SMP-534 ameliorates progression of glomerular fibrosis and urinary albumin in diabetic db/db mice

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Suguru, Eiji, Tsutomu Nakagawa, Michiko Ono-Kishino, Jun Nagamine, Teruhisa Tokunaga, W. Ewan Hume, Ryu Nagata, and Mutsuo Taiji. SMP-534 ameliorates progression of glomerular fibrosis and urinary albumin in diabetic db/db mice. Am J Physiol Renal Physiol 290: F813–F820, 2006. First published November 8, 2005; doi:10.1152/ajprenal.00357.2005.—Diabetic nephropathy is currently the most common cause of end-stage renal disease. Diabetic nephropathy patients, whether insulin dependent or not, develop fibrotic changes in glomeruli that manifest as overt nephropathy. Previously, we demonstrated that 5-chloro-2-[(1E)-3-[2-(4-methoxybenzoyl)-4-methyl-1H-pyrrol-1-yl]prop-1-en-1-yl]-N-(methylsulfonyl)benzamide (SMP-534) reduces extracellular matrix (ECM) production induced by transforming growth factor-β (TGF-β) in vitro and prevents the accumulation of ECM in glomeruli in rat Thy-1 nephritis models. In this study, we examined the long-term effects of SMP-534 on renal insufficiency and glomerulosclerosis in db/db mice, which are models of type 2 diabetes. A diet containing SMP-534 was given to the mice from the age of 9 to 25 wk, and blood and urine analysis were performed at 8, 17, and 25 wk. At the end of study, kidney tissues were analyzed histologically. Treatment with SMP-534 dose dependently suppressed the increase of urinary albumin and type IV collagen excretion in db/db mice. The renal histological analysis showed that SMP-534 dose dependently suppressed the increase of mesangial expansion in the kidney. In the immunohistological analysis, fibronectin and type IV collagen expression were lower in SMP-534-treated db/db mice compared with vehicle-treated db/db mice. This study suggested that SMP-534 ameliorated the increase of ECM production in kidney of db/db mice, possibly through the inhibition of TGF-β action. Hence, antifibrotic agents such as SMP-534 might be a new therapeutic option for the treatment of diabetic nephropathy.

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MATERIALS AND METHODS

Chemicals. SMP-534 (Fig. 1) was synthesized in our laboratories. Animals and study design. Male db/db mice and control db/m mice were purchased from a breeder (Nihon Clea, Tokyo, Japan). The animals received dietary administration of SMP-534 in powdered food CE-2 (Nihon Clea) at concentrations of 0.0007% (low dose), 0.0020% (intermediate dose), and 0.0067% (high dose) from age 9 to 25 wk. Body weight was measured at ages 8, 17, and 25 wk, and serum biochemical parameters such as blood glucose, serum creatinine, and blood urea nitrogen levels were determined at 8, 17, and 25 wk by collecting blood via a tail vein, as described below. The animals were individually housed in metabolic cages for 24 h at 8, 17, and 25 wk to pool urine for analysis of urine parameters. The animals were allowed free access to diet and water and were kept in a room at a controlled temperature of 23 ± 2°C and humidity of 55 ± 10%, with a 12:12-h illumination cycle (lights on from 0800 to 2000). All procedures were approved by the Dainippon Sumitomo Pharma Committee on Animal Research. Analysis of urine parameters. The creatinine concentration in pooled urine samples was determined by the Jaffé method using the Creatinine Test Wako (Wako Pure Chemical Industries, Osaka, Japan). Albumin and type IV collagen were determined by the competitive ELISA method using Albuwell M and Collagen IV M (Exocell, Philadelphia, PA), respectively. All analyses were performed in accordance with the manuals provided by the manufacturer. Analysis of serum biochemical parameters. The creatinine concentration was determined by the Jaffé method using the Creatinine Test Wako (Wako Pure Chemical Industries), and blood urea nitrogen (BUN) was determined by the diacetylmonoxime method using the BUN Test Wako (Wako Pure Chemical Industries). All analyses were performed in accordance with the manuals provided by the manufacturer. Analysis of blood glucose levels. Blood was collected via a tail vein and mixed with 0.4 N perchloric acid. To this mixture, 0.37 M potassium carbonate was added and the mixture was centrifuged. The resulting supernatant was used to determine the blood glucose level by the glucose-oxidase method, using the Glucose-oxidase method (Wako Pure Chemical Industries). The analysis was performed in accordance with the manuals provided by the manufacturer. Renal histological analysis. At the age of 25 wk, mice were anesthetized and perfused with ice-cold Ringer solution before being perfused and fixed with 10% buffered formalin. For morphometric analysis, the kidney was removed and embedded in paraffin to prepare 4-μm tissue slices. The tissue slices were stained with periodic acid-Schiff (PAS). The mesangial expansion index (MEI) was scored in four levels from 0 to 3, with the index scores defined as follows (6): 0, normal glomeruli; 1, matrix expansion occurred in up to 50% of a glomerulus; 2, matrix expansion occurred in 50 to 75% of a glomerulus; 3, matrix expansion occurred in 75 to 100% of a glomerulus. Scores were assigned for at least 30 glomeruli from kidney slices from each animal, and the means were calculated. The investigator scoring the sections was blinded to the dose group of the animal. Immunohistological analysis. Immunohistological analysis of fibronectin and type IV collagen was performed using renal tissue slices. Anti-human fibronectin polyclonal antibody (DAKO, Kyoto, Japan) and anti-mouse collagen IV antisera (LSL, Tokyo, Japan) were used for immunostaining, which was performed by the streptavidin-biotin-immunoperoxidase method with an Immunocruz Staining Kit (Santa Cruz Biotechnology, Santa Cruz, CA). Immunoreactive products were made visible using diaminobenzidine as a chromogen and counterstained with crystal violet. The procedure was conducted in accordance with the manufacturer. To evaluate the immunostaining for fibronectin and type IV collagen, a total of more than 20 randomly chosen glomeruli per mouse was coded and graded in a blind manner. The degree of fibronectin and type IV collagen expression in four mice from each group was graded as follows: 0, absent staining to 5%; 1, 5 to 25%; 2, 25 to 50%; 3, 50 to 75%; 4, >75% (26).

Statistical analysis. All data are presented as means ± SD. Differences between individual groups were analyzed by a Student’s t-test, Wilcoxon test, or Shirley-William’s test. Statistical calculations were performed using SAS software (SAS Institute, Cary, NC), and P values <0.05 (Student’s t-test, Wilcoxon test), <0.025 (William’s test, Shirley-William’s test) were considered statistically significant.

RESULTS

Effects of dietary administration of SMP-534 on body weight and blood glucose. Db/db mice are a genetic model of obesity associated with hyperphagia and hyperglycemia (8, 29). These mice also develop glomerular mesangial expansion and histological lesions, which might resemble those found in human diabetic nephropathy (37). We evaluated the effectiveness of long-term administration of SMP-534, an antifibrotic agent, in preventing glomerulosclerosis and renal insufficiency in db/db mice. Db/db mice received dietary administration of SMP-534 in powdered food at concentrations of 0.0007% (low dose), 0.0020% (intermediate dose), and 0.0067% (high dose) from the age of 9 to 25 wk old (Fig. 2). As a normoglycemic control group, nondiabetic db/m mice received powdered food without SMP-534. SMP-534 did not have a significant effect on food consumption in db/db mice (data not shown), and thus the approximate daily doses of SMP-534 were calculated to be 1.1 mg/kg (low dose), 3.2 mg/kg (intermediate dose), and 10.7 mg/kg (high dose), based on food consumption. In db/db mice, marked obesity and hyperglycemia were observed throughout the study period, compared with nondiabetic db/m mice (Fig. 3). The blood glucose level was ~300 and 500 mg/dl, respectively, at the age of 8 and 25 wk in db/db mice, indicating deterioration of diabetes during the study period. In contrast, the blood glucose level remained stable at ~150 mg/dl in db/m mice throughout the study period.

Effects of SMP-534 on renal parameters. Serum creatinine and BUN levels, which are generally considered as markers of renal function, were determined to evaluate the effect of dietary administration of SMP-534 on renal function in db/db mice. During the study period, serum creatinine and BUN levels of db/db mice were higher than those of db/m mice. The serum creatinine levels of db/db mice that received the high dose of SMP-534 were significantly higher than those of the vehicle-treated group at the age of 25 wk, whereas the BUN levels of db/db mice did not differ significantly among all the groups (Table 1). The creatinine clearance (Ccr) level was also determined to evaluate the effect of SMP-534 on renal function. The Ccr levels of db/db mice were higher than those of db/m mice, implying the presence of diabetic kidney disease.
with renal hyperfiltration (Table 1). At the age of 25 wk, the high dose of SMP-534 significantly suppressed the increase in Ccr levels, compared with those in the vehicle-treated group (Table 1).

**Table 1. Serum creatinine and BUN and Ccr in nondiabetic db/m mice, diabetic db/db mice, and SMP-534-treated db/db mice**

<table>
<thead>
<tr>
<th></th>
<th>8 wk</th>
<th>17 wk</th>
<th>25 wk</th>
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<tbody>
<tr>
<td><strong>Serum Creatinine, mg/dl</strong></td>
<td></td>
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<tr>
<td><em>db/m</em> Vehicle</td>
<td>0.35±0.04*</td>
<td>0.43±0.04*</td>
<td>0.41±0.04*</td>
</tr>
<tr>
<td>SMP-534 (low)</td>
<td>0.49±0.06</td>
<td>0.62±0.10</td>
<td>0.57±0.04</td>
</tr>
<tr>
<td>SMP-534 (intermediate)</td>
<td>0.53±0.07</td>
<td>0.60±0.10</td>
<td>0.58±0.08</td>
</tr>
<tr>
<td>SMP-534 (high)</td>
<td>0.48±0.06</td>
<td>0.61±0.09</td>
<td>0.62±0.06</td>
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<tr>
<td><strong>BUN, mg/dl</strong></td>
<td></td>
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<tr>
<td><em>db/m</em> Vehicle</td>
<td>23.2±2.8*</td>
<td>29.1±3.3</td>
<td>21.6±2.3*</td>
</tr>
<tr>
<td>SMP-534 (low)</td>
<td>27.4±3.0</td>
<td>31.6±3.6</td>
<td>29.9±3.1</td>
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<tr>
<td>SMP-534 (intermediate)</td>
<td>28.1±3.0</td>
<td>32.2±4.4</td>
<td>31.1±5.6</td>
</tr>
<tr>
<td>SMP-534 (high)</td>
<td>26.3±2.6</td>
<td>35.8±5.0</td>
<td>31.3±5.2</td>
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<tr>
<td><strong>Creatinine Clearance, ml/min</strong></td>
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<tr>
<td><em>db/m</em> Vehicle</td>
<td>0.122±0.047†</td>
<td>0.129±0.026*</td>
<td>0.109±0.037*</td>
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<tr>
<td>SMP-534 (low)</td>
<td>0.172±0.032</td>
<td>0.212±0.049</td>
<td>0.339±0.160</td>
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<tr>
<td>SMP-534 (intermediate)</td>
<td>0.184±0.028</td>
<td>0.206±0.052</td>
<td>0.334±0.078</td>
</tr>
<tr>
<td>SMP-534 (high)</td>
<td>0.175±0.071</td>
<td>0.194±0.047</td>
<td>0.301±0.049</td>
</tr>
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Data are shown as means ± SD. *n = 10 for *db/m* mice and *n = 11–12 for *db/db* mice. **P < 0.01, †P < 0.05 vs. *db/db* mice treated with vehicle (Student’s t-test).

**Effect of SMP-534 on urine parameters.** Because urinary albumin excretion has been demonstrated to be a good clinical predictor of renal lesions in diabetic nephropathy (32, 42), the effect of SMP-534 on urinary albumin excretion in *db/db* mice was determined. As previously reported (26), the urinary albumin excretion of *db/db* mice was higher than that of *db/m* mice, and this further increased with the age (Fig. 4A). Throughout the study period, SMP-534 dose dependently sup-

Fig. 2. Study design. Diabetic *db/db* mice received dietary administration of SMP-534 in powder food CE-2 at concentrations of 0.0007% (low dose), 0.0020% (intermediate dose), and 0.0067% (high dose) from age 9 to 25 wk. As a control, nondiabetic *db/m* mice received powder food CE-2 without SMP-534. Blood and urine analysis and body weight measurement were performed at 8, 17, and 25 wk.

![Fig. 3. Effect of SMP-534 on body weight (A) and blood glucose level (B).](image-url)
pressed the increase in the urinary albumin excretion of \( \text{db/db} \) mice. Furthermore, at the age of 25 wk, the high dose of SMP-534 significantly suppressed the increase in urinary albumin excretion, compared with the vehicle-treated group (585.5 \pm 176.1 \mu g/24 h, \( P < 0.005 \); Fig. 4B).

Effect of SMP-534 on renal histology. Mesangial matrix expansion is considered to be a hallmark of the pathological features of established diabetic nephropathy in humans (21). Of the several known mouse models associated with hyperglycemia, the \( \text{db/db} \) mouse appears to most closely mimic the progressive nature of mesangial matrix expansion seen in human diabetic nephropathy (37).

In PAS-stained images of glomeruli at the end of the treatment period, significant accumulation of ECM was observed in \( \text{db/db} \) mice, compared with \( \text{db/m} \) mice, demonstrating the occurrence of glomerular fibrosis (Fig. 5A). Representative light micrographs of glomeruli are shown in Fig. 5A. The increase in the MEI was dose dependently suppressed by SMP-534 treatment, and this effect reached a maximum level at the high dose of SMP-534, compared with vehicle-treated group (1.2 \( \pm \) 0.1 vs. 0.5 \( \pm \) 0.2, \( P < 0.005 \); Fig. 5B).

To clarify further the effect of SMP-534 on glomerular fibrosis, immunohistological staining of fibronectin and type IV collagen in glomeruli was performed. In \( \text{db/db} \) mice, fibronectin and type IV collagen accumulated in the mesangial area of glomeruli (Fig. 6), and both proteins were expressed at lower levels in the glomeruli of \( \text{db/db} \) mice treated with SMP-534, compared with the vehicle-treated group (Fig. 6). Semiquantitative scores for fibronectin and type IV collagen increased from 0.5 \( \pm \) 0.1 and 3.0 \( \pm \) 0.2 in \( \text{db/m} \) mice to 3.2 \( \pm \) 0.4 and 3.0 \( \pm \) 0.2 in \( \text{db/db} \) mice, respectively (\( \text{db/m} \) vs. \( \text{db/db} \), \( P < 0.05 \)). Treatment with the high dose of SMP-534 reduced scores for fibronectin and type IV collagen expression to 2.0 \( \pm \) 0.4 and 1.8 \( \pm \) 0.1, respectively (\( \text{db/db} \) treated with vehicle vs. \( \text{db/db} \) treated with the high dose of SMP-534, \( P < 0.05 \)).

**DISCUSSION**

In the present study, SMP-534, a low-molecular-weight compound that has an inhibitory effect on TGF-\( \beta \)-stimulated ECM production, prevented the progression of renal lesions in \( \text{db/db} \) mice, a rodent model for diabetic nephropathy with obesity and hyperglycemia. More specifically, SMP-534 suppressed an increase in urinary albumin excretion and ameliorated the progression of glomerular fibrosis in \( \text{db/db} \) mice. Previously, we reported that SMP-534 inhibits TGF-\( \beta \)-stimulated ECM production in vitro and prevents deterioration of renal fibrosis in a rat anti-Thy1 nephritis model in vivo (38). Because deterioration of renal function was not observed in that model (30, 40), it was not known whether an antibiotic agent such as SMP-534 would show a renoprotective effect. To address this question, we assessed the effect of SMP-534 on urinary albumin excretion in \( \text{db/db} \) mice. There have been many reports suggesting that urinary albumin excretion is a predictive factor for prognosis of diabetic nephropathy (11), and it has also been reported that urinary albumin itself impairs renal function (9). For example, the results of the RENAAL study (7) have demonstrated that losartan significantly reduces the risk of a doubling of serum creatinine (risk reduction, 25%; \( P = 0.006 \)) and progression to ESRD (risk reduction, 28%; \( P = 0.002 \)), while also significantly lowering the levels of urinary albumin (\( P < 0.001 \) for comparison with placebo). Hence, the RENAAL study verified that urinary albumin re-

![Figure 4](http://www.ajprenal.org)

**Fig. 4.** Effect of SMP-534 on urinary albumin excretion (A) and urinary type IV collagen excretion (B). A 24-h pooled urine sample was collected in a metabolic cage at 8, 17, and 25 wk of age for each mouse. Urine samples were processed to measure urinary albumin or urinary type IV collagen concentrations using a competitive ELISA. Data are shown as means \( \pm \) SD; \( n = 10 \) for \( \text{db/db} \) mice and \( n = 11–12 \) for \( \text{db/db} \) mice. \( **P < 0.005 \), *P < 0.005 vs. \( \text{db/db} \) mice treated with vehicle (Student’s \( t \)-test). Table 1 summarizes the protein excretion at the high dose of SMP-534, compared with vehicle-treated group (1.2 \( \pm \) 0.1 vs. 0.5 \( \pm \) 0.2, \( P < 0.005 \); Fig. 5B).
duction in type 2 diabetic nephropathy is associated with renal protection (16).

In the present study, the urinary albumin excretion increased significantly throughout the study period in \( db/db \) mice, and SMP-534 dose dependently prevented this increase. This result indicates that SMP-534 exhibits a renoprotective effect in an animal model of diabetic nephropathy. Furthermore, SMP-534 did not affect the blood glucose levels or body weight of these mice.

**Fig. 5.** Effect of SMP-534 on mesangial matrix expansion. A: representative photomicrographs of PAS-stained kidney sections from \( db/m \) mice (left), \( db/db \) mice (middle), and \( db/db \) mice treated with a high dose of SMP-534 (right). B: expansion of the glomerular matrix was scored using 4 levels, and an average value was obtained from analyses of more than 30 glomeruli per mouse. Data are shown as means ± SD: \( n = 10 \) for \( db/m \) mice and \( n = 11–12 \) for \( db/db \) mice. ***\( P < 0.01 \) vs. \( db/db \) mice treated with vehicle (Wilcoxon test). **\( P < 0.005 \) vs. \( db/db \) mice treated with vehicle (Shirley-William’s test).

**Fig. 6.** Effect of SMP-534 on glomerular fibronectin (top) and type IV collagen expression (bottom). Fixed sections were used in an immunohistochemical study of fibronectin and type IV collagen. Immunostaining was performed by the streptavidin-biotin-immunoperoxidase method. Immunoreactive products were visualized using diaminobenzidine as a chromogen and counterstained with crystal violet. Representative photomicrographs of kidney sections from \( db/m \) mice treated with vehicle (left), \( db/db \) mice treated with vehicle (middle), and \( db/db \) mice treated with a high dose of SMP-534 (right).
mice, indicating that its renoprotective effect is independent of its hypoglycemic action. In addition to the increase in urinary albumin excretion, one of the most remarkable renal pathological findings in diabetic nephropathy is mesangial expansion due to accumulation of ECM in glomeruli (18, 46). The glomerular appearance in db/db mice showed accelerated mesangial expansion, which was histologically characterized by an increase in the PAS-positive mesangial matrix area, compared with that observed in db/m mice. Db/db mice also demonstrated accumulation of ECM components such as fibronectin and type IV collagen in glomeruli, compared with db/m mice. The renal histological analysis revealed that SMP-534 inhibited progression of glomerular fibrosis in db/db mice. Furthermore, in recent years it has been reported that the urinary concentrations of type IV collagen increase in diabetic nephropathy patients and in db/db mice (13, 14). Because type IV collagen in the urine is considered to be derived from mesangial matrix, glomerular basement membrane, and tubulointerstitial tissue, it is likely that urinary excretion of type IV collagen reflects fibrotic changes in diabetic kidneys (23, 25). Therefore, the observed SMP-534-induced inhibition of the increase in urinary type IV collagen excretion may also reflect an inhibitory effect of this compound on deterioration of renal fibrosis. Db/db mice have also been reported to have increased expression of TGF-β and TGF-β receptors in the kidney, which results in activation of TGF-β signaling (22). In addition, it has been reported that a TGF-β-neutralizing antibody inhibits renal deterioration of fibrosis in db/db mice (47), suggesting that SMP-534 may inhibit deterioration of fibrosis by inhibiting TGF-β-induced ECM production. There are two major pathways involved in TGF-β signal transduction, Smad and p38 MAP kinase (12, 31). Smad and p38 MAP kinase activation are reported to occur in the kidney of db/db mice (1, 22). We previously reported that SMP-534 inhibited TGF-β-induced p38 MAP kinase activation in fibroblast cells (38). Taken together, these data have implications that SMP-534 showed a renoprotective effect, at least in part, by inhibiting p38 MAP kinase signaling in the kidney of db/db mice.

In contrast to the obvious outcomes on urinary albumin and histological changes in db/db mice, remarkable changes were not observed in BUN or serum creatinine levels, which are generally considered to be markers of renal function. Although these levels in db/db mice were significantly higher than those in db/m mice, the differences were small, remained within the normal range, and did not change with age. Therefore, it is difficult to draw a conclusion regarding the effect of SMP-534 on these parameters in db/db mice. Similarly, the Ccr data were also inconclusive. In db/db mice, Ccr levels were significantly higher than those of db/m mice and further increased with age. These results are consistent with reports by other groups (19, 20) and may possibly reflect hyperfiltration, an early symptom of diabetic nephropathy. In our experience, however, the changes of Ccr in db/db mice seem to vary from experiment to experiment (data not shown). Although the results of the present study suggest that SMP-534 inhibits hyperfiltration, a further detailed study may be required to draw a definite conclusion.

It has long been known that hypertension is an aggravating factor in diabetic nephropathy, and it is therefore well recognized that blood pressure control is important in diabetic patients (4). Recently, the results of clinical studies in patients with diabetic nephropathy have demonstrated that antihypertensive agents such as ACEIs (33) and ARBs (7, 28) exhibit renoprotective effects. Hence, ACEIs or ARBs are now the first choice for treatment of diabetic nephropathy, but the renoprotective effect of ACEIs or ARBs is not potent enough to prevent the progression of diabetic nephropathy completely.

In this connection, we also confirmed that SMP-534 does not affect blood pressure in normal rats or spontaneously hypertensive rats, a hypertension model (17) (data not shown). It has also been reported that a notable increase in blood pressure was not observed in db/db mice (26, 37), indicating that SMP-534 exhibits a renoprotective effect via a nonantihypertensive mechanism in this model. These data suggest that the combined use of SMP-534 and antihypertensive agents such as ACEIs or ARBs may produce an even stronger renoprotective action, and this possibility warrants further study.

A dramatic worldwide increase in the number of patients with diabetes, and especially type 2 diabetes, has been reported (43), and the disease is becoming a serious social problem. Among diabetic complications, nephropathy is also a very critical disease, which requires renal transplantation or dialysis in its final stages. In the United States, diabetic patients are said to account for ~40% of those who start dialysis (2). Although large-scale epidemiological surveys such as the Diabetes Control and Complications Trial and UK Prospective Diabetes Study studies have shown that hyperglycemia plays an important role in the development of diabetic nephropathy and other diabetic complications (39, 41), it is still difficult for many patients to achieve strict blood glucose control. Therefore, a new drug with a different mechanism of action is awaited for treatment of diabetic nephropathy (45). The present study suggests that antifibrotic agents such as SMP-534 represent a novel approach for the treatment of diabetic nephropathy.

Diabetic nephropathy is a progressive disease that causes glomerular fibrosis and impairment of renal function, with progression over time. Because TGF-β is known not only to stimulate ECM production but also to inhibit ECM degradation (5), inhibition of TGF-β action may block new ECM production and enhance degradation of already accumulated ECM, with the potential to arrest or even reverse the progressive course of diabetic nephropathy. In fact, it has been reported that a TGF-β-neutralizing antibody is effective in db/db mice, even when administration was started long after the onset of diabetes and after the establishment of fibrosis (10). In the present study, SMP-534 was prophylactically administered to db/db mice before the apparent development of renal lesions, and it would be interesting to evaluate the effect of this compound using a protocol in which treatment is started at an advanced disease stage.

In summary, SMP-534, a low-molecular-weight compound that has an inhibitory effect on TGF-β-induced ECM production, ameliorated the progression of renal lesions in db/db mice, a model of type 2 diabetes, without affecting the blood glucose levels. These data suggest that antifibrotic agents such as SMP-534 may be a new therapeutic option for the treatment of diabetic nephropathy.

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