Free Radical Research, June 2011; 45(6): 728–734

informa
healthcare

Repression of apurinic/apyrimidinic endonuclease by p53-dependent apoptosis in hydronephrosis-induced rat kidney

IN YOUB CHANG[1,2], JIN NAM KIM[3], JAE YEOUL JUN[1,4], HO JIN YOU[1,5], YOUNG JIN JEON[1,5], KYEONG-SOO PARK[6] & SANG PIL YOON[1,7]

[1]*Korean DNA Repair Research Center,* [2]*Department of Anatomy, College of Medicine, Chosun University, Gwangju, Republic of Korea,* [3]*Department of Internal Medicine, Seoulpaik Hospital, Inje University College of Medicine, Seoul, Republic of Korea,* [4]*Department of Physiology,* [5]*Department of Pharmacology, College of Medicine, Chosun University, Gwangju, Republic of Korea,* [6]*Department of Preventive Medicine, College of Medicine, Seonam University, Namwon, Jeollabuk-Do, Republic of Korea, and* [7]*Department of Anatomy, School of Medicine, Jeju National University, Jeju-Do, Republic of Korea*

(Received date: 18 January 2011; Accepted date: 17 March 2011)

Abstract

p53 plays a major role in apoptosis through activation of pro-apoptotic gene Bax. It also regulates apurinic/apyrimidinic endonuclease (APE) expression in the base excision repair pathway against oxidative DNA damages. This study investigated whether p53-dependent apoptosis is correlated with APE using an experimental rat model of hydronephrosis. Hydronephrosis was induced by partial ligation of the right ureter. Animals were sacrificed on scheduled time after unilateral ureteral obstruction and the expression of 8-OHdG, γ-H2AX, apoptotic proteins and APE was determined. The accumulated p53 activated Bax and caspase-3 7 days after hydronephrosis induction and the resulting high levels of p53-dependent apoptotic proteins and γ-H2AX tended to decrease APE. The intensities of 8-OHdG and caspase-3 immunolocalization significantly increased in obstructed kidneys than in sham-operated kidneys, although APE immunoreactivity increased after hydronephrosis induction. These results suggest that oxidative DNA damages in obstructed kidneys may trigger p53-dependent apoptosis through repression of APE.

Keywords: *APE, apoptosis, hydronephrosis, p53*

Introduction

Obstructive uropathy refers to any obstruction of urinary flow. An established animal model of obstructive uropathy can be created by unilateral ureteric obstruction, which causes hydronephrosis (HN) [1,2], while the intact contralateral kidney undergoes compensatory growth [3,4]. HN may cause cell injury and death in all components of the nephron. Tubular apoptosis is a principal consequence of HN [2] and proximal tubular cells undergo necrosis also [5,6]. Reactive oxygen species (ROS) produced during the development of HN are thought to be at least partially responsible for apoptosis [7,8]. Caspase-dependent apoptosis in renal tubular cells has been linked to increases in oxidative stress [9].

The initial response to oxidative DNA damage is to repair the damage; however, with increasing levels of DNA damage the affected cell may switch to cell cycle arrest or apoptosis [10]. Recently, DNA double-strand breaks (DSB) were suggested to be the main mechanism of HN [11]. In that study, the expression of γ-H2AX, a DSB marker, increased with the level of the pro-apoptotic factor p53 3 weeks after the initiation of HN. Apoptotic responses did not prevent the development of HN, although similar results were also observed with non-homologous end joining (NHEJ), Ku70 and Ku80. The expression of these proteins in the tubules exceeded that in the glomeruli. However, the efficiency of NHEJ in DSB repair is poor in rat kidney and liver [12] and this could cause

Correspondence: Sang Pil Yoon, Department of Anatomy, School of Medicine, Jeju National University, Jeju-Do 690-756, Republic of Korea Tel.: +82-64-754-3823. Fax: +82-64-725-2593. Email: spyoon@jejunu.ac.kr

ISSN 1071-5762 print/ISSN 1029-2470 online © 2011 Informa UK, Ltd.
DOI: 10.3109/10715762.2011.574289

DNA damage in experimental HN. Thus, we hypothesized that a more effective DNA repair system should work against oxidative DNA damages in the kidney.

Base excision repair (BER) is a major DNA repair pathway protecting cells against single-base DNA damage due to oxidative stress [10]. In response to ROS-induced DNA damage, 8-oxo-deoxyguanine (8-oxodG) is produced and the damage is repaired primarily via 8-oxoguanine-DNA glycosylase (Ogg1). An apurinic/apyrimidinic (AP) site can also be generated by oxidative stress and AP endonuclease (APE or redox factor-1) is involved in BER. APE is a multifunctional protein that acts as a transcriptional regulator of p53 [10,13] and as a *trans*-acting factor in repression of the human renin gene [14]. A recent study [15] of human embryonic kidney 293 cells suggested that APE is required for cellular defense responses and that silencing of APE increases apoptosis following oxidative stimulation.

Previous studies have suggested that renal tubular apoptosis and APE are associated with experimental HN, because APE is expressed ubiquitously at a relatively high level in the rat kidney [16]. Transforming growth factor-β1 (TGF-β1) mediates the injurious effects of obstructive uropathy [17] through p53, which is a major protein involved in cellular apoptosis via activation of the pro-apoptotic gene, Bax [18,19] and also regulates APE expression [20]. Therefore, we hypothesized that there is a close relationship between APE and p53 in the development of HN. We investigated whether p53-dependent apoptosis is correlated with the appearance of APE and in which cells oxidative damage, apoptosis and APE appear in response to obstructive nephropathy.

Materials and methods

Animals and treatments

The experiments were performed using 3-month-old male Sprague-Dawley rats (Experimental Animal Center, Chosun University, Gwangju, Republic of Korea). The animals were housed under standard conditions in a controlled environment with a 12-h dark–light cycle, with free access to food and water *ad libitum*. All experimental procedures and care of animals were conducted in accordance with the guidelines of Chosun University's Animal Care and Use Committee.

An HN model was created as previously described [11,21]. Briefly, rats were anaesthetized by intraperitoneal injection with sodium pentobarbital (30 mg/kg) before midline laparotomy. The right ureter was exposed and partially ligated to an external diameter of 50% of its original size with a 3-0 silk suture, which was made by a metal probe of 0.8 mm in diameter and placed at the transition of the proximal to distal ureter. After tying the ligature, the probe was carefully removed and the ureter was allowed to expand against the loop of the suture.

A sham-operation was performed in the same way, except for the ligation. The kidneys of the sham-operated rats and the contralateral kidneys of the rats with obstructive uropathy served as controls. The results were evaluated 1 week after the induction of HN by Western blotting and immunohistochemistry. The time course of developing HN was established by sacrificing rats 3, 5 and 7 days after the surgery.

Antibodies

The primary antibodies used in this study were: polyclonal anti-p53 (1:500; Santa Cruz biotechnology Inc., Santa Cruz, CA), polyclonal anti-Bax (BD Bioscience Pharmingen, San Diego, CA), polyclonal anti-cleaved caspase-3 (Cell Signaling Technology Inc. Danvers, MA), monoclonal anti-Ku70 (BD Bioscience Pharmingen), monoclonal anti-phospho-Histone H2AX (γ-H2AX, Millipore, Billerica, MA), monoclonal anti-APE (Santa Cruz Biotechnology Inc.), monoclonal anti-8-hydroxy-2'-deoxyguanosine (8-OHdG, JaICA, Shizuoka, Japan) and polyclonal anti-β-actin (1:1000; Santa Cruz Biotechnology Inc.).

Western blotting

Isolated kidney sections were suspended in 1 ml of cold homogenizing buffer (20 mM HEPES (pH 7.4), 2 mM EGTA, 50 mM glycerol phosphate, 1% Triton X-100, 10% glycerol, 1 mM dithiothreitol, 1 mM phenylmethylsulphonyl fluoride, 10 g/ml leupeptin, 10 g/ml aprotinin, 1 mM Na_3VO_4 and 5 mM NaF) containing a protease inhibitor cocktail (Roche Diagnostics, Mannheim, Germany) and homogenized three times using an ultrasonic cell disruptor (Branson Ultrasonics Co., Danbury, CT) for 30 s in 30 s intervals, then centrifuged at 10 000 × *g* for 10 min at 4°C. The protein concentrations of the supernatants were determined using a Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). An aliquot of the supernatant (30 μg protein) was then suspended in 20 μl loading buffer composed of a 1:1 mixture (v/v) of the above homogenizing buffer and sample buffer (50 mM Tris–HCl (pH 6.5), 0.5 mg/ml bromophenol blue, 10% glycerol, 10% SDS and 1% β-mercaptoethanol). This was then boiled for 5 min at 100°C, subjected to 10% SDS-PAGE and transferred to polyvinyldifluoridine membranes (GE Healthcare Bio-Sciences Corp., Piscataway, NJ).

Immunoblotting was carried out with each primary antibody. The horseradish peroxidase-linked secondary antibodies (GE Healthcare Bio-Sciences Corp.) were diluted 1:4000. The blotted proteins were then detected using the iNtRON Biotech Enhanced Chemiluminescence Detect System (Seoul, Republic of Korea) and quantified using ImageQuant 350

(GE Healthcare Korea, Seoul, Republic of Korea). The data expressed as densitometric units of each primary antibody relative to β-actin and in reference to the value of the control sample for each gel.

Cytoarchitecture and immunohistochemistry

After fixation with 4% paraformaldehyde, the kidneys were embedded in paraffin wax (Tissue-Tek, Sakura, Japan) using standard procedures. Next, 5-μm-thick serial sections were cut using a Leica RM 2155 rotary microtome (Nussloch, Germany) and mounted on slides coated with 3-aminopropyl-tri-ethoxy-silane (Sigma-Aldrich, St Louis, MO). Randomly selected samples were stained with the Harris's haematoxylin and eosin (Sigma-Aldrich) for 4 min and 20 s, respectively, using a routine protocol.

Immunohistochemical staining was carried out by the routine method. In brief, incubation with primary antibodies was performed for 48 h at 4°C. The binding was visualized using an ImmPRESS™ avidin-biotin-peroxidase kit (Vector Laboratories Inc., Burlingame, CA) according to the manufacturer's instructions. Omission of incubation with the primary or secondary antibody served as a control for false-positives. Immunolabelled images were captured directly using a C-4040Z digital camera and Olympus BX-50 microscope (Olympus Corp., Tokyo, Japan). The captured images were saved and subsequently processed using Adobe Photoshop (Adobe System, San Jose, CA). The brightness and contrast of the images were adjusted only for the purpose of background consistency.

Statistical analysis

Three independent densitometric results are expressed as mean ± SE. Statistical significance was assessed by one-way analysis of variance (ANOVA) with Bonferroni test between time courses. All statistical analyses were conducted using SPSS, version 12.0 (SPSS, Chicago, IL). A p-value of less than 0.05 was taken as statistically significant.

Results

Experimental HN resulted in cyst formation in ipsilateral kidney (Figure 1A) with tubular dilatation, flattening of the epithelium and deterioration of the glomeruli (Figure 1C). No significant changes were

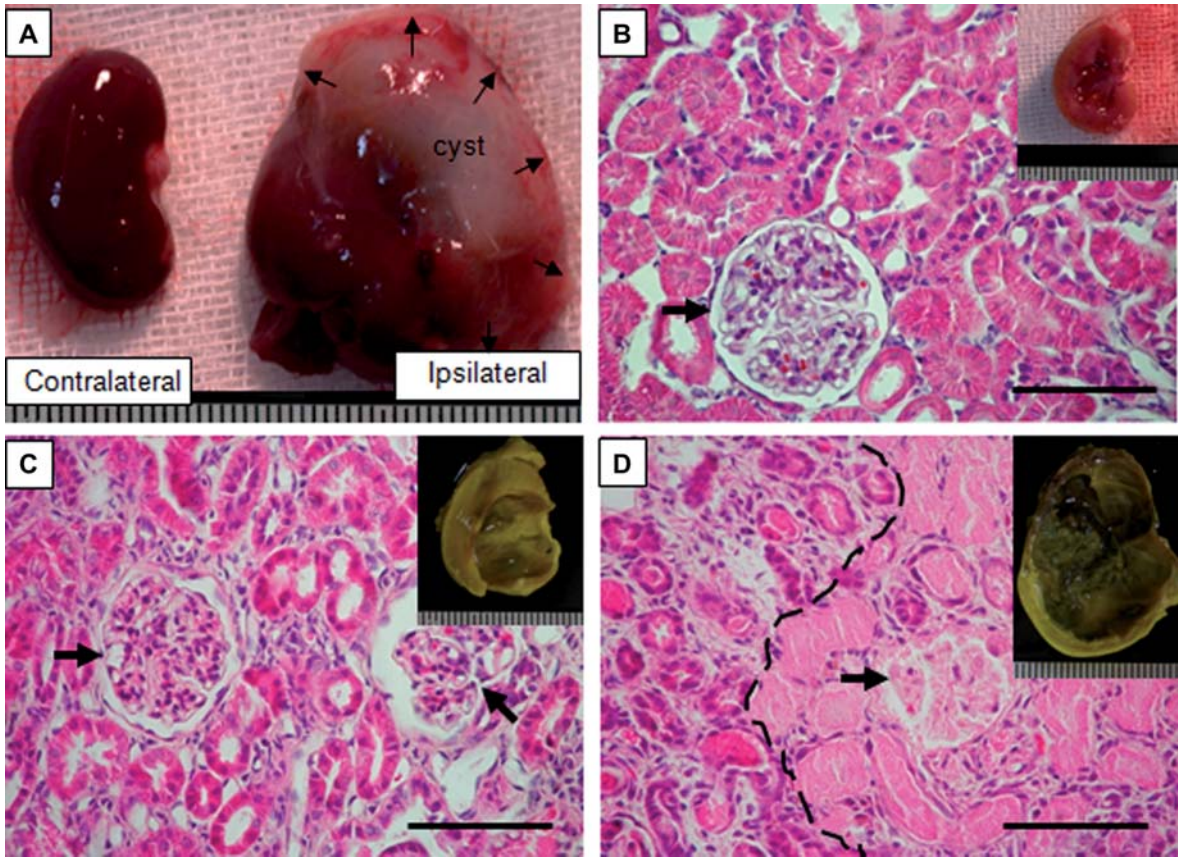

Figure 1. Macroscopic and microscopic features of experimental hydronephrosis. Partial ureteric obstruction caused cyst formation (arrows in A) in the ipsilateral kidney but had little effect on the contralateral kidney (A) 1 week after surgery. Compared to control kidneys (B), obstructed kidneys showed degenerative changes in the glomeruli (arrows in B and C) and tubules of the renal cortex. Note the dilated lumen of distal tubules and collecting ducts (C). Cell deaths (dotted line) were the main finding 3 weeks after surgery (D). SB = 100 μm.

noted 1 week after surgery in the sham-operated and contralateral kidneys (Figure 1B). Time-dependent cystic changes were not observed until 3 weeks after the induction of experimental HN, but cell deaths in all components of the nephron were noted (Figure 1D).

In the second part of the study, Western blot analysis (Figure 2) and immunohistochemistry (Figure 3) were done 1 week after surgery. p53, Bax and cleaved caspase-3 were higher in ipsilateral kidneys than in sham-operated and contralateral kidneys (Figure 2, left column). Similary γ-H2AX, Ku70 and APE were higher in ipsilateral kidneys during the development of HN (Figure 2, right column). Neither apoptotic proteins nor DNA repair proteins changed considerably in contralateral kidneys after HN induction. Immunohistochemical markers for 8-OHdG, cleaved caspase-3 and APE were mainly seen in the distal tubules and collecting ducts of sham-operated kidneys (Figure 3, left column). Immunolocalizations were noted across the entire nephron, including the glomeruli and proximal tubules, in ipsilateral kidneys during HN (Figure 3, right column).

Lastly, we observed a trend toward a negative correlation among apoptotic proteins (Figure 4, upper column), γ-H2AX and APE in developing HN (Figure 4, lower column). The level of p53 rose during the course of the experiment; however, the change was not statistically significant. The level of Bax significantly increased after 7 days (1.93 ± 0.03) compared to the sham-operated kidneys. The cleaved caspase-3 level rose considerably 3 days (1.63 ± 0.38) and 7 days (4.2 ± 0.55) after HN surgery compared to sham-operated kidneys and 3 days compared to 7 days after HN creation, respectively. As a consequence, the level of p53-dependent caspase-3 activation was considerable 7 days after surgery, when APE decreased. Densitometric results showed that APE was significantly elevated 3 days (1.63 ± 0.09) after HN induction, but considerably lower 7 days (1.13 ± 0.12) after HN surgery compared to 3 days after HN operation. γ-H2AX tended to increase until 7 days (2.57 ± 0.34) after HN surgery, significance was observed compared to sham-operated kidneys and 5 days (1.17 ± 0.23) after HN induction.

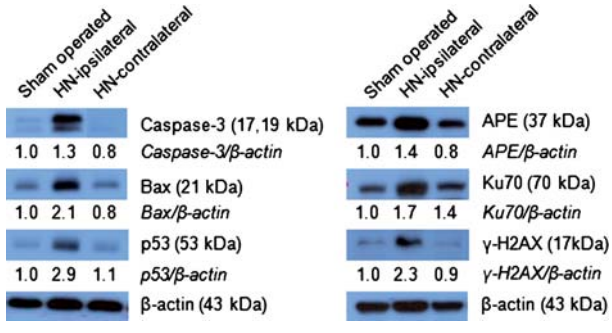

Figure 2. Western blot analysis 1 week after experimental hydronephrosis (HN) induction. HN caused the up-regulation of p53, Bax, caspase-3 (left column), γ-H2AX, Ku70 and APE (right column). These proteins were not considerably affected in sham-operated and contralateral kidneys.

Discussion

This report is the first to show that BER is associated with experimental HN, suggesting that repression of APE by augmented p53 level may play a role in obstructed rat kidneys. Elevated levels of γ-H2AX increase the likelihood of apoptosis by p53 augmentation, which showed a negative correlation with APE in developing HN. At the end of the experiment, the accumulated p53 activated pro-apoptotic factor Bax and effector caspase-3. With the high levels of p53-dependent apoptotic proteins and γ-H2AX, the expression of APE tended to decrease in developing HN. This result was reinforced by the immunohistochemical findings for 8-OHdG, caspase-3 and APE. Collectively, these results suggest that oxidative DNA damages in developing HN may trigger p53-dependent apoptosis through the repression of APE.

Oxidative stress has been identified as important in a variety of diseases. Major cellular strategies have evolved for coping with oxidative DNA damage, repair and removal [10]. Various DNA repair pathways are activated upon DNA damage. The DNA-binding proteins Ku70 and Ku80 are centrally involved in NHEJ, which has been investigated in experimental HN and found to be ineffective at preventing cellular injury [11]. Ogg1 and APE are major proteins in BER that protect cells against oxidative DNA damage [10,13]. A decrease in Ogg1 activity is accompanied by increased 8-oxodG production, resulting in degenerative changes in ischemia-reperfusion of the kidney [22], diabetic nephropathy [23] and renal tumours [24]. However, the protective effects of Ogg1 in obstructive uropathy have not been demonstrated. Contrary to Ogg1, the kidneys contain relatively high levels of APE [16]. In the present study, early during the development of HN, augmented APE was associated with relatively low levels of p53, Bax and caspase-3, whereas augmented γ-H2AX was observed. Hence, APE might have renoprotective effects against developing HN by blocking p53-dependent apoptosis.

Increased APE might protect the kidneys in developing HN through various pathways, including BER. The production of angiotensin in obstructed kidneys is thought to increase during oxidative stress and contribute to tubular cell death via the induction of TGF-β1 [1,2]. Anti-angiotensin treatment in rats with obstructive nephropathy has been shown to have positive effects [25,26] or no effect [21,27] on renal deterioration. Nonetheless, the anti-renin effect of APE [14] is worth noting. APE could suppress renin expression, resulting in inactivation of the renin-angiotensin system and reduced hypoxic injury.

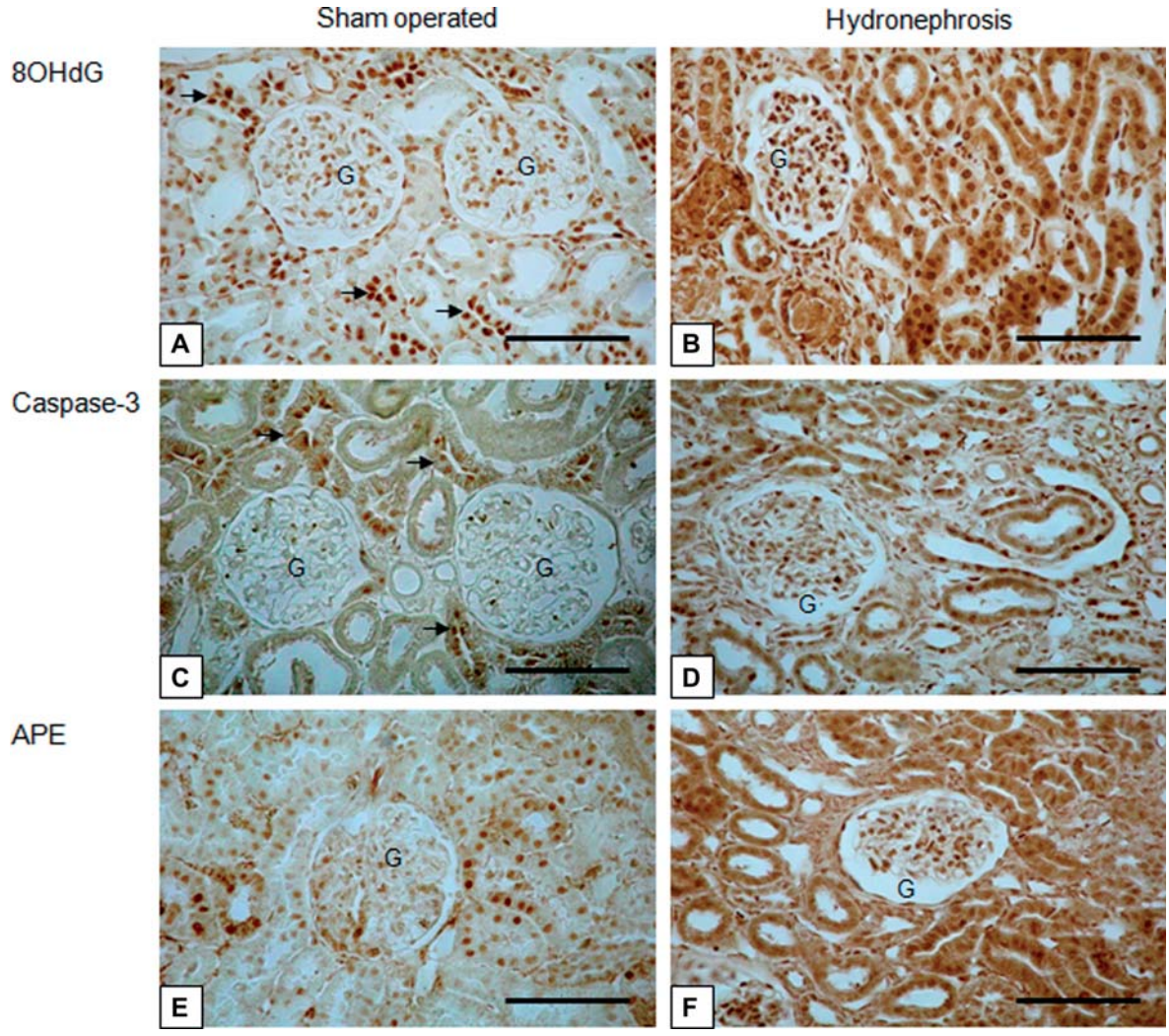

Figure 3. Immunohistochemical analysis of 8-OHdG, caspase-3 and APE 1 week after experimental hydronephrosis (HN) induction. Oxidative damage (8-OHdG, A) and apoptotic signals (cleaved caspase-3, C) were mainly seen in the distal tubules (arrows) of normal renal cortex, whereas DNA repair activity (APE, E) was ubiquitously distributed. HN (B, D, F) caused increased immunolocalization of all the parameters in the distal tubules, proximal tubules and glomeruli (G). SB = 100 μm.

However, the time-dependent decrease in APE observed in HN may not repress renin expression. Therefore, increased angiotensin causes vasoconstriction and hypoxia in obstructed kidneys as previously reported. In this context, the present study suggests that APE might play a role in maintaining renal function and that the induction of APE could be a useful treatment strategy in renal diseases.

A recent report [15] demonstrated that silencing of APE increases Bax, resulting in the activation of caspase-3 in human embryonic kidney cells. Renal tubular apoptosis in experimental HN is also activated by a p53-dependent caspase pathway or enhanced by the down-regulation of survival factors [1,2]. Activated p53 mediates Bax [18,19] and APE expression [20], although APE is a regulator of p53 transcription [10,13]. Our results also supported the notion that p53 activated Bax, resulting in caspase cascades at the end of the experimental period. The intensity of 8-OHdG immunolocalization was significantly higher in the nephrons of the animals with HN compared to sham-operated kidney, although APE immunoreactivity increased after surgery. This finding is reinforced by the fact that caspase-3 immunolocalization was only seen in the distal tubules and collecting ducts in sham-operated kidneys, compared to all parts of the nephron in HN. These results indicate that the level of APE was not sufficient to repair the degree of oxidative DNA damage in HN.

In summary, this study demonstrated that p53-dependent apoptosis is correlated with HN and that it causes increased 8-OHdG and cleaved caspase-3 in all components of the nephron. Apoptosis was stimulated by suppressed APE activation contrary to the increases in p53, Bax, cleaved caspase-3 and γ-H2AX seen in HN. Although p53 and APE can be induced by oxidative stress, they might be inversely correlated with HN. This study might extend our understanding of the apoptotic responses induced by obstructive nephropathy; however, additional studies are needed

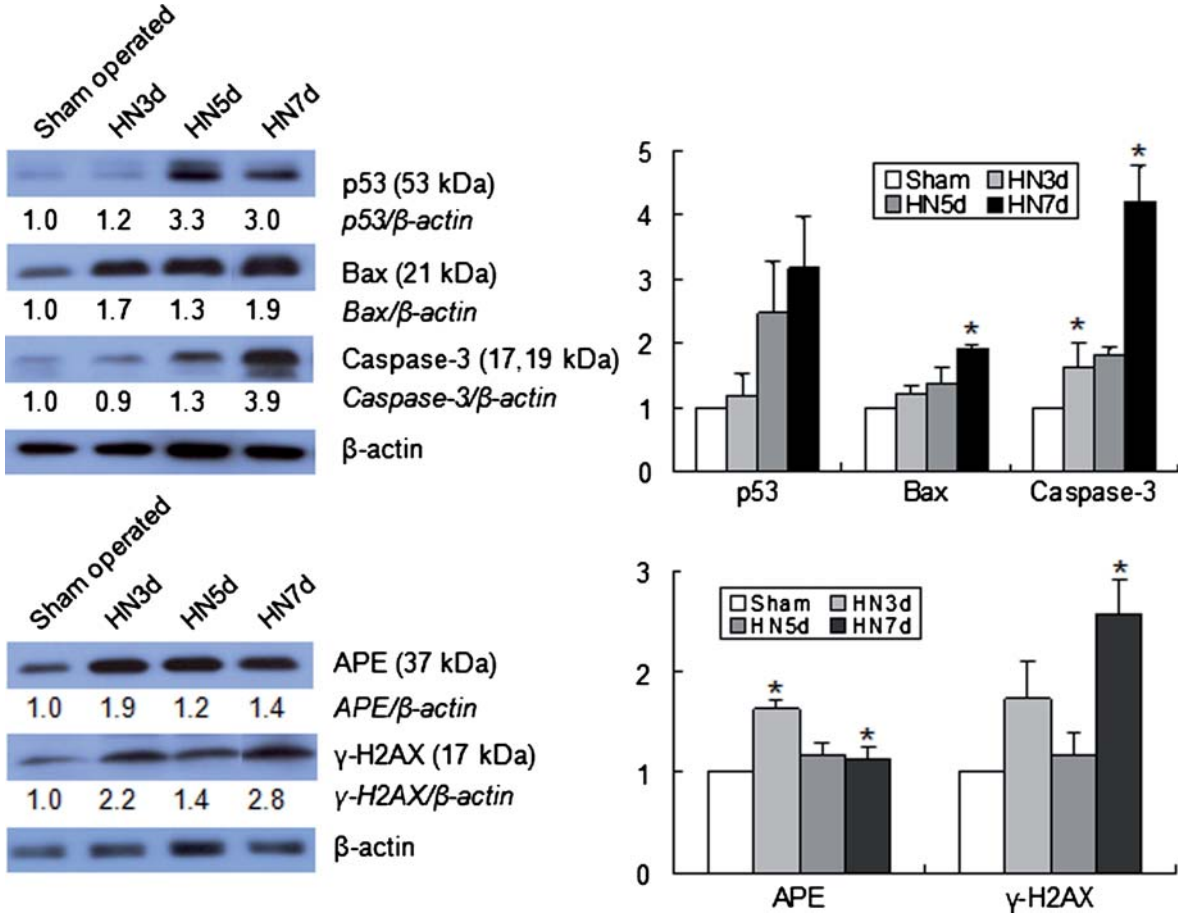

Figure 4. Western blot analysis and densitometric results after experimental hydronephrosis (HN) induction. Apoptosis-related protein levels increased up to 7 days after HN induction, with significance for Bax and cleaved caspase-3. Note the negative correlation between γ-H2AX and APE in developing HN. APE was considerably higher 3 days after HN surgery and lower 7 days after HN induction, whereas γ-H2AX was significantly elevated 7 days after HN surgery. $^{*}p < 0.05$.

to elucidate the multifunctional roles of APE in various renal diseases.

Acknowledgements

We thank Professor Hyung Youn Moon (Department of Urology, College of Medicine, Chosun University) for establishing the hydronephrosis model. This study was supported by research grant by Korea Government, Ministry of Education, Science and Technology (2010-0002099).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Chevalier RL. Pathogenesis of renal injury in obstructive uropathy. Curr Opin Pediatr 2006;18:153–160.

[2] Docherty NG, O'Sullivan OE, Healy DA, Fitzpatrick JM, Watson WG. Evidence that inhibition of tubular cell apoptosis protects against renal damage and development of fibrosis following ureteric obstruction. Am J Physiol Renal Physiol 2006;290:F4–F13.

[3] Chevalier RL, Thornhill BA, Wolstenholme JT, Kim A. Unilateral ureteral obstruction in early development alters renal growth: dependence on the duration of obstruction. J Urol 1999;161:309–313.

[4] Hauser P, Kainz A, Perco P, Bergmeister H, Mitterbauer C, Schwarz C, Regele HM, Mayer B, Meyer TW, Oberbauer R. Transcriptional response in the unaffected kidney after contralateral hydronephrosis or nephrectomy. Kidney Int 2005; 68:2497–2507.

[5] Cachat F, Lange-Sperandio B, Chang AY, Kiley SC, Thornhill BA, Forbes MS, Chevalier RL. Ureteral obstruction in neonatal mice elicits segment-specific tubular cell responses leading to nephron loss. Kidney Int 2003;63:564–575.

[6] Thornhill BA, Forbes MS, Marcinko ES, Chevalier RL. Glomerulotubular disconnection in neonatal mice after relief of partial ureteral obstruction. Kidney Int 2007;72:1103–1112.

[7] Sunami R, Sugiyama H, Wang DH, Kobayashi M, Maeshima Y, Yamasaki Y, Masuoka N, Ogawa N, Kira S, Makino H. Acatalasemia sensitizes renal tubular epithelial cells to apoptosis and exacerbates renal fibrosis after unilateral ureteral obstruction. Am J Physiol Renal Physiol 2004;286: F1030–F1038.

[8] Pat B, Yang T, Kong C, Watters D, Johnson DW, Gobe G. Activation of ERK in renal fibrosis after unilateral ureteral obstruction: modulation by antioxidants. Kidney Int 2005; 67:931–943.
[9] Power RE, Doyle BT, Higgins D, Brady HR, Fitzpatrick JM, Watson RW. Mechanical deformation induced apoptosis in human proximal renal tubular epithelial cells is caspase dependent. J Urol 2004;171:457–461.
[10] Bernstein C, Bernstein H, Payne CM, Garewal H. DNA repair/pro-apoptotic dual role proteins in fibe major DNA repair pathways: fail-sale protection against carcinogenesis. Mutat Res 2002;511:145–178.
[11] Moon C, Moon HY, Kim CS. The expressions of p53, γ-H2AX and Ku70/Ku80 that was caused by hydronephrosis in the kidney of rats. Korean J Urol 2007;48:976–983.
[12] Sharma S, Choudhary B, Raghavan SC. Efficiency of nonhomologous DNA end joining varies among somatic tissues, despite similarity in mechanism. Cell Mol Life Sci 2011;68:661–676.
[13] Tell G, Quadrifoglio F, Tiribelli C, Kelley MR. The many functions of APE1/Ref-1: not only a DNA repair enzyme. Antioxid Redox Signal 2009;11:601–620.
[14] Fuchs S, Philippe J, Corvol P, Pinet F. Implication of Ref-1 in the repression of rennin gene transcription by intracellular calcium. J Hypertens 2003;21:327–335.
[15] Xiong JJ, Zhang Y, Wang JL, Bao GD, Zhang Y, Zhu ZY. Silencing of Ref-1 expression by retrovirus-mediated shRNA sensitizes HEK293 cells to hydrogen peroxide-induced apoptosis. Biosci Biotechnol Biochem 2008;72:3206–3210.
[16] Tan Y, Nakagawa Y, Akiyama K, Wakabayashi H, Sarker AH, Seki S. cDNA cloning of rat major AP endonuclease (APEX nuclease) and analyses of its mRNA expression in rat tissues. Acta Med Okayama 1996;50:53–60.
[17] Chevalier RL, Cachat R. Role of angiotensin II in chronic ureteral obstruction. In: Wolf G, editor. The renin-angiotensin system and progression of renal diseases, edn 1. Basel: Karger; 2001. p 250–260.
[18] Lane DP. p53, guardian of the genome. Nature 1992;358: 15–16.

This paper was first published online on Early Online on 18 April 2011.

[19] Chipuk JE, Bouchier-Hayes L, Kuwana T, Newmeyer DD, Green DR. PUMA couples the nuclear and cytoplasmic proapoptotic function of p53. Science 2005;309:1732–1735.
[20] Zaky A, Busso C, Izumi T, Chattopadhyay R, Bassiouny A, Mitra S, Bhakat KK. Regulation of the human AP-endonuclease (APE/Ref-1) expression by the tumor suppressor p53 in response to DNA damage. Nucleic Acids Res 2008;36:1555–1566.
[21] Radovic N, Cuzic S, Knotek M. Effect of unilateral ureteral obstruction and anti-angiotensin II treatment on renal tubule and interstitial cell apoptosis in rats. Croat Med J 2008;49: 600–607.
[22] Tsuruya K, Furuichi M, Tominaga Y, Shinozaki M, Tokumoto M, Yoshimitsu T, Fukuda K, Kanai H, Hirakata H, Iida M, Nakabeppu Y. Accumulation of 8-oxoguanine in the cellular DNA and the alteration of the OGG1 expression during ischemia-reperfusion injury in the rat kidney. DNA Repair (Amst) 2003;2:211–219.
[23] Simone S, Gorin Y, Velagapudi C, Abbound HE, Habib SL. Mechanism of oxidative DNA damage in diabetes: tuberin inactivation and downregulation of DNA repair enzyme 8-oxo-7,8-dihydro-2'-deoxyguanosine-DNA glycosylase. Diabetes 2008;57:2626–2636.
[24] Habib SL, Simone S, Barnes JJ, Abboud HE. Tuberin haploinsufficiency is associated with the loss of OGG1 in rat kidney tumors. Mol Cancer 2008;7:10.
[25] Jones DA, Shahed J, Shoskes DA. Modulation of apoptotic and inflammatory genes by bioflavonoids and angiotensin II inhibition in ureteral obstruction. Urology 2000; 56:346–351.
[26] Satoh M, Kahihara N, Yamasaki Y, Maruyama K, Okamoto K, Maeshima Y, Sugiyama H, Sugaya T, Murakami K, Makino H. Renal interstitial fibrosis is reduced in angiotensin II type 1a receptor-deficient mice. J Am Soc Nephrol 2001;12:317–325.
[27] Chen CO, Park MH, Forbes MS, Thornhill BA, Kiley SC, Yoo KH, Chevalier RL. Angiotensin-converting enzyme inhibition aggravates renal intersticial injury resulting from partial unilateral ureteral obstruction in the neonatal rat. Am J Physiol Renal Physiol 2007;292:F946–F955.