Advanced Glycation End Products Increase Collagen-specific Chaperone Protein in Mouse Diabetic Nephropathy*

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Advanced glycation end products (AGEs) appear to contribute to the diabetic complications. This study reports the inhibitory effect of OPB-9195 (OPB), an inhibitor of AGEs formation, and the role of a collagen-specific molecular chaperone, a 47-kDa heat shock protein (HSP47) in diabetic nephropathy. Transgenic mice carrying nitric-oxide synthase cDNA fused with insulin promoter (iNOSTg) leads to diabetes mellitus. The iNOSTg mice at 6 months of age showed diffuse glomerulosclerosis, and the expression of HSP47 was markedly increased in the mesangial area in parallel with increased expression of types I and IV collagens. OPB treatment ameliorated glomerulosclerosis in the iNOSTg mice associated with the decreased expression of HSP47 and types I and IV collagen genes. The expression of transforming growth factor-β (TGF-β) was increased in glomeruli of iNOSTg mice and decreased after treatment with OPB. To confirm these mechanisms, cultured mesangial cells were stimulated with AGEs. AGEs significantly increased the expression of HSP47, type IV collagen, and TGF-β mRNA. Neutralizing antibody for TGF-β inhibited the overexpression of both HSP47 and type IV collagen in vitro. In conclusion, AGEs increase the expression of HSP47 in association with collagen, both in vivo and in vitro. The processes may be mediated by TGF-β.

Nephropathy is a morbid complication associated with diabetes mellitus and is the leading cause of end-stage renal disease (1). Diabetic nephropathy is characterized by a mesangial expansion followed by glomerulosclerosis. The mechanism of these processes remains unknown. Advanced glycation end products (AGEs) have been recently reported to play an important role in the pathogenesis of diabetic complications, particularly in the progression of retinopathy and nephropathy (2). AGEs, late compounds formed from early Amadori compounds produced during the Maillard reaction, slowly accumulate in various tissues. Direct evidence indicating the importance of AGEs in the progression of diabetic nephropathy has been reported previously (3–5). The administration of exogenous AGEs to normal rats induces glomerular hypertrophy and mesangial sclerosis, gene expression of matrix proteins, and production of various growth factors. An inhibitor of AGE formation, amloguanidine, ameliorates the mild glomerular changes and functional changes found in streptozocin-induced diabetic rats (6). Recently, a synthetic thiazolidine derivative, OPB-9195, was shown to have a strong inhibitory effect of AGE formation (7).

The 47-kDa heat shock protein (HSP47) has been identified as a collagen-binding stress protein and plays a role in the intracellular processing of procollagen molecules as a collagen-specific molecular chaperone. We recently reported that the expression of HSP47 was markedly increased in parallel with the development of glomerulosclerosis in a rat renal ablation model (8). We also found that the inhibition of HSP47 ameliorated glomerulosclerosis (9). Despite a possible pathophysiological role of collagen-binding HSP47 in the fibrotic process in various organs, factors that modulate its expression remain undefined.

To understand the pathogenesis of diabetic nephropathy and to develop prophylactic and therapeutic measures against it, suitable animal models are needed. However, no single animal model that develops the renal changes seen in humans is available. Spontaneously diabetic animals such as the non-obese diabetic mouse develop only limited lesions, at most mild mesangial sclerosis (10). The same is the case with chemically induced diabetic rodents. In this study, we analyzed transgenic mice carrying the mouse, type 2-inducible nitric-oxide synthase (iNOS) cDNA under the control of an insulin promoter (iNOSTg) (11). The nitric oxide-mediated destruction of β cells results in a markedly reduced pancreatic islet mass and in the development of type 1 diabetes mellitus. These characteristics were followed by glomerulosclerosis that resembled human diabetic nephropathy (3).

Transforming growth factor (TGF)-β was originally identified in neoplastic cells and subsequently reported to be present in various other tissues and cell types. TGF-β is a multifunctional cytokine that regulates tissue repair, differentiation, and proliferation. In diabetic nephropathy, TGF-β has been implicated in the development of glomerulosclerosis. TGF-β promotes the synthesis of extracellular matrix proteins, including collagens and proteoglycans. The increased expression of TGF-β in diabetic kidneys suggests a role in the pathogenesis of glomerulosclerosis. TGF-β is also involved in the regulation of cell proliferation and the inhibition of apoptosis, which may contribute to the progression of diabetic nephropathy.

In conclusion, advanced glycation end products (AGEs) are implicated in the pathogenesis of diabetic nephropathy through their ability to induce the expression of collagen-specific chaperone proteins such as HSP47. The inhibition of AGE formation using OPB-9195 ameliorates glomerulosclerosis, suggesting a potential role for these compounds in the prevention and treatment of diabetic nephropathy.
in most cells in which it exerts a variety of effects on cell proliferation, cell differentiation, and embryogenesis. It has also been shown to stimulate the production of extracellular matrix components including collagens and fibronectin and to play a pivotal role in fibrogenesis (12). Thus, TGF-β is considered to be a mediator of collagen production in the models of fibrogenesis. Significant progress has recently been made in our understanding of the expression of the collagen genes and their transcriptional regulation by TGF-β (8, 9). A recent report has shown that high glucose transiently induces a transcriptional activity of c-fos responsible for stimulation of the TGF-β (13). However, there is little information regarding the interaction between AGE and c-Fos. We investigated here the expression of c-Fos in cultured mesangial cells treated with AGE and examined whether c-Fos affected the expression of TGF-β.

Furthermore, our recent report demonstrates that type IV collagen is up-regulated by AGE and its overexpression is transcriptionally regulated by Smad1 (14). Smad1 also enhances the levels of expression of type I collagen and osteopontin and plays a critical role in TGF-β-mediated overexpression of extracellular matrix in diabetic nephropathy (14). Therefore, we examined the role of Smad1 for regulating HSP47 expression by AGE stimulation in mesangial cells.

In this study, we reported on a study of the inhibitory effect of OPB-9195 (OPB), a novel inhibitor of AGE formation, in a model of diabetic nephropathy. The pathogenic role of HSP47 in the development of the glomerulosclerotic lesions in diabetes was examined. We also confirmed the mechanism of these processes with the use of cultured mesangial cells.

**MATERIALS AND METHODS**

**Experimental Animals**—iNOSTg were maintained on CD-1 mouse background (11). Male littermates were screened for the transgenes by the PCR amplification and used for analysis. The primers used for the detection of iNOSTg were as follows: forward primer 5′-GTGGGCTATGGTTTTGGAGAGA-3′, and reverse primer 5′-CGATGTCACA-TGCGAGCTGT-3′.

No expression of iNOS protein, whose synthesis is directed only in pancreatic islets, was detected in the kidney. The mice were divided into four groups: CD-1 as control mice (Control); control mice treated with OPB (Control + OPB); iNOSTg; and iNOSTg treated with OPB (iNOSTg + OPB). Each group was fed either normal chow or the chow containing 0.28% OPB (provided by Fujii Memorial Research Institute, Otsuka Pharmaceutical, Tokushima, Japan) from 1 to 6 months after birth.

**Blood Glucose and HbA1c Concentration**—The levels of blood glucose and HbA1c were measured from the tail vein blood using Dexter Z sensor (Bayer-Medical, Tokyo, Japan) and DCA2000 analyzer (Bayer-Medical), respectively.

**Determination of AGEs Concentration**—Levels of serum carboxymethyllysine (CML) and non-CML AGEs were determined using a competitive enzyme-linked immunosorbent assay as described previously (15). 1 unit/ml CML or non-CML AGEs corresponded to a protein concentration of 1 μg/ml CML-bovine serum albumin (BSA) or non-CML AGE-BSA, respectively.

**Renal Histology and Morphometric Analysis**—Kidneys were processed for light microscopy examination, and the severity of the renal sclerosis was scored on an arbitrary scale from 0 to 4. The mean glomerular volume was determined as described previously (3, 16).

**Immunofluorescence Analysis for HSP47, Types I and IV Collagens, and TGF-β**—Immunofluorescence analysis was carried out as described previously using an affinity-purified polyclonal antibody specific to HSP47, types I and IV collagens, and TGF-β (8, 9).
**Laser-manipulated Microdissection and Laser Pressure Catapulting**—Laser-manipulated microdissection is a method to cut out a small region from a specimen under microscope observation by means of laser beam. Laser pressure catapulting is a method to push up and collect samples that have been microdissected using laser-manipulated microdissection by means of a strong laser. These methods were performed using the Robot-Microbeam (P.A.L.M) and an inverted microscope (Carl Zeiss, Oberkochem, Germany) (17). By tracing around the glomeruli shown on the monitor, the targeted glomeruli were cut out by the laser. For laser pressure catapulting, the setting for the laser energy should be sufficiently high to catapult the microdissected glomeruli of the specimen into the microcentrifuge cap, which was held in place by the micromanipulator. When the laser pressure catapulting was performed, the microdissected glomeruli “jumped up” and were attached to the cap 60–80 glomeruli for each experiment were collected from this procedure. Glomeruli were obtained from those of control, iNOSTg, and iNOSTg-OPB mice at 24 weeks of age.

**Quantitative PCR**—Total RNA was prepared from isolated glomeruli, and a cDNA synthesis was performed with reverse transcription. Real-time PCR was performed by using the ABI Prism 7700 sequence detection system (PerkinElmer Life Sciences). Primers for mouse glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (PerkinElmer Life Sciences) were used for internal control. The primers for HSP47, type IV collagen, and TGF-β were as follows: HSP47 (forward primer, 5′-GCGAGATAATCGAGCGGCT-3′; reverse primer, 5′-CCACGCCCCAATCTTGAGCT-3′); type IV collagen (forward primer, 5′-CTTGGACT-3′/H11032; reverse primer, 5′-CCACGCCCACTCGAGATAATCAGAGCGGCT-3′/H11032); TGF-β (forward primer, 5′-GGACGATTCGAGCGGCTAATG-3′/H11032; reverse primer, 5′-CTTGCTCTTCATTGGCCGCC-3′/H11032); and TaqMan Probe, 5′-TGGACCGCAACAACGCAATCTATG-3′. The cleavage of the sequence-specific probe (TaqMan Probe) by 5′-3′ nuclease activity of the TaqDNA polymerase releases the reporter dye, resulting in an emission increase. With each cycle, the fluorescence intensity of additional reporter dye molecules is monitored by the system. The threshold cycles were selected in the line in which all of the samples were in the logarithmic phase. The quantity of PCR products was calculated from the threshold cycle value. This real-time detection generates quantitative data based on PCR at early cycles when PCR fidelity is highest (18, 19).

**Cell Culture**—A glomerular mesangial cell line was established from glomeruli isolated from normal 4-week-old mice (C57BL/6JxSJL/J) and was identified according to a method described previously (4, 5). The mesangial cells were plated in 100-mm plastic dishes (Nunc) that were maintained in B medium (a 3:1 mixture of minimal essential medium/F12 modified with trace elements) supplemented with 1 mM glutamine, penicillin at 100 units/ml, streptomycin at 100 μg/ml, and 20% fetal calf serum (Irvine Scientific). The cells were passaged weekly with trypsin-EDTA. The cultured cells fulfilled the previously described criteria generally accepted for glomerular mesangial cells (20).

**AGE-BSA**—AGE-BSA was prepared by the method described previously (5, 21). BSA was incubated with glucose 6-phosphate for 60 days at 37 °C. AGE content was measured by the fluorescence intensity at a protein concentration of 1 mg/ml. Control BSA was prepared by incubating BSA without glucose 6-phosphate under the same conditions as those for AGE-BSA. AGE-BSA and control BSA contained 61.3 and 8.31 AGE units/mg protein, respectively. Protein concentrations were determined by the method of Bradford using BSA as the standard.

Mesangial cells were plated in B medium, 20% fetal bovine serum at 5 × 10^4/well in six-well dishes, that had been coated with AGE-BSA or control BSA at 50 μg/cm² for 72 h. After the treatment, the cells were
washed with phosphate-buffered saline and total RNA was isolated using TRIzol reagent (Invitrogen).

**TGF-β-neutralizing Antibody Assay**—The cells were resuspended at a concentration of $1 \times 10^6$ cells/ml and plated onto 100-mm dish either in the presence of 10 μg/ml TGF-β-neutralizing antibody (R&D Systems) or a control normal IgG (22). After 24 h of incubation, the cells were harvested and underwent RNA isolation on real-time reverse transcription-PCR.

**Smad1 Morpholino Antisense Oligonucleotide**—The antisense oligonucleotide for Smad1 was a 25-nucleotide morpholino oligomer (Genetools LLC) with the base composition of 5'-CAAGCTGGTCACATTCATAGCGGCT-3'. A standard morpholino oligomer with the base composition of 5'-CATGCTCAGTCACATTCAAGCcGCT-3' (points of mismatch are shown by small letters) was used as a control. Microinjection of *in vitro* transcribed RNA was performed as described previously (14).

**Western Blotting**—Cultured mesangial cells were harvested in sample buffer, resolved by SDS-polyacrylamide gel electrophoresis, transferred to nitrocellulose membrane, subjected to Western blot using a 1:500 dilution of antibody for HSP47, type IV collagen, and TGF-β (8, 9), and detected using an enhanced chemiluminescence detection system (Invitrogen).

**RNase Protection Assay**—Total RNA was isolated from mesangial cells using the TRIzol reagent, and an RNase protection assay was performed as described previously (14, 22). The RNA probes were prepared by linearizing the PvuII fragment of type IV collagen from p1234, the SacI fragment of Smad1 from pGEM-T, and the EcoRI fragment of GAPDH from pMGAP1. In addition, mouse riboprobe for HSP47 (5'-T-CCTATACGTGGGTGTTACAGATGA-3' and 5'-TACAAGCTCAGTCACATTCAAGCcGCT-3' (points of mismatch are shown by small letters) was used as a control. Microinjection of *in vitro* transcribed RNA was performed as described previously (14).

**FIG. 3. Immunofluorescence analysis of HSP47, collagens, and TGF-β.** A remarkable increase in the expression of HSP47, types I and IV collagens, and TGF-β was seen. OPB treatment led to show a significant decrease. A–C, type I collagen; D–F, type IV collagen. G–I, HSP47, J–L, TGF-β. A, D, G, and J, control. B, E, H, and K, iNOSTg. C, F, I, and L, iNOSTg + OPB.
were cloned into a pGEM-T plasmid. After digesting the plasmid with SacI, an antisense riboprobe was synthesized in vitro using T7 RNA polymerase. The RNA probes and the test RNA were hybridized over-night at 45 °C. RNase A (40 μg/ml) and RNase T1 (2 μg/ml) were added to each tube, and the tubes were incubated for 1 h at 30 °C. The RNase resistant fragments were analyzed by 5% polyacrylamide, 8 M urea gel electrophoresis. The protected bands for each RNA probe had the same size as the coding sequence for the specific mRNA.

Small Interfering RNA (siRNA) and Transfections—The siRNA sequence targeting c-fos (5′-CCAATCTGCTGAAGAGAAGGAAAA-3′) was purchased from Dharmacon (7.5 μg/ml) and RNase T1 (2 μg/ml) were added to each tube, and the tubes were incubated for 1 h at 30 °C. The RNase resistant fragments were analyzed by 5% polyacrylamide, 8 M urea gel electrophoresis. The protected bands for each RNA probe had the same size as the coding sequence for the specific mRNA.

RESULTS

Blood Glucose, HbA1c, and AGE Concentration—Blood glucose levels of iNOSTg mice were >500 mg/dl (503 ± 19 mg/dl, n = 9), and OPB had no effect on this parameter (586 ± 74 mg/dl, n = 5). HbA1c levels were over 7% in iNOSTg mice (7.5 ± 0.8%), whereas that of controls was below the detection limit. Both serum levels of CML and non-CML AGEs were significantly higher in iNOSTg mice (0.4 and 12.6 μg/ml, respectively) than controls (0.0 and 1.0 μg/ml, respectively), whereas OPB treatment of iNOSTg mice led to a decrease to the control levels (2.5 and 2.6 μg/ml, respectively).

Response of Matrix Expansion to Treatment with OPB—The microscopic lesions in iNOSTg mice were observed as a diffuse proliferation of the mesangial matrix and the expansion of the mesangial area (Fig. 1). These lesions were ameliorated by treatment with OPB. OPB markedly improved the glomerulosclerosis of iNOSTg mice with no decrease in glomerular volume. No significant differences in glomerular cell number were detected among these groups (Fig. 2).

Response of Expressions of Collagens and HSP47 to Treatment with OPB—Although only traces of type I collagen could be detected in control glomeruli, it was strongly expressed in the mesangial area of glomeruli in iNOSTg mice. OPB treatment decreased this expression. Type IV collagen was expressed in both the glomerular basement membrane and the mesangium in control mice. Mesangial expression was increased in iNOSTg mice, which decreased after treatment with OPB. Immunofluorescent staining also revealed a remarkable increase in the expression of HSP47, which paralleled the expression of type I and type IV collagen and TGF-β in iNOSTg mice. These expressions were decreased as the result of OPB treatment (Figs. 3 and 4).

Quantitation of the Expression Ratio of HSP47/GAPDH mRNA and Type IV Collagen/GAPDH mRNA in Glomeruli by Real-time RT-PCR—Isolated mRNA of 50 glomeruli randomly selected from 5-μm frozen sections by laser-manipulated microdissection and laser pressure catapulting was used to quantitate the expression of HSP47 and type IV collagen mRNA in this diabetic nephropathy model. A remarkable increase in the expression of HSP47, type IV collagen, and TGF-β was seen in iNOSTg mice, and OPB treatment showed a significant decrease (Fig. 5).

Stimulation by AGEs in Cultured Mesangial Cells—To confirm the mechanism, cultured mesangial cells were stimulated with AGEs. AGEs significantly increased both HSP47 and type IV collagen expressions. In addition, AGEs were found to enhance the expression of TGF-β in cultured mesangial cells (Fig. 6a). Similarly, the levels of both HSP47 and type IV collagen proteins increased in accordance with the elevation of TGF-β protein (Fig. 6b). Neutralizing antibody for TGF-β inhibited overexpression of both HSP47 and type IV collagen (Fig. 7, a and b).
To further elucidate the mechanism for AGE-mediated induction of TGF-β, we investigated the expression of c-fos in mesangial cells. We found that AGE treatment caused a significant increase of c-fos mRNA by RNase protection assay. The AGE-mediated induction of c-fos was completely abolished in the presence of the specific siRNA but not in the presence of control siRNA. Consistent with the inhibition of c-fos, the induction of TGF-β was strongly attenuated (Fig. 8).

We next examined the involvement of Smad1 in TGF-β-mediated induction of HSP47 and type IV collagen expression. We transfected antisense morpholino oligomers to block Smad1-mediated effect in mesangial cells. Mesangial cells transfected with Smad1-antisense oligomers showed much less expression of HSP47 and type IV collagen transcripts after AGE stimulation than those with control oligomers (Fig. 9).

**DISCUSSION**

This study shows that the collagen-specific chaperone protein, HSP47, is strongly expressed in glomerulosclerotic lesions in parallel with increased expression of collagens I and IV in diabetic nephropathy. The findings of the study also suggest that AGEs are a key factor in the synthesis of increased expression of both HSP47 and collagens in vitro and in vivo. Our in vitro study indicates that AGEs-mediated induction of HSP47 and collagens may be through TGF-β.

Collagen is synthesized in the form of pro-α chains, and three pro-α chains form procollagen with a triple-helical structure in the endoplasmic reticulum. HSP47 is a collagen-binding stress protein and has been shown to be localized exclusively in the endoplasmic reticulum. Procollagen polypeptides form a complex with HSP47 in the endoplasmic reticulum, which plays an important role as a collagen-specific molecular chaperone in the intracellular processing/folding of procollagen molecules (23, 24). The crucial role of HSP47 in regulating biosynthesis of collagen molecules has been reported previously (25), and transcriptional regulation for HSP47 expression was clarified (26, 27). However, its role in kidney diseases in relation to sclerosis/fibrosis in diabetic nephropathy and IgA nephropathy is completely unknown. We and others (8, 28) have demonstrated that HSP47 in glomerulosclerosis is associated with collagen staining. Furthermore, the blocking of HSP47 with antisense
oligonucleotides caused a dramatic amelioration of glomerular lesions in the rat glomerulonephritis model (9). These findings suggest that HSP47 is a key factor in the development of various glomerular injuries. In this study, a close relationship of HSP47 to glomerulosclerosis in diabetic nephropathy was found.

The blocking of AGEs formation inhibited the overproduction of HSP47 and collagens, thereby suppressing the gene expression of type IV collagen, extracellular matrix accumulation, and glomerulosclerosis in diabetic nephropathy in vivo. AGEs also increased mRNA expression of both HSP47 and type IV collagen in vitro. Thus, our study implicates that AGEs are a key factor in the synthesis of both HSP47 and collagens in diabetic nephropathy in vivo and in vitro. The mechanism of these processes remains unclarified, but we demonstrated that AGEs stimulate several novel transcription factors in gene expression for glomerulosclerosis (5). We have recently reported that Smad1 transcriptionally regulates type IV collagen under AGE stimulation (14). Here, we also observed that the expression of HSP47 was regulated by Smad1 under AGE exposure. Yamamura et al. (29) has reported that TGF-β transcriptionally activates HSP47 gene expression. Thus, Smad1 may partially participate in the TGF-β-mediated up-regulation of HSP47.

It has been shown that TGF-β stimulates the production of extracellular matrix components including collagens and fibronectin and that it plays a key role in glomerulosclerosis (12). TGF-β regulates the expression of the collagen genes and their transcriptional activities. In particular, the promoter analysis of the collagen genes revealed that TGF-β1 regulates the transcription of collagen genes via several cis-elements of their promoters (13). TGF-β also increases HSP47 gene expression in other cell types (29). We first demonstrated that TGF-β stimulates not only collagen but also HSP47 in mesangial cells. In addition, we showed that c-Fos participates in the induction of...
TGF-β under AGE exposure. These data suggest that TGF-β and its signaling pathway are important targets for treating diabetic nephropathy.

Most experimental models of diabetic nephropathy are different from human pathological lesions (10, 30). On the other hand, the iNOSTg mice showed remarkably advanced glomerular lesions that resemble human diabetic glomerulosclerosis. From the analysis of this model, we confirmed that glomerular hypertrophy is important in the development of diabetic nephropathy because the iNOSTg mice showed glomerular hypertrophy in association with typical glomerulosclerosis. However, the intervention of AGE formation showed a decreased level of glomerulosclerosis with no evidence for diminished glomerular hypertrophy. The mechanism for this is unclear, but the regulation of HSP47 and collagens seemed to be independent of the control of glomerular hemodynamics. Further investigation will be needed to clarify the mechanism of these findings.

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