, Haupl, & Winchester, 1998). In CD26-deficient mice with AIA, the disease severity is increased due to a lower DPP4 activity in synovial fluids, which results in an increase in SDF-1 levels in those mice (Fig. 1C) (Busso et al., 2005). The major extracellular proteolytic enzymes involved in cartilage resorption are matrix metalloproteinases (MMPs) and serine proteases (Proost et al., 2001). Ospelt et al. found that inhibition of serine protease activity of DPP4 promotes invasion of RASFs into cartilage in a mouse model of RA and leads to an increase in SDF-1 levels in concert with its downstream effectors MMP-1 and MMP-3 in vitro (Ospelt et al., 2010). These results indicate a central role of DPP4/SDF-1 signaling in protecting articular cartilage against RASFs invasion.

Busso et al. explored DPP4 expression in RA patients and also found a reduced plasma DPP4 activity (Busso et al., 2005). The concentration of SDF-1 is greatly elevated in the synovial fluid from patients with RA in contrast to its concentration in healthy individuals (Kanbe, Takagishi, & Chen, 2002). However, the functional role of DPP4/CD26 in human observed in the present cohort findings contradicts that in animal studies. In a large cohort of diabetic patients, those initiating DPP4i combination therapy appeared to have a decreased risk of autoimmune diseases including RA (hazard ratio 0.66) compared with those initiating non-DPP4i combination therapy (Kim et al., 2015). Similar result was found in a large population-based cohort study conducted by Seong (Seong, Yee, & Gwak, 2019). However, using the United Kingdom CPRD, Douros conducted a cohort study among 144,603 patients with T2DM initiating OADs between 2007 and 2016, and found that use of

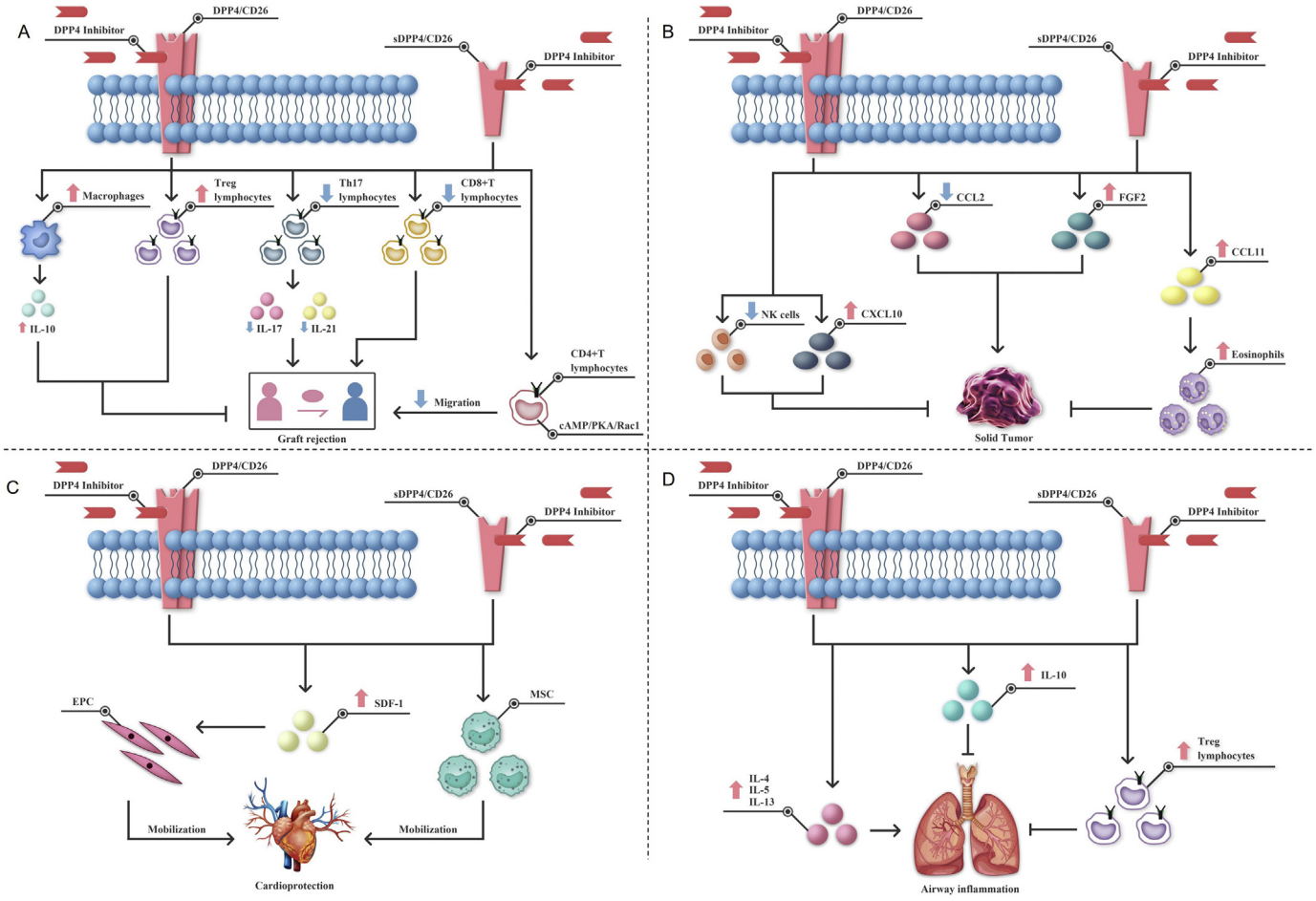

Fig. 2. The underlying mechanisms of DPP4 inhibition in allograft rejection (A), cancer (B), cardiovascular disease (C), and asthma (D).

DPP4is is not associated with any increased/decreased risk of incident RA (Douros et al., 2018). Nevertheless, these results may suggest possible pharmacological pathways for prevention or treatment of RA by gliptins.

The contradictory findings between rodent DPP4 and human DPP4 limit the usage of murine models for elucidating the function of human DPP4 in RA. By now, there is no research investigating the mechanism of such distinction. We assumed that, except SDF-1, there should be other cytokines/immune cells regulated by DPP4/CD26 that participate in the inflammatory process of human RA. Future investigations specifically focusing on the direct biological effects of DPP4 on human RA will undoubtedly contribute to a better understanding of its role, as a possible therapeutic target, in RA.

3.2. DPP4/CD26 inhibition on non-autoimmune diseases

3.2.1. DPP4/CD26 inhibition on allograft rejection

The last and most effective therapeutic strategy for many end-stage diseases is organ transplantation. However, one of the biggest challenges is to maintain the long-term survival of the grafts by preventing allograft rejection.

Study by Kim et al. demonstrated that treatment with MK0431 in NOD mice reduces the effect of autoimmunity on islet graft survival, partially, by decreasing the homing of CD4(+) T cells into pancreatic β cells through cAMP/PKA/Rac1 pathway (Fig. 2A) (Kim et al., 2009).

Moreover, there are several studies investigating whether the inhibition of DPP4 activity plays a role in acute pulmonary rejection. Treatment with AB192, a Pro-Pro-diphenyl phosphonate derivative, abrogates acute rejection and preserves early graft function after pulmonary transplantation in animal models (Jung et al., 2006; Zhai et al., 2007). A recent study from Yamada group concluded that CD26 blockade promotes lung allograft acceptance due to reduced T cell infiltration, lower expression of IL-17 and IL-21, and increased expression of IL-10, which is likely to be derived from alternatively activated macrophages (Yamada et al., 2016). These results expand the role of DPP4/CD26 in alloantigen-mediated immune responses.

Moreover, CD26 knockout mice have been used to investigate the potential role of DPP4 in allogeneic skin graft rejection. It is shown that CD26 knockout mice display a reduced necrosis of grafts and a delayed graft rejection with significantly reduced secretion levels of the cytokines such as IFN-γ, IL-2, IL-6, IL-4, IL-17, and IL-13 but increased level of IL-10 after skin transplantation (Zhao et al., 2019). Additionally, a lower percentage of Th17 and CD8(+) T cells but a higher percentage of Treg cells are detected in peripheral blood lymphocytes of CD26 knockout mice in the same study (Zhao et al., 2019), indicating that CD26 deficiency leads to feebler rejection due to lower activation and less proliferation of host immune cells.

So far, there is still few clinical studies focusing on the potential effect of DPP4i on allograft rejection. Future investigations in this field are necessary and may expand the clinic application of DPP4is.

3.2.2. DPP4/CD26 inhibition on cancer

Increasing evidences have demonstrated that the application of immunotherapy can improve the clinic outcome of cancer. Encouraging findings from experimental works regarding DPP4/CD26 suppression in melanoma, liver and breast tumors (Barreira da Silva et al., 2015; Herrmann et al., 2014; Hollande et al., 2019; Nishida, Hayashi, Morimoto, Sakamoto, & Yamada, 2018; Qin et al., 2018) pave the way

for future clinical studies (Table 3). But in other locations, DPP4 inhibition possibly leads to the tumor development (Russo et al., 2018; Shingu et al., 2003; Wesley et al., 2005; Xie et al., 2017).

It has been found that both gene ablation and pharmacological inhibition of DPP4 notably prevents HFD-associated hepatocellular carcinoma (HCC) progression in rat model of carcinogen-triggered liver cancer by down-regulating chemokine CCL2 production and angiogenesis (Fig. 2B) (Qin et al., 2018). Hollande and colleagues have further investigated the mechanism by which inhibition of DPP4 reduces tumor growth in HCC and breast cancer syngeneic mouse models and found that administration of DPP4i sitagliptin results in higher concentrations of the eosinophil chemoattractant CCL11, a known target for DPP4-mediated truncation (Table 2), and increased migration of eosinophils into solid tumors (Hollande et al., 2019). Moreover, Barreira da Silva et al. have showed that melanoma growth is significantly delayed in DPP4 knockout mice of tumor-transplant model and the authors estimated that CXCL10-mediated T cell trafficking may be involved (Barreira da Silva et al., 2015).

On the contrary, using in vitro model system in metastatic prostate cancer cells, Wesley indicated that DPP4 may inhibit malignant phenotype of prostate cancer (PCa) by enhancing degradation of FGF2 (Wesley et al., 2005). In a rat model of lung metastasis, DPP4 can drastically change the outcome of metastatic disease which may be partially mediated by NK cell cytotoxicity (Shingu et al., 2003), while DPP4 inhibition diminishes such effect.

Besides experimental studies, plenty of clinic trials have also been conducted for assessing possible cancer risk of DPP4is including sitagliptin (Green et al., 2015), alogliptin (Mita, et al., 2016), saxagliptin (Leiter, et al., 2015), and linagliptin (Barnett et al., 2012). All these trials demonstrate that gliptins do not increase tumor risk in T2DM patients. Zhao performed a meta-analysis with a total of 72 trials enrolled and no significant associations are detected between the use of gliptins and cancer development (Zhao et al., 2017), indicating the safety rather than benefits of gliptins in tumor.

The different conclusions from animal models and clinic trials may be attributed to relative weak effect of DPP4 on tumor immunity and the complexity of tumor microenvironment in human beings. Further studies that fully characterize the effects of DPP4i in various clinical settings will be required to comprehensively evaluate the administration of DPP4i in cancer patients with T2DM.

3.2.3. DPP4/CD26 inhibition on CVD

Patients with T2DM are at an increased risk of developing CVD, which is the prevailing cause of death worldwide. Atherosclerosis, the main underlying factor of CVD, is considered to be a chronic inflammatory disease with various cell types involved in this pathogenic process including differentially activated T and B lymphocytes, monocytes and macrophages, DCs, neutrophils, and endothelial cells (Rafieian-Kopaei, Setorki, Doudi, Baradaran, & Nasri, 2014). Abundant pre-clinical evidences implicate the beneficial role of DPP4 inhibition in atherosclerosis and CVD, which has been summarized by several reviews (Aroor, Manrique-Acevedo, & DeMarco, 2018; Avogaro & Fadini, 2014, 2018; Vedantham, Kluever, & Deindl, 2018; Zhong, Maiseyeu, Davis, & Rajagopalan, 2015).

Macrophages play a central role in the development of atherosclerosis by the maintenance of the local inflammatory response, propagate plaque development, and promote thrombosis (Barrett, 2020). Shah et al. identified that DPP4i decreases aortic plaque, exerts antiatherosclerotic effects and reduces inflammation via inhibition of macrophages activation/recruitment in a LDL receptor-deficient mouse model, indicating important implications of the use of this class of drugs in atherosclerosis (Shah et al., 2011).

Sitagliptin has been found to attenuate the adverse remodeling following MI in Fischer F344 rats with STZ-diabetes (Connelly et al., 2013). Notably, DPP4 inhibition in normoglycemic rodents also significantly improves cardiac function and decreases the infarct size within 5–7 days after MI (Hocher, Sharkovska, Mark, Klein, & Pfab, 2013; Kubota et al., 2016). Endothelial progenitor cells (EPCs) derived from the bone marrow are known to promote vascular repair and neoangiogenesis. Importantly, it has been revealed that inhibition of DPP4 potentially enhances the delivery of EPCs towards injured vascular sites after MI in rats (Hocher et al., 2013), probably due to an increased concentration of SDF-1 (Fig. 2C). A 4-week clinic trial in T2DM patients treated with linagliptin identified a significant increase in EPCs and SDF-1 (Fadini et al., 2010). In addition to EPCs, we have described that SDF-1 could also attract other stem cells through the CXCR4. Zhang et al. reported that the combination of overexpression of CXCR4 in mesenchymal stem cells (MSC) with diprotin A, a DPP4 inhibiter, in rat MI model enhances MSC recruitment and penetration into ischemic myocardium via SDF-1 pathway, leading to the inhibition of myocardial ischemia-induced apoptosis, tissue angiogenesis, and an improvement in heart function after MI (Zhang et al., 2010). Furthermore, the cardioprotective effect is abolished by the pretreatment with a CXCR4 antagonist or a signal transducer and activator of transcription 3 (STAT3) inhibitor in mice with MI, indicating that DPP4 inhibition may have direct protective effects on the post-MI heart through SDF-1/CXCR4-mediated STAT3 signaling pathway (Kubota et al., 2016). Fadini also reported a profile of increased CD34(+)CD133(+) progenitor cells, CD34(+)KDR(+) EPCs, and CX3CR1(bright) monocytes along with significantly elevated SDF-1 in T2DM patients with 4-day treatment of linagliptin (Fadini et al., 2016), which further demonstrates the potential favorable cardiovascular implications of gliptins.

In contrast, chronic administration of vildagliptin to normoglycemic rats either prior to or after 12 weeks' induction of MI fails to avert the reduction of ejection fraction or modify cardiac remodeling (Yin, Sillje, Meissner, van Gilst, & de Boer, 2011). The inconsistent findings may be attributed to the long duration of disease, and it is accordingly assumed that DPP4 inhibition has no substantial protective effects on cardiac function in this well established long-term post-MI cardiac remodeling model.

Reduced interstitial fibrosis in hearts is observed in MK-0626 (a selective DPP4i)-treated C57BL/6 J mice fed a high fat/high fructose diet for 16 weeks (Bostick et al., 2014). In consistence with these findings, Mulvihill et al. identified that young normoglycemic DPP4(−/−) mice also exhibit a significant reduction in cardiac fibrosis and a cardioprotective response after transverse aortic constriction (TAC) surgery (Mulvihill et al., 2016). Surprisingly, diabetic mice treated with MK-0626 exhibit modest cardiac hypertrophy, impairment of cardiac function, and dysregulated expression of genes and proteins involved in inflammation and cardiac fibrosis (Mulvihill et al., 2016). We assumed that metabolic status may affect the cardiovascular benefits from DPP4 inhibition, which is remained to be investigated.

Although clinical studies have emphasized cardiovascular safety, no evidences of reduced major adverse cardiovascular events with different DPP4is were observed (Aroor et al., 2018; Green et al., 2015; Scirica et al., 2013; White et al., 2013). More than that, some cardiovascular outcome trials revealed an increase in hospitalization rates for heart failure (HF) among subjects treated with saxagliptin or alogliptin (Scirica et al., 2013; White et al., 2013).

According to these results, it is speculated that the cardiovascular benefits from DPP4 inhibition may be dependent on the disease duration (transient or long-term) and metabolic phenotype (diabetic or non-diabetic), which may explain, at least in part, the insignificant cardioprotective effect of DPP4is in T2DM patients. Further clinical studies to investigate these factors may be of importance.

3.2.4. DPP4/CD26 inhibition on asthma

Allergic asthma is a disease that causes the swelling and narrowing of airways, resulting in wheezing, shortness of breath and coughing (Umetsu, McIntire, Akbari, Macaubas, & DeKruyff, 2002). Whether CD26/DPP4 plays a role in the pathogenesis of asthma or allergic-like airway inflammation is still controversial.

Determined by biopsies, the expression of CD26/DPP4 in the lamina propria of human bronchi is firstly described by the group of van der Velden (van der Velden et al., 1998); but there are no differences between asthmatics and healthy controls. Subsequently, a rat model of asthma indicated a significant increase of CD26-expressing T cells in the lungs, the amount of which arises along with the severity of airway inflammation (Skripuletz et al., 2007). Recently, Nieto-Fontarigo detected the higher number of CD26 molecules on CD4+ T cells from both allergic and non-allergic asthma patients when compared to healthy subjects. However, circulating levels of sCD26 are reduced in asthma patients, which may be explained by the expansion of CD26 (−/low) T lymphocyte populations in peripheral blood (Nieto-Fontarigo et al., 2019).

A study from Yan et al. indicated an enhanced ovalbumin-induced airway inflammation in DPP4/CD26-deficient mice with increased Th2 cytokines such as IL-4, IL-5, and IL-13 (Fig. 2D) (Yan et al., 2012). On the contrary, another study reported that CD26 deficiency leads to a decrease in airway inflammation. They found a significantly increased influx of Tregs into the lungs in CD26-deficient rats and an increased IL-10 production in draining lymph node cells (Schmiedl et al., 2010).

Currently, there is no population-based studies or analysis from CPRD on the association of DPP4is with asthma. Despite the inconsistence and limited evidences, the preclinical results indicate an important role of CD26 in regulating the allergic immune response, thus raising the safety questions for clinical application of gliptins. It is highly suggested that the application of DPP4is to patients with asthma should be carefully estimated.

3.2.5. DPP4/CD26 inhibition on infectious diseases

The risk of infectious diseases induced by DPP4i has been widely investigated. A meta-analysis including 29 clinic trials concluded that DPP4is could increase the risk of infections for nasopharyngitis (risk ratio, 1.2) and urinary tract infection (risk ratio, 1.5) but not for upper respiratory tract infections (Amori, Lau, & Pittas, 2007). Using the UK-based CPRD, Gamble also identified that initiation of a DPP4i is not associated with an increased risk of respiratory tract infections compared to other glucose-lowering therapies (Gamble et al., 2018). However, there is no experimental studies that investigate the molecular/immune-related mechanisms in DPP4i-related bacterial infections.

Newer anti-diabetic agent sodium glucose cotransporter 2 (SGLT2) inhibitor (SGLT2i) is very useful due to its potential benefits on HF and diabetic nephropathy (Heerspink et al., 2020; Marx, Grant, & Cosentino, 2020). Thus the combination of SGLT2i and DPP4i is used more and more widely in T2DM patients. It is reported that genital mycotic infection is one of the most common adverse effects of SGLT2i (Adimadhyam et al., 2019). Of note, the risk of genital infections with combination therapy of Dapagliflozin and saxagliptin is lower than observed with dapagliflozin alone, suggestive of a protective effect of saxagliptin (Matthaei et al., 2015; Matthaei et al., 2016; Rosenstock et al., 2015), although the potential mechanism is unclear. However, a totally different conclusion is drawn by Min and colleagues. They analyzed 7 RCTs and identified that the risk of genital infection increases (Min, Yoon, Moon, Hahn, & Cho, 2018). We speculate that different combinations of SGLT2is and DPP4is together with the add-on method (simultaneous combination/sequential combination) may contribute to the inconsistent the risk of infections. Further investigations to figure out the underlying mechanism should be of significance.

Middle East respiratory syndrome coronavirus (MERS-CoV) is a β-coronavirus which is genetically associated to the severe acute respiratory syndrome (SARS) coronavirus (Hilgenfeld & Peiris, 2013). Interestingly, sDPP4 is identified as a functional receptor for MERS-CoV through its interaction with the spike protein (Raj et al., 2013). It is known that the sDPP4 level in plasma varies depending on pathophysiological conditions (Lambeir, Durinx, Scharpe, & De Meester, 2003). Inn and colleagues observed that sDPP4 in the plasma of MERS patients is significantly lower than those of normal volunteers. The levels of immune-suppressive cytokine IL-10 and protective growth factor epidermal growth factor (EGF) are significantly negatively and positively correlated with plasma sDPP4 concentration, respectively (Inn et al., 2018). Thus, it is assumed that exogenous sDPP4 may have therapeutic potential in MERS patients and that application of gliptins in MERS patients may adversely affect the pathological and immune processes of this disease.

Conversely, increased sDPP4 activity was found in chronic infections by hepatitis C virus (HCV), hepatitis A virus (HAV), and Epstein-Barr virus (Andrieu et al., 2003). The pathogenesis of HCV infection is strongly influenced by the nature of the host's antiviral immunity. It has been described that CXCL10 can be truncated by DPP4 (Table 2). Riva et al. reported that subjects developing chronic hepatitis C have higher concentrations of truncated CXCL10 and DPP4 activity; whereas DPP4 activity progressively decreases over time in patients who spontaneously clears the infection (Riva et al., 2014). A follow-up study was conducted to test the effects of DPP4 inhibition on CXCL10 processing in chronic HCV patients. Participants were treated daily with 100 mg sitagliptin, which results in a significant decrease in truncated CXCL10 but a reciprocal increase in full length form (Decalf et al., 2016). These data provide the direct evidence that therapeutic abrogation of DPP4 activity by gliptins in humans can preserve the bioactive form of CXCL10, suggesting that DPP4i may be a novel strategy to target both the virus and the host (Fig. 3).

In addition, DPP4is can block RANTES cleavage, thereby potentially facilitating human immunodeficiency virus (HIV) entry into T lymphocytes (Lusso et al., 2011), and inhibit cleavage of SDF-1, potentially blocking HIV entry into T lymphocytes (Bleul et al., 1996). Accordingly, it is significant to evaluate the immune and virological safety of DPP4 inhibition in HIV. Dube et al. evaluated inflammation and immune markers during treatment with the sitagliptin among virologically suppressed HIV patients without diabetes. It is found that sitagliptin has no effect on sCD14 levels, a biomarker of monocyte activation (Dube et al., 2019). In addition, there are no differences in any of the immune markers except a significant fall in CXCL10 (Dube et al., 2019). Similar investigation was performed by Goodwin which indicated that, despite

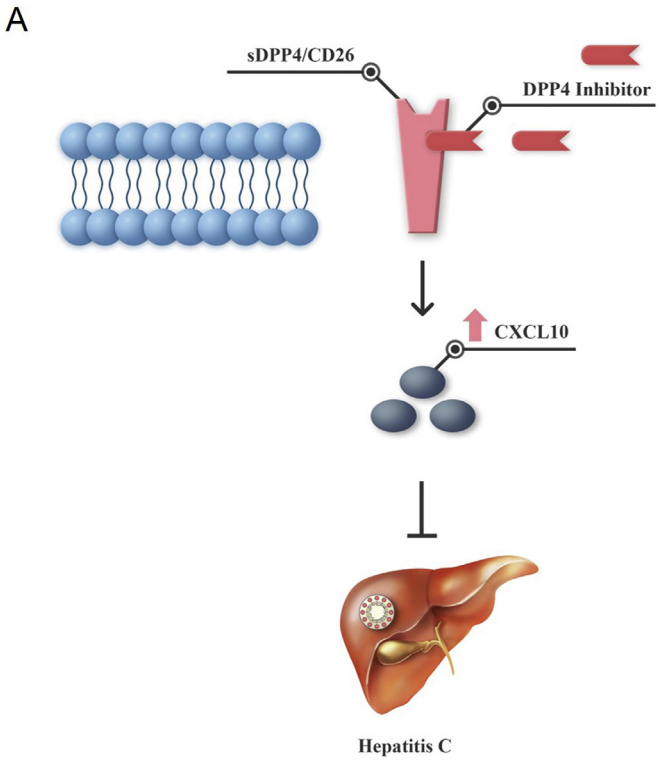

Fig. 3. The underlying mechanisms of DPP4 inhibition in infectious diseases.

lowering SDF-1 levels, sitagliptin does not adversely affect immune or virological status, or increase immune activation in nondiabetic HIV-positive adults (Goodwin et al., 2013).

3.2.6. DPP4/CD26 inhibition on other diseases

T2DM patients present an increased risk of peripheral artery disease (PAD); however, the pharmacological options for PAD are limited (Yang et al., 2020). We have described in section 3.2.3 that SDF-1 is a chemokine that attracts EPCs and promotes angiogenesis. SDF-1 engineered to be resistant to DPP4/CD26 and delivered by nanofibers improves blood flow in a mouse model of PAD (Segers et al., 2011). Both DPP4i MK-0626 (Shih et al., 2014) and sitagliptin (Huang et al., 2012) are found to increase the number of circulating EPCs, elevate the level of SDF-1, and promote the neo-vasculogenesis in a hind limb ischemia mouse model. All these results indicate that administration of DPP4is may have therapeutic potential as an inducer of vasculogenesis.

Besides PAD, linagliptin significantly improves the outcome of functional stroke in mouse model by a transient middle cerebral artery occlusion (MCAO) and the author concluded that the beneficial effect of linagliptin may be accomplished in a SDF-1/CXCR4-dependent manner (Chiazza et al., 2018).

DPP4 also regulates hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) by truncating multiple CSFs (Table 2). It is reported by Broxmeyer et al. that inhibition of DDP4 augments the ability of G-CSF or GM-CSF to induce myeloid colony formation and EPO to induce erythroid colony formation in vitro (Broxmeyer et al., 2012). Additionally, an accelerated hematopoietic recovery after myeloablative chemotherapy, radiotherapy, or stem cell transplantation is observed in DPP4-deficient mice and, to a lesser extent, pharmacologic inhibition of DPP4 with sitagliptin (Broxmeyer et al., 2012). Among the peripheral blood cells, the recovery of neutrophils, lymphocytes, and monocytes is more significant than red blood cells (RBCs) (Broxmeyer et al., 2012). Although there are potential concerns that need to be addressed in clinical trials, treatment with DDP4is holds considerable promise as a new strategy to stimulate hematopoietic recovery after chemotherapy or stem cell transplantation. Furthermore, due to the potential influence on EPO and RBC recovery, it will be interesting to investigate the hematopoiesis effect of gliptins in patients with diabetic nephropathy and anemia.

3.3. DPP4/CD26 inhibition and BP

BP is a potentially severe autoimmune skin disease, the typical clinical features of which include the widespread blisters, often preceded by or associated with urticarial or eczema-like lesions (Tasanen, Varpuluoma, & Nishie, 2019).

Currently, DPP4i-associated BP is attracting increasingly attentions. Howbeit, the pathogenesis and underlying mechanisms remain unclear. It has been shown that inhibition of DPP4 in F344 rats induces the infiltration of eosinophils into the skin (Fig. 4) (Forssmann et al., 2008), which is a typical histopathologic feature of BP. The major BP autoantigen BP180, known as a transmembrane collagen XVII, is responsible of anchoring epidermis into the underlying dermis. Under the condition of BP, anti-BP180 autoantibodies could impair BP180 function, leading to dermal-epidermal separation (Algaissi et al., 2019). It should be noted that DPP4 converts plasminogen to plasmin, which is known to cleave BP180 into 120 and 97 kDa fragments (Hofmann et al., 2009; Nishimura et al., 2016). Accordingly, it is speculated that the suppression of DPP4 may be involved in the disruption of BP180 immunotolerance and the subsequent development of epitopes for BP autoantibodies. Further studies are needed to elucidate the detailed mechanisms.

Over the last few years, case reports and pharmacovigilance analyses have suggested a risk of BP after the application of DPP4is, and the highest risk are observed with linagliptin and vildagliptin (Aouidad et al., 2013; Bene, et al., 2016). Studies from European and French pharmacovigilance databases were the first epidemiological investigations which identify a high BP incidence in gliptins treated T2DM patients (Bene, et al., 2016; Garcia, Aranburu, Palacios-Zabalza, Lertxundi, & Aguirre, 2016). More recently, Douros et al. conducted a cohort study using the U.K. CPRD among 168,774 patients taking OADs and found that current use of DPP4is doubles the risk of BP, albeit the absolute incidence is low. Moreover, hazard risks gradually increased along with the extension of use, reaching a peak after 20 months' application of gliptins (Douros et al., 2019). Likewise, a similar increase was also observed in a Japanese pharmacovigilance database, particularly among patients treated with vildagliptin, linagliptin, or teneligliptin (Arai, Shirakawa, Konishi, Sagawa, & Terauchi, 2018).

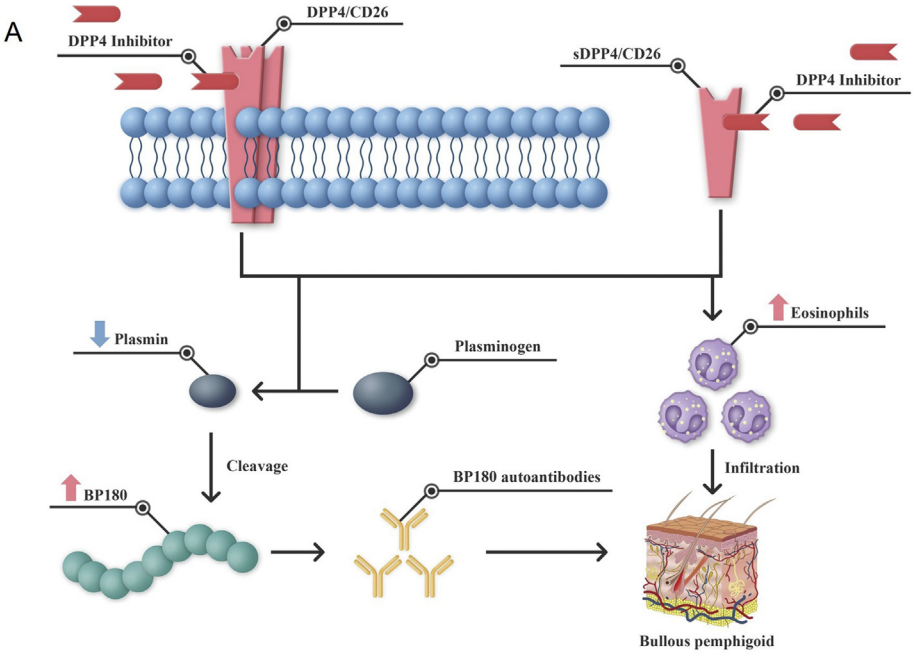

Fig. 4. The underlying mechanisms of DPP4 inhibition in bullous pemphigoid.

Several observational studies (all case-control designs) have also been conducted and it was reported that a significantly increased or a trend towards an increased risk of BP is associated with the usage of DPP4is with odds ratios ranging between 1.58 and 3.16 (Benzaquen et al., 2018; Kridin & Bergman, 2018; Lee, Lee, Yoon, & Kim, 2019; Plaquevent, et al., 2019; Varpuluoma et al., 2018). Moreover, Benzaquen et al. has reported that application of DPP4is increases the risk of BP of almost 3-fold, and the increase is associated with vildagliptin rather than other gliptins (Benzaquen et al., 2018). It is affirmed by another similar nationwide study from Korea that vildagliptin displays the highest risk among the DPP4is (Lee et al., 2019).

Based on the above findings, vildagliptin appears strongly associated with BP. This medicine differs from other DPP4is since it has a relatively lower DPP4 selectivity (Baetta & Corsini, 2011). Accordingly, it is speculated that off-target inhibition on other members of DPP family, such as DPP8 and DPP9 may cause the pathophysiology of gliptin-related BP (Lee et al., 2019). However, patients treated with linagliptin, which is a high selective DPP4i, showed an equal risk of BP as well (Baetta & Corsini, 2011), when compared with vildagliptin (Kridin & Bergman, 2018). Therefore, it is assumed that the DPP4i itself rather than the off-target effect contributes to the high risk of BP suffering.

It is doubt whether DPP4is alone can drive BP or if other factors, such as concomitant autoimmune diseases, are also involved. However, there are no published studies that compare the incidence of DPP4i-induced BP in patients who have autoimmune diseases with those patients without comorbidities. In addition, it is unclear whether these patients have different genetic characteristics, such as human leukocyte antigen (HLA) haplotypes. This question was recently worked on in a study conducted by Ujiie (Ujiie et al., 2018). The results suggested that HLA-DQB1*03:01 may be strongly associated with gliptin-related BP (Ujiie et al., 2018).

With the rapid growth of investigations on the potential association between gliptins and BP, the clinical, immunological and genetic features of patients with DPP4i-associated BP will be gradually unveiled. Of note, although the absolute incidence is low, BP is still fatal for patients (Langan et al., 2008). Hence, physicians should be aware of this risk.

4. Outlook

This review introduces the functions of DPP4/CD26 in immune system and summarizes the application of DPP4is, as an immunomodulator, to a range of disease settings. In conclusion, these gliptins are generally well tolerated without specific contraindications. However, regarding to the more recent findings, DPP4is might be considered to be a double-edged sword. Apart from the metabolic benefit, the associated immunological effects induced by DPP4 inhibition, may bring out benefits or side effects under different conditions (Table 3). It is recommended that physicians should be cautious about pre-existing inflammatory diseases in T2DM patients when DPP4is are initiated.

The controversial effects of DPP4is on autoimmune or inflammatory diseases may be attributed to the wide tissue distributions and multifunctions of DPP4/CD26. Tissue-specific regulation of DPP4/CD26 should be considerable to figure out its immunomodulatory effects. In addition, effects observed from animal models are inconsistent with clinical trials, which indicates that animal models may not be completely appropriate to estimate clinical outcomes. Researches should focus on studies in human beings with more detailed subgroup designs, for example, according to the disease duration and metabolism status. Future research would also be needed to determine the effect of DPP4i in the non-diabetic population.

Nevertheless, gliptins do represent an exciting and novel drug class for the treatment of autoimmune or inflammatory disease. Of note, it is essential to define and optimize the molecular mechanisms of this drug class before advocating any clinical use.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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