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Dipeptidyl Peptidase-4: Potential Pathogenic Roles in Diabetic Complications and More

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Both the disruption of endothelial homeostasis and tissue fibrosis are characteristics of diabetic complications. Accumulating evidence has revealed the significant role of vascular endothelial cells in tissue fibrogenesis via endothelial-mesenchymal transition (EndMT). We have recently focused on the overexpression of endothelial dipeptidyl peptidase (DPP)-4, a critical pathological feature of the molecular mechanisms of EndMT, and suggest that DPP-4 inhibitors have great therapeutic potential via their antifibrotic effects. However, the diverse pleiotropic effects of DPP-4, both its enzyme-dependent and enzyme-independent effects, can be detrimental in some cases. This review provides an update on the biology of DPP-4, a profibrotic molecule, in addition to a discussion of cancer biology.

Key words: fibrosis, microRNA, integrin, extracellular matrix, cancer

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INTRODUCTION

The pandemic of type 2 diabetes will result in a rise in the incidence of diabetic complications. Kidney complications in diabetes, including both classical diabetic nephropathy and diabetic kidney disease, are major causes of end-stage renal disease (ESRD), which requires renal replacement therapy. The normalization of blood glucose levels may be essential to combat diabetic kidney complications, as concluded by a pancreas transplantation study in a patient with advanced diabetic nephropathy [1]. However, the normalization of blood glucose levels in advanced overt diabetes is challenging. In “The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study,” intensive glucose control in type 2 diabetic patients to normalize blood glucose levels was shown to increase cardiovascular events and death. A recent meta-analysis investigating the effects of intensive blood glucose control on clinically significant renal outcomes revealed that intensive glucose control may have a significant effect on the retardation of early diabetic nephropathy; advanced outcomes, such as renal death, the doubling of serum creatinine, and the onset of ESRD, are not altered by intensive blood glucose control [2]. It is apparent that appropriate blood glucose control is fundamental in diabetic medicine, yet these results clearly indicate the need for a strategy to retard diabetic nephropathy progression on the basis of molecular mechanisms independent of blood glucose control.

Approximately 45% of deaths in developed countries originate from chronic fibrogenic disorders [3]. Tubulointerstitial fibrosis of the kidney is the final common pathway of progressive kidney diseases. Diabetes can induce progressive fibrosis in the kidney, which is characterized by matrix deposition and

glomerulosclerosis. Fibrosis is an important tissue repair process; however, progressive kidney fibrosis may be the consequence of disruption of the normal wound healing process [3, 4]. The factors primarily responsible for this disruption have not yet been completely elucidated. Many cell types, including both resident and nonresident kidney cells, are involved in this process. Resident cell types, such as resident fibroblasts, tubular epithelial cells, pericytes, endothelial cells, vascular smooth muscle cells, mesangial cells and podocytes, and many nonresident cells, such as inflammatory cells, could be involved in the disruption of normal wound healing [5, 6]. In kidney fibrosis, both resident and nonresident cells play distinct roles but cooperate in the fibrogenic process. In addition, alterations in the transition of an epithelial or endothelial cell to a cell with a matrix-producing mesenchymal-like phenotype through the epithelial-mesenchymal transition (EMT) and endothelial mesenchymal transition (EndMT) programs may play vital roles in this process [5, 6]. Endothelial damage caused by multiple insults has emerged as important in diabetic complications, and transforming growth factor (TGF)-βs plays mechanistic roles in this process. Among the various processes of the mesenchymal programs mentioned above, there has been a focus on the EndMT program in kidney fibrosis. We have reported that dipeptidyl peptidase (DPP)-4, a vital molecule for blood glucose homeostasis via its modulation of incretin hormones, plays a pathogenic role in endothelial damage and the subsequent production of extracellular matrix.

DPP-4

DPP-4, a serine peptidase/prolyl oligopeptidase gene family member, is characterized as a T-cell differentiation antigen (CD26). DPP-4, which is involved in a wide range of biological functions, acts as a protease or a coreceptor for viral entry; interacts with adenosine deaminase (ADA) or the extracellular matrix (ECM); and fine-tunes intracellular signals associated with proliferation and/or migration [7-11]. DPP-4 is expressed in various cell types and organs. The enzymatic activity of DPP-4 and its expression levels are the highest in the kidney per organ weight. DPP-4 digests at least 30 substrates, including incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [12].

DPP-4 also acts as a signaling molecule via transmitting signals across cell membranes through interacting with other cell membrane proteins. DPP-4 is a cell membrane-anchored type II transmembrane protein comprised of 766 amino acids. The transmembrane domain of DPP-4 is a single hydrophobic segment located at its N-terminus followed by a short cytoplasmic tail of six amino acids [13]. DPP-4 is active as a dimer, and the extracellular C-terminal loop of DPP-4 is essential for both catalytic efficacy and dimerization [14]. C-terminal lesion of DPP-4 displayed as glycosylated, cysteine-rich catalytic domains [12]. The DPP-4 protein also adopts a tetrameric form by interacting with two soluble and two membrane-bound DPP-4 proteins. Such interactions may influence DPP-4 catalytic activities via its substrate affinity or the cleavage of its substrates on the catalytic site, but the details of these effects are unclear [14]. The interaction between DPP-4 proteins could be important for cell-cell communication [14]. The DPP-4 dimer is dissociated with (and potentially cleaved from) the plasma membrane; the resultant soluble form of DPP-4, sDPP-4 (727 aa), is a major source of DPP-4 enzymatic activity in human serum [15, 16]. sDPP-4 does not contain amino acid residues 1-39 and a cytoplasmic domain [residues 1-6], transmembrane domain [residues 7-28], and flexible stalk [residues 29–39]) [12, 15]. Independent of its catalytic action, sDPP-4 induces the proliferation of human lymphocytes via influencing cell signaling [17]. sDPP-4 also was shown to inhibit Akt activation in human adipocytes, skeletal muscle cells, and smooth muscle cells [18]. The enzymatic activities of DPP-4 are differentially regulated at several levels, e.g., its protein expression and binding partners. Many papers have described the role of inflammation and mitogenic stimuli in DPP-4 expression in lymphocytic leukemia [19, 20]. A recent paper reported that in mice fed a high-fat diet, hypoxia-inducible factor-1α in hepatocytes, but not adipocytes, played a fundamental role in DPP-4 enzymatic activity required for GLP-1 cleavage [21].

The mechanism of sDPP-4 production is poorly understood. Lamers *et al*. reported that differentiated adipocytes released more sDPP-4 than preadipocytes. Additionally, TNF-α and insulin were found to increase sDPP-4 levels together with DPP-4 mRNA levels in human adipocytes from visceral adipose tissue [18]. The highest DPP-4 activity per organ weight is found in the kidney; kidney is not a major source of sDPP-4 [22]. In human adipocytes and smooth muscle cells, the shedding of DPP-4 is significantly suppressed by the inhibition of MMPs and cysteine and serine proteases. Furthermore, hypoxia increases the shedding of DPP-4 associated with the induction of MMP 1 and MMP 9 levels [23]. sDPP-4 can originate from diverse cell types. A recent paper demonstrated that adipocytes and (potentially to a much higher degree) the liver are the major sources of sDPP-4 [24]. Interestingly, the inhibition of DPP-4 enzymatic activity was also found to elevate levels of the sDPP-4 protein in plasma from endothelial or hematopoietic cells [24].

MicroRNA regulation of DPP-4

MicroRNAs (miRs) have emerged as significant players in diverse biological actions. Known antifibrotic miRs, miR 29s, have been shown to protect the diabetic kidney from fibrosis [25-27]. We have identified a conserved miR-binding site in the 3'UTR of DPP-4 that functionally suppresses DPP-4 gene expression [26]. CD-1 diabetic mice with kidney fibrosis displayed suppressed levels of miR 29s, and the DPP-4 inhibitor linagliptin inhibited kidney fibrosis and functions associated with restoration of the expression of miR 29s [26]. TGF-β2 induced endothelial mesenchymal transition associated with the suppression of miR 29s; linagliptin restored the levels of miR 29s, which was associated with suppression of EndMT in primary cultured endothelial cells. MiR 29 induction by a DPP-4 inhibitor played further roles in endothelial protection via inducing miR let-7 and vice versa (Fig. 1). MiR let-7 is another miR that targets TGFβR1 and subsequently inhibits TGF-β/smad signaling and EndMT [28]. TGF-β signaling is a major suppressor of miR 29; therefore, that miR let-7 induction in endothelial cells results in miR29 induction is reasonable (Fig. 1). However, another pathway by which miR 29 induces an increase in miR let-7 levels cannot be explained by known molecular mechanisms. To investigate this mechanism, we focused on endothelial fibroblast growth factor receptor (FGFR) 1 regulation. FGFR1 is a key mediator of miR let-7 induction and the suppression of EndMT [28]. Importantly, FGFR1 levels are suppressed by cytokine interferon (IFN)γ [28], and IFNγ is indeed a target of miR 29 [29, 30] (Fig. 1). DPP-4 inhibitor-treated cells displayed suppressed levels of IFNγ associated with the restoration of both miR 29s and miR let-7s. A functional study demonstrated that neutralizing antibody against FGFR1 abolished the miR 29-induced induction of miR let-7 [30]. These data demonstrate the inhibition of DPP-4 as a possible strategy of endothelial protection in diabetes (Fig. 1).

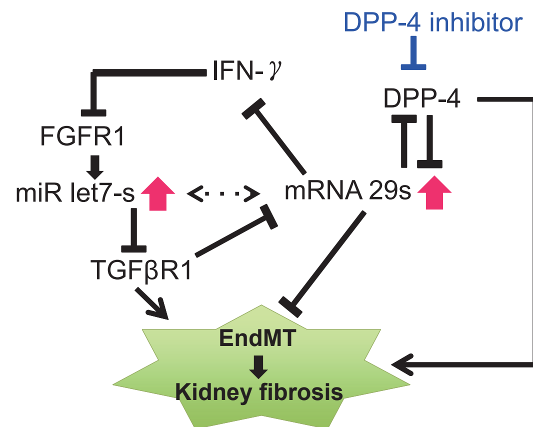

Fig. 1. Potential anti-EndMT miR cross-talk between miR 29 and miR let-7
DPP-4 inhibition resulted in the induction of miR 29. miR 29 suppresses all of DPP-4, integrin β1, and interferon-γ. Interferon-γ suppression induces FGFR1; subsequently, miR let-7 is induced its level. miR let-7 is known to suppress TGF-β receptor-1, resulting in much higher level of miR 29s. Consequently miR 29 and miR let-7 comprise positive feedback loops of anti-EndMT programs.

DPP-4 and integrin β1: a hub for the fibrogenic program in endothelial cells

Integrins are essential players in cell-cell and cell-matrix interactions via αβ heterodimer formation. Eighteen α- and 8 β-subunits of integrins have been reported. Each integrin binds to different ligands and plays diverse signaling roles via generating an αβ heterodimer [31]. Integrin subunits recognize their

specific ligands by their extracellular domains. Additionally, integrins contain a transmembrane domain and small cytoplasmic domain through which integrins form a focal adhesion complex by binding to multiple cytosolic and transmembrane proteins (with the exception of β4) [32].

Integrin β1, which is ubiquitously expressed through embryos to adults, forms a heterodimer with at least 11 α-subunits in which integrin β1 acts as a receptor for specific ECM [33-35]. Integrin β1 gene knockout mice are embryonic lethal due to preimplantation development failure. Mice deficient in the α1, α2, α10, or α11 integrin subunits display disrupted formation of the integrin αsβ1 heterodimer, which are the primary collagen receptors; these mice are all viable and fertile with distinct abnormalities [36]. The activation of integrin β1 is essential for TGF-β1 induction; the inhibition of integrin β1 results in suppression of TGF-β1 levels, indicating the presence of crosstalk between integrin β1 and TGF-β in fibrogenesis [37, 38].

The phosphorylation of integrin β1 at residue S785 plays a key role in the cellular adhesion of integrin β1 to the ECM [39]. The suppression of membrane-bound DPP-4 resulted in the suppression of integrin β1 S785 phosphorylation. We have shown that the interaction between DPP-4 and integrin β1 plays vital profibrogenic roles in endothelial cells [40] (Fig. 2). TGF-β2-induced EndMT is accompanied by both DPP-4 and integrin β1 induction. Both DPP-4 and integrin β1 deficiency led to the suppression of both EndMT and TGF-βR heterodimerization in TGFβ2-stimulated endothelial cells. These data strongly suggest that the DPP-4 and integrin β1 interaction is indispensable in TGF-β2-induced cell signaling required for EndMT. The biological significance of this integrin β1 and DPP-4 interaction is not limited to TGF-β signaling. Vascular endothelial growth factor (VEGF) is essential for the health of endothelial cells [41]. Importantly, the endothelial DPP-4 and integrin β1 interaction induces VEGF receptor (VEGFR) 1, a “decoy” receptor for VEGF-induced endothelial cell growth, and suppresses VEGFR2, a vital receptor for VEGF-mediated endothelial health [40]. The functions of VEGF in endothelial cells are finely tuned via several VEGF receptors with distinct functions in EndMT, e.g., VEGFR1 favors EndMT, while VEGFR2 inhibits EndMT induction [42]. Therefore, these data clearly demonstrated the significance of the DPP-4 and integrin β1 interaction in both endothelial integrity and fibrogenesis [40] (Fig. 2).

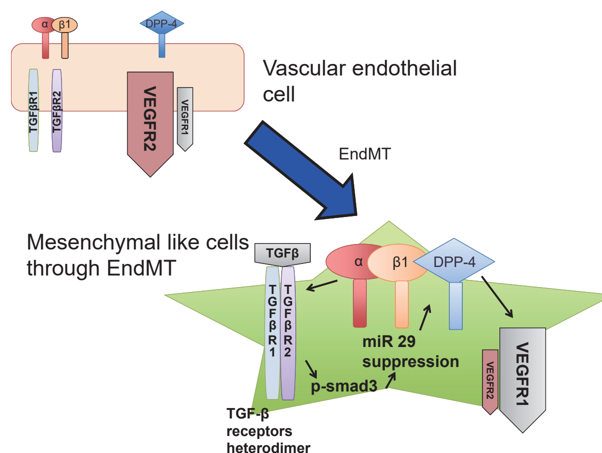

Fig. 2. DPP-4 and integrin β1 interaction: endothelial-mesenchymal phenotype ‘hub’. DPP-4 and integrin β1 interaction stimulates TGF-β receptor (I and II) heterodimer; receptor-activated smad3 induces key mesenchymal programs in endothelial cells, subsequently. TGF-β signaling suppresses miR 29, and such miR 29s suppression induces both integrin β1 and DPP-4.
Integrinβ1 overproduction induces VEGFR1, a decoy receptor for VEGF-mediated signaling in endothelial cells; VEGFR2, the angiogenic receptor for VEGF, is compromised. This circle of events completes the transition of endothelial cells to mesenchymal cells.

Perspective and concern

In this review, the diverse roles of DPP-4, especially those in endothelial integrity and EndMT, are described. From this point of view, DPP-4 inhibitors play a large potential role in preserving endothelial homeostasis and suppressing fibrosis via EndMT [26, 40]. Although current knowledge from large clinical trials has not had a large impact on contributing to human health, when compared to the results on that of other anti-diabetic medicines, preclinical studies and characteristics increase our hope for the possible contributions of DPP-4 inhibitors to human health apart from their use for blood glucose control [43]. However, there are also concerns about this class of drug [43]. As described above, the DPP-4 protein exerts diverse enzymatic and non-enzymatic effects. In our recent paper, DPP-4 inhibition inhibited EMT

in the kidney tubular cells of diabetic mice; unexpectedly, DPP-4 inhibition increased EMT program without apparent fibrosis [44]. We also found that a DPP-4 inhibitor induced EMT in cancer cells[45]. Human and mouse breast cancer cells underwent EMT when exposed to a DPP-4 inhibitor or DPP-4 suppression by siRNA [45]. In a mechanistic analysis, we found that DPP-4 inhibition increased the level of CXCL12, a well-known substrate of DPP-4, and subsequently activated CXCR4 [45]. Activation of CXCR4 resulted in mTOR phosphorylation and mTOR-dependent EMT [45]. EMT is important for tumor metastasis; CXCR4 inhibition in mice completely abolished DPP-4 inhibitor-induced EMT and tumor metastasis [45] (Fig. 3). In general, DPP-4 inhibitors are safe to prescribe to human diabetic patients. However, because of the unexpected detrimental effects of DPP-4 inhibitors, clinicians need to be aware and exercise some caution, especially in diabetic patients, who display a higher incidence of cancer and require anti-diabetic drugs for a long time period. Regard with this, epidemiological study suggested DPP-4 inhibitor use and the onset of certain cancer [46], but not always [47, 48]. These reports are all short observational periods and would not be adequate to conclude the interaction between DPP-4 inhibitor use and cancer biology. The pleotropic effects of DPP-4 inhibitors are not always favorable, as reported [49-51]. We need to carefully monitor the safety of this widely prescribed class of anti-diabetic drug.

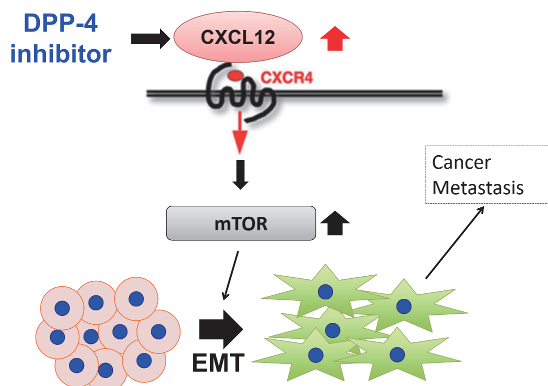

Fig. 3. DPP-4 inhibition could potentially increased risk of cancer metastasis via CXCL12/CXCR4/mTOR axis. CXCL12 is known target of DPP4 and DPP-4 inhibitor treatment increased CXCL12. CXCL12 stimulates signaling from CXCR4 to mTOR activation, the essential player for cancer metastasis via EMT.

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ETHICS POLICY

This article does not contain any studies in human or animal subjects performed by the author.

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