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REVIEW

Dipeptidyl peptidase-4: A key player in chronic liver disease

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Abstract

Dipeptidyl peptidase-4 (DPP-4) is a membrane-associated peptidase, also known as CD26. DPP-4 has widespread organ distribution throughout the body and exerts pleiotropic effects *via* its peptidase activity. A representative target peptide is glucagon-like peptide-1, and inactivation of glucagon-like peptide-1 results in the development of glucose intolerance/diabetes mellitus and hepatic steatosis. In addition to its peptidase activity, DPP-4 is known to be associated with immune stimulation, binding to and degradation of extracellular matrix, resistance to anti-cancer agents, and lipid accumulation. The liver expresses DPP-4 to a high degree, and recent accumulating data suggest that DPP-4 is involved in the development of various chronic liver diseases such as hepatitis C virus infection, non-alcoholic fatty liver disease, and hepatocellular carcinoma. Furthermore, DPP-4 occurs in hepatic stem cells and plays a crucial role in hepatic regeneration. In this review, we described the tissue distribution and various biological effects of DPP-4. Then, we discussed the impact of DPP-4 in chronic liver disease and the possible therapeutic effects of a DPP-4 inhibitor.

Key words: Incretin; Viral hepatitis; Insulin resistance; Steatohepatitis; Cancer; Sitagliptin; Vildagliptin; Alogliptin; Teneligliptin; Linagliptin

Core tip: Dipeptidyl peptidase-4 (DPP-4) is a membrane-associated peptidase, also known as CD26. DPP-4 has widespread organ distribution throughout the body and exerts pleiotropic effects *via* its peptidase activity. In this review, we described the tissue distribution and various biological effects of DPP-4. Then, we discussed the impact of DPP-4 in chronic liver disease and the possible therapeutic effects of a DPP-4 inhibitor.

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DISTRIBUTION OF DIPEPTIDYL PEPTIDASE-4

Dipeptidyl peptidase-4 (DPP-4, enzyme code number 3.4.14.5) is a 110 kDa membrane-associated peptidase, which was originally identified in 1966 as a dipeptide naphthylamidase that hydrolyzed glycyl-prolyl-beta-naphthylamide[1]. DPP-4, also known as CD26[2-4], is expressed on the apical surfaces of epithelial and acinar cells and in endothelial cells, fibroblasts, and lymphocytes[5-8]. DPP-4 also exists as a soluble circulating form in plasma[9].

DPP-4 occurs in all organs including the small intestine, biliary tract, exocrine pancreas, spleen, and brain in both rodents and humans[10-12]. This widespread organ distribution indicates that DPP-4 has pleiotropic biological activities. The liver is one of the organs that highly ex-

Table 1 Target peptide of dipeptidyl peptidase-4

Category	Peptide	Ref.
Glucose metabolism	GLP-1	[94-97]
	GIP	[97-99]
	Glucagon	[97,100,101]
	PACAP-38	[102-104]
Gut motility	GLP-2	[97,105,106]
	VIP	[107-109]
	NPY	[109,110]
	GRP	[103]
	Peptide histidine methionine	[94,102]
Appetite regulation	Peptide YY	[107,111]
Chemokine	CCL5/RANTES	[112-114]
	CCL11/eotaxin	[115,116]
	CCL22/MDC	[112]
	CXCL9/MIg	[117-119]
	CXCL10/IP10	[114,119,120]
	CXCL11/I-TAC	[121,122]
	CXCL12/SDF-1	[93,113]
Growth	IGF-1	[123,124]
	GHRH	[94,125]
Reproduction	Prolactin	[126-128]
	hCGα	[129]
	LHα	[123]
Vasodilation	CGRP	[107,110]
	Bradykinin	[107,108]
Pain regulation	Enkephalin	[130]
	Endomorphins	[109,130-132]
	Substance P	[109,110,133,134]
Homeostasis	Thyotropin α	[123,135]
Inhibition of endothelial cell growth	Vasostatin- I	[136]

GLP: Glucagon-like peptide; GIP: Glucose-dependent insulinotoropic peptide; PACAP-38: Pituitary adenylate cyclase-activating polypeptide-38; VIP: Vasoactive intestinal peptide; NPY: Neuro-peptide Y; GRP: Gastrin-releasing peptide; CCL: Chemokine (C-C motif) ligand; RANTES: Regulated upon activation; MDC: Macrophage-derived chemokine; CXCL: Chemokine (C-X-C motif) ligand; MIg: Monokine induced by gamma interferon; IP-10: Protein 10 from interferon (γ)-induced cell line; I-TAC: Interferon-inducible T-cell α chemoattractant; SDF-1: Stromal-derived factor-1; IGF-1: Insulin-like growth factor-1; GHRH: Growth hormone releasing hormone; hCGα: Human chorionic gonadotropin α subunit; LHα: Leutinizing hormone α chain; CGRP: Calcitonin-related peptide.

presses DPP-4[8]. In the healthy human liver, intense staining for DPP-4 is seen in hepatic acinar zones 2 and 3, but not in zone 1. Similar lobular heterogeneity is also seen in the expression of cytochrome p450, gamma-glutamyltranspeptidase (GGT), and glutamine synthetase[13-15]. This heterogeneous lobular distribution suggests that DPP-4 may be involved in the regulation of hepatic metabolism.

BIOLOGICAL ACTIVITIES OF DPP-4

Peptidase

DPP-4 is an enzyme that cleaves N-terminal dipeptides of proline or alanine-containing peptides including incretin, appetite-suppressing hormones (neuropeptide), and chemokines as listed in Table 1. Representative targets are glucagon-like peptide (GLP)-1, GLP-2, peptide YY, chemokine ligand 12/stromal-derived factor-1 (CXCL12/SDF-1), and substance P. Thus, DPP-4 exerts pleiotropic effects on glucose metabolism, gut motility, appetite regulation, inflammation, immune system function, and pain regulation though its peptidase activity (Figure 1).

Immune stimulation

DPP-4 expression is downregulated in the resting state of T-cells; however, expression is upregulated by antigenic or mitogenic stimulation via an interleukin-12-dependent mechanism[16-18]. DPP-4 activates intracellular molecules including $p56^{lck}$, phospholipase C-γ, and mitogen-activated protein kinase (MAPK)[11]. This activation enhances T-cell maturation and migration, cytokine secretion, antibody production, immunoglobulin isotype switching of B cells, and activation of cytotoxic T cells[19,20]. In addition, soluble CD26 binds to mannose 6-phosphate receptor and is taken up by CD14 positive monocytes, increasing their antigen presenting activity and T-cell proliferation[11,21,22].

Binding to extracellular matrix

DPP-4 has the ability to bind to the Binding to extracellular matrix (ECM), preferentially to the collagens I and Ⅲ, and fibronectin[23,24], and is involved in hepatocyte-extracellular matrix interactions[23,25]. The putative collagen binding site of DPP-4 is located at the C-terminal portion of the molecule, separate from the peptidase catalytic site[26].

In a mouse xenograft model, treatment with anti-DPP-4 monoclonal antibody inhibits the growth of renal cell carcinoma via disruption of binding to the extracellular matrix[27]. On the other hand, over expression of DPP-4 induces apoptosis of prostate cancer cells by inhibition of cell migration and invasion through down-regulation of MAPK-extracellular signal-regulated kinase-1/2 activation[28]. Thus, the role of DPP-4 may differ in different types of cancer.

Degradation of ECM

DPP-4 binds to adenosine deaminase and activates plasminogen-2, leading to an increase in plasmin levels[11]. The increased plasmin degrades type Ⅳ collagen, fibronectin, laminin, and proteoglycan, and activates matrix metalloproteinases. These changes result in the degradation of the ECM[29,30].

Resistance to anti-cancer agents

DPP-4 is thought to be associated with sensitivity to anti-cancer agents in hematologic malignancies. DPP-4 has been linked to high topoisomerase Ⅱα levels, resistance to anti-cancer agents, and the malignant potential of T-cell lymphoma[11,21,22]. Treatment with anti-DPP-4 monoclonal antibody causes dephosphorylation of both MAPK and integrin β1 in T-cell lymphoma, leading increased sensitivity to anti-cancer agents and greater survival[31]. Similar beneficial effects of anti-DPP-4 monoclonal antibody have been reported in renal cell carcinoma[27] and malignant mesothelioma tumors[32].

Lipid accumulation

DPP-4 affects lipid metabolism by the inactivation of

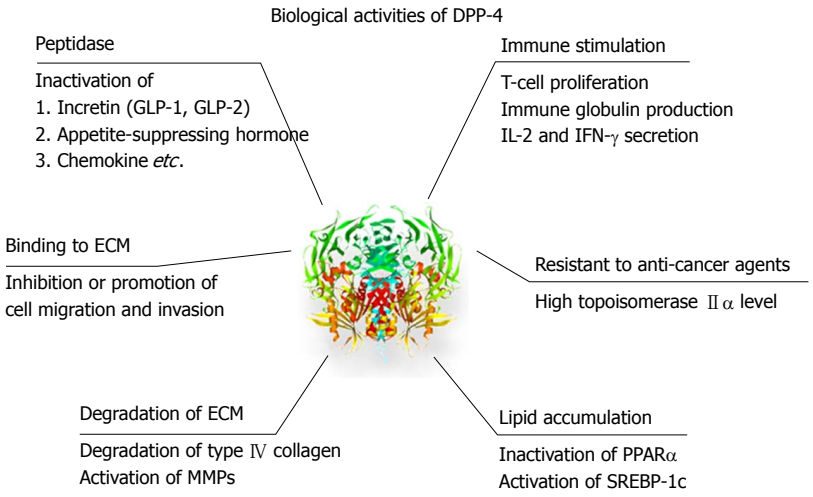

Figure 1 Pleiotropic effects of dipeptidyl peptidase-4. Dipeptidyl peptidase-4 (DPP-4) exerts various effects on metabolism and chemokine through peptidase activity. In addition, DPP-4 is involved in immune stimulation, binding to and degradation of extracellular matrix, and resistant to anti-cancer agents. DPP-4 also directly affects lipid accumulation. GLP: Glucagon-like peptide; ECM: Extracellular matrix; MMPs: Metalloproteinases; IL: Interleukin; IFN: Interferon; PPAR: Peroxisome proliferator-activated receptor; SREBP: Sterol regulatory element binding protein.

peptides such as GLP-1, neuropeptide Y, and peptide YY. In addition, DPP-4 is known to directly affect lipid metabolism. Knock-out of the gene encoding DPP-4 directly causes activation of the peroxisome proliferator-activated receptor-α pathway and inactivation of the sterol regulatory element binding protein-1 pathway[33], thereby increasing lipid oxidation, reducing lipogenesis, and resulting in the prevention of high-fat diet-induced hepatic steatosis.

CHANGES IN DPP-4 IN PATIENTS WITH LIVER DISEASE

Serum level of DPP-4 is elevated in patients with liver cirrhosis[34,35] and up-regulation of hepatic DPP-4 expression is thought to be responsible for this elevation[36]. Here, we describe the effects of DPP-4 according to each pathophysiology.

Hepatitis C virus infection

Patients with hepatitis C virus (HCV) infection show increased serum DPP-4 expression in hepatocytes[37,38]. Lymphocyte subset analysis has also shown that CD8+ T-cells, which express DPP-4, are present in the portal and periportal areas in patients with HCV infection[39]. Since HCV infects CD8+ T-cells[39-41], HCV-infected T-cells may be responsible for the increased serum DPP-4 activity in patients with HCV infection.

In addition, glucose intolerance with insulin resistance is a feature of HCV infection and is associated with disease progression as well as prognosis[42-52]. Besides hepatic inflammation and steatosis, HCV itself is involved in the development of insulin resistance through the impairment of insulin receptor substrate-1/2[52-54]. Moreover, HCV infection is known to be associated with increased DPP-4 expression in the ileum, liver, and serum[38]. Transfection with cDNA encoding part of the HCV nonstructural genome region 4B/5A induces expression of DPP-4 in hepatocyte cell lines[55]. Furthermore, eradication of HCV by interferon therapy results in a decrease in serum DPP-4 levels[56-61] and administration of sitagliptin significantly improves HCV-related glucose intolerance[62]. Since there is no significant association between serum DPP-4 activity and severity of liver disease in patients with HCV infection[38], HCV infection may directly up-regulate DPP-4 activity, leading to impairment in glucose metabolism.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome and the most common cause of chronic liver disease[63-66]. Although various factors are responsible for the development of NAFLD, a high glucose load is known to induce DPP-4 expression in HepG2 cells[67] and hepatic DPP-4 mRNA expression level in the livers is significantly higher in patients with NAFLD, compared to healthy subjects[67]. In fact, serum DPP-4 activity and hepatic expression of DPP-4 are correlated with hepatic steatosis and NAFLD grading[68]. Moreover, DPP-4 deficient rats show lower levels of hepatic proinflammatory and profibrotic cytokines and reduced hepatic steatosis compared to wild type rats. These favorable changes in lipid metabolism are independent of glucose metabolism[69]. Similar to these results from animal experiments, in patients with NAFLD, DPP-4 activity in serum and liver specimens correlate with markers of liver damage such as serum GGT and alanine aminotransferase levels, but do not correlate with fasting blood glucose levels and glycosylated hemoglobin (HbA1c) values[68,70]. Thus, hepatic DPP-4 expression in NAFLD may be directly associated with hepatic lipogenesis and liver injury.

Recently, DPP-4 inhibitor has been reported to improve hepatic steatosis in mice and humans[71]. We also experienced a case of refractory NAFLD that was successfully treated with sitagliptin, a DDP-4 inhibitor[72]. Moreover, it is reported that sitagliptin ameliorates liver enzymes and hepatocyte ballooning in patients with non-alcoholic steatohepatitis[73]. Taken together, these findings may indicate that DPP-4 inhibitors ameliorate hepatic injury and glucose impairment in patients with NAFLD.

Hepatocellular carcinoma

Increased DPP-4 expression is seen in various malignant

tumors, such as breast cancer[74,75], brain glioma[76], malignant mesothelioma[77], and squamous cell laryngeal carcinoma[78]. In hepatocellular carcinoma (HCC), increased DPP-4 expression is also seen in liver specimens and serum from both rats[79] and humans[80].

Inhibition of DPP-4 in human hepatoma cells is reported to suppress tyrosine kinase, leading to anti-apoptotic effects[81]. However, Yamamoto *et al*[82] recently reported a case in which dramatic regression of HCC was seen after four weeks' treatment with DPP-4 inhibitor in a patient with HCV-related chronic hepatitis. Although it is unclear whether DPP-4 inhibitor is directly involved in the regression of HCC, marked invasion of CD8+ T-cells was seen around the HCC tissue[82], suggesting that the DPP-4 inhibitor may have improved immune response, which has been impaired by chronic HCV infection[38]. Although exogenous insulin or sulfonylurea treatment increases the risk of HCC[83], treatment with DPP-4 inhibitor does not show any tumor promoting effects in mice[84]. Thus, a DPP-4 inhibitor may safely exert beneficial effects on HCV-related HCC through modulation of immunity.

Stem cell and hepatic regeneration

Increased hepatic DPP-4 expression has been reported to occur in the cirrhotic liver[85,86]. Although the impact of increased DPP-4 expression remains unclear, Lee *et al*[87] recently reported that human liver stem cells express DPP-4, but not CD34 and CD45, which are hematopoietic stem cell and endothelial progenitor cell markers. Thus, DPP-4 is a specific marker of adult hepatic stem and progenitor cells, indicating that DPP-4 may be involved in the regeneration in chronically inflamed liver.

CXCL12/SDF-1 causes hematopoietic stem cell (HSC) homing and is an important chemokine for hepatic regeneration[88-91]. CXCL12/SDF-1 is a target peptide of DPP-4 and the inhibition of the cell-surface DPP-4 activity of HSC/hematopoietic progenitor cell populations increases their CXCL12/SDF-1 directed chemotaxis, homing, and engraftment[92]. Therefore, inhibition of DPP-4 may be an effective therapy for increasing the efficacy and success of HSC/hematopoietic progenitor cell transplantation[92]. DPP-4 inhibition also increases number of progenitor cells, and stabilization of endogenous CXCL12/SDF-1 by DPP-4 inhibition is achievable and may be a promising strategy to intensify sequestration of regenerative stem cells[93].

CONCLUSION

In this review, we described the tissue distribution and biological effects of DPP-4. Then, we discussed the impact of DPP-4 in chronic liver disease and the possible effects of a DPP-4 inhibitor. DPP-4 plays crucial roles in the development of various chronic liver diseases, and DPP-4 inhibition seems to have beneficial effects in chronic liver diseases. However, DPP-4 inhibitors also modulate the immune system, and further studies will be focused on the effects of long-term administration of a DPP-4 inhibitor on infection and carcinogenesis.

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