Renoprotective effects of incretin-based drugs: A novel pleiotropic effect of dipeptidyl peptidase-4 inhibitor

Diabetic nephropathy is a leading cause of end-stage renal disease worldwide, and is a serious problem that must be addressed. Incretin-based drugs stimulate insulin secretion from pancreatic β-cells blood glucose-dependently with low risk for hypoglycemia and bodyweight gain. In addition, incretin acts on the multiple organs through the incretin receptors as well as the pancreas. Several reports showed the effects of incretin on the kidneys including anti-inflammation, antioxidative stress, anti-apoptosis and the decrease in sodium reabsorption, which could explain in part the antihypertensive action. These effects might be related to preventing progression of diabetic nephropathy.

Recently, two types of incretin-based drugs have been developed; glucagon-like peptide 1 (GLP-1) receptor agonist and dipeptidyl peptidase-4 (DPP-4) inhibitor. GLP-1 receptor agonist decreases the blood glucose level by stimulating insulin secretion and decreasing glucagon secretion through the GLP-1 receptor on the islet cells. GLP-1 receptor agonist might also act on many organs through a GLP-1 receptor other than the pancreas. In contrast, DPP-4 inhibitor not only elevates the endogenous incretin level in the blood, but also affects the pathways independent of the incretin receptors. DPP-4 could promote degradation of several molecules including chemokines and cytokines, as well as DPP-4. Furthermore, DPP-4 is known to be expressed on the cell membrane of many types of cells including immune cells (Figure 1). Therefore, DPP-4 inhibitor and GLP-1 receptor agonist are in fact different drugs, although these drugs are included in the same category.

In previous studies using GLP-1 receptor agonist or DPP-4 inhibitor, the mechanism of the renal protective effect of incretin is mainly mediated through the GLP-1 receptor. Some reports showed that the renal protection of DPP-4 inhibitor contributed in part to several substrates influenced by DPP-4 enzyme activity, including stromal-derived factor-1α (SDF-1α). To our knowledge, there has been no report of the renoprotection by DPP-4 inhibitor through the direct action on DPP-4 per se or on DPP-4 expression in the kidney. Interestingly, Kanasaki et al.1 recently published an article that showed that DPP-4 inhibitor prevented kidney fibrosis through DPP-4 itself, entitled ‘Linagliptin-mediated DPP-4 inhibitor ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen’ in Diabetes in June 2014.

Kanasaki et al. used a fibrotic diabetic kidney disease model – streptozotocin-induced diabetes in CD-1 mice. Diabetic mice showed severe fibrosis, increased DPP-4 protein levels in the glomerular basement membrane, tubules and peritubular vascular cells, and increased DPP-4 enzyme activity at 24 weeks after the initiation of diabetes. Mice were treated with linagliptin for 4 weeks at 20 weeks after the onset of diabetes, which improved kidney fibrosis associated with the endothelial-to-mesenchymal transition (EndMT), and DPP-4 activity/protein expression through microribonucleic acid (miR)-29s restoration. The therapeutic effects of linagliptin on diabetic kidneys were associated with the suppression of profibrotic process, as assessed by messenger ribonucleic acid microarray analysis. In diabetic nephropathy, transforming growth factor (TGF)-β plays a central role in renal fibrosis and also induces EndMT, which is considered as a part of diverse sources in kidney fibrosis. They examined the profibrotic molecules mechanism by using cultured endothelial cells to evaluate the relationship between DPP-4 and EndMT, and the contribution to miR-29s. As a result, they showed that linagliptin inhibited the TGF-β2-induced DPP-4 expression and EndMT by blocking Smad3 phosphorylation. The expression of DPP-4 was elevated by downregulation of miR-29s by using antagonists of miR-29s or inhibitors, and reduced by upregulation of miR-29s by mimetic miR-29s transfection. These data show that miR-29s regulates the DPP-4 expression.

DPP-4 is expressed on the cell surface in the liver, kidney, intestine and immune cells, such as lymphocytes and macrophages. Independent of serine protease enzymatic activity, DPP-4 interacts with extracellular matrix components and regulates cell-cell and cell-extracellular matrix interactions. Through these functions, DPP-4 regulates diverse biological processes, including cell differentiation, adhesion, immune modulation, apoptosis and neoplastic transformation.

In the previous reports, DPP-4 inhibitor suppressed cardiac fibrosis in the 5/6-nephrectomy-induced chronic renal failure model2, and attenuated hepatic fibrosis in porcine serum-induced liver fibrosis model3.

In their study, diabetic mice treated with DPP-4 inhibitor showed a signifi-
cant suppression of TGF-β2 protein levels in the kidney when compared with untreated diabetic mice. Accordingly, the result raised the possibility that the suppression of TGF-β2 protein levels itself results in the increase of miR-29s levels and the decrease of DPP-4 levels leading to a block of EndMT induction. We reported the renal protective effects through anti-inflammatory action for DPP-4 inhibitor in a streptozotocin-induced type 1 diabetic model of rats. In our study, DPP-4 inhibitor treatment also tended to decrease TGF-β expression in the kidney of diabetic rats. Although we have not investigated the effect of DPP-4 inhibitor independent of incretin actions, it is speculated that the anti-inflammatory action of DPP-4 inhibitor contributed to the suppression of TGF-β expression. In fact, the previous reports showed that DPP-4 inhibitor blocked toll-like receptor 4-mediated extracellular signal-regulated kinase activation and extracellular signal-regulated kinase-dependent matrix metalloproteinases-1 expression in U937 histiocytes regarded as cultured macrophages. It is suggested that inflammation is involved at an early stage of the progression of diabetic nephropathy, and EndMT participates at the later stage.

Their study reported the relationship between miR-29s and fibrosis. MiR had been interpreted as the nonsense part in the past, but it has been found that it is important in the connection with disease. It has been suggested that miR-200, miR-21, miR-192, miR-377, miR-34a and so in are related to fibrosis in the kidney. For example, miR-192 is involved in TGF-β1-mediated collagen I and III synthesis, and upregulated miR-377 increases fibronectin production in diabetic nephropathy. MiR-29s is not only a specific regulatory factor of kidney fibrosis, but is also related to pulmonary fibrosis and cardiac fibrosis.

In addition, they focused on EndMT as a source of the fibroblasts in diabetic kidney fibrosis. Fibroblasts play a key role in the pathogenesis of renal fibrosis. Although the origins of fibroblasts involved in kidney fibrosis are still controversial, kidney fibroblasts might be derived from residential fibroblasts, vascular pericytes, EndMT or endothelial-to-myoﬁbroblast transition. The clarification of the mechanism of kidney fibrosis including the origin of the fibroblasts would lead to developing a novel strategy. Fibrosis is the final common pathway of end-stage renal disease and many organ failures. The beneﬁcial effects of DPP-4 inhibitor reported by Kanasaki et al. might raise the possibility that the therapeutic strategy using DPP-4 ameliorates the progression of other fibrotic diseases.

DPP-4 inhibitor is now widely used for patients with type 2 diabetes worldwide. Incretin-based drugs are suggested to exert many pleiotropic effects through GLP-1 receptor and GLP-1 independent pathways. These antidiabetic drugs are multipotent, and might be beneﬁcial for other diseases including diabetic nephropathy, although long-term prospective clinical study is required to develop novel therapeutic strategies using incretin-based drugs.

**DISCLOSURE**

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