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Cell proliferation and apoptosis in Wistar rat kidney after renal mass ablation and low-dose irradiation

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Key words: *remnant kidney; rat; low-dose radiation; cell proliferation; apoptosis.*

Summary. *Cell proliferation and apoptosis in the remnant rat kidney after treatment with low-dose irradiation was investigated.*

Material and methods. In the first group (n=9), adult male Wistar rats underwent 5/6 nephrectomy (NPX); in the second group (n=9), NPX was combined with low-dose irradiation. Rats without surgery and irradiation formed the control group (n=9).

Results. Hypertension and proteinuria induced by NPX were decreased by 3-Gy irradiation. The 5/6 NPX rats showed a dramatic increase in proliferating and apoptotic cells in the glomeruli and in the distal tubules at week 2, which was significantly decreased by low-dose irradiation.

Conclusion. The data demonstrate that low-dose irradiation is a factor slowing the process of chronic renal injury.

Introduction

During the last years, the understanding of pathophysiological processes leading to the progression of chronic renal disease has significantly changed and advanced (1). Irrespective of the renal primary detractive mechanism, immune or nonimmune, the remaining parts of the kidney undergo adaptive changes. A critical amount of nephrons are destroyed during the development of chronic renal disease (2), but the remaining ones undergo compensatory changes. Many experiments demonstrate that alterations in glomerular hemodynamics associated with renal ablation are accompanied by structural lesions and changed single nephron hyperfiltration (1, 2). Five-sixths nephrectomy (5/6 NPX) is a very useful and widely studied model for the analysis of progression of chronic renal disease (3, 4). Experimental studies incriminate glomerular hypertension in mediating progressive renal damage after any of a variety of initiating injuries (5, 6). The main mechanisms involved in this process can be different: hemodynamic (7), cellular (1), or molecular (7). Alterations appearing as a result of 5/6 nephrectomy in the remnant kidney give a possibility to study various aspects of the damage (4). Nowadays, knowing the pathogenesis of glomerulosclerosis (8), it is theoretically possible to slow down the process of fibrinogenesis (9), but it is complicated as many factors participate in the process: various interleukins in early stages (9), chemokines (10), cytokines, and growth factors (11). Later structural changes appear in tissues, which will lead to pathological changes in physiological functions of the organ (12). Few effective possibilities exist to mimic early alterations in the kidney with the exception of compounds blocking the renin-angiotensin system (13). It is known from literature that as a result of radiation in therapeutic doses, radiation nephropathy develops in the kidneys (14, 15), but the use of low-dose radiation to slow down the progression of renal disease has been studied insufficiently (16). In our previous studies (17), we investigated the effect of low-dose irradiation on the development of chronic kidney disease, and based on our results, it had a renoprotective effect on the kidneys. Chronic renal disease is characterized by perishing of the cells in renal tissue. This process is a particular type of cell death, which has several distinguishing features from necrosis, and is often referred to as programmed cell death or apoptosis (18). Typical patomorphological changes are observed during this process in the tubular epithelial and mesangial cells (8). Apoptosis plays an important role in the regulation of the number of renal cells in the diseased kidneys (19). When the structure of glomerular basement membrane (GBM) is altered, GBM is not able to prevent the passage of proteins with a large molecular mass and diameter, which leads to proteinuria.

Assuming that low-dose irradiation diminishes apoptotic changes in the early stages of chronic kid-

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ney disease, we investigated the expression of proliferative and apoptotic cells in the remnant kidney after experimental renal 5/6 nephrectomy.

Material and methods

Experimental design and animals. Adult male Wistar rats (Laboratory Animal Center, University of Kuopio, Finland) were studied. An acclimatization period of 10 days was allowed before any experimental work was undertaken. Rats were kept in a climate-controlled facility at the Faculty of Medicine, University of Tartu, where animals were housed under standard conditions on a 12-h light/dark cycle and fed with standard rodent chow (70, Lactamin AB, Sweden) and tap water *ad libitum*. At approximately 8 weeks of age, rats weighing 240–262 g were anesthetized with intraperitoneal methohexital sodium (5 mg per 100 g body weight [BW], Brietal, LILLY GmbH, Germany). Renal ablation was then accomplished by right nephrectomy and selective ligation of extrarenal branches of the left renal artery. All together 18 rats were randomized after the surgery, divided into two groups, and studied during two weeks: 5/6 NPX–2wk (n=9), 5/6 NPX + 3 Gy–2wk (n=9). The left kidney of 3 Gy group rats was irradiated (^{60}Cobalt) 24 hours after surgery in anesthetized (Brietal) animals with 3 Gy in a single dose in the Clinic of Radiology, Tartu University Hospital. Healthy Wistar rats (n=9, without surgery) were studied as controls. All animal procedures were approved by the Animal Care Committee, University of Tartu, in accordance with the European Communities Directive of November 24, 1986 (86/609/EEC).

Analysis of kidney function. Systolic blood pressure (SBP, mm Hg) was measured weekly by the tail-cuff method (Harvard Apparatus, USA) in awake, prewarmed rats at weeks 1 and 2. Animals were placed in metabolic cages for 24 h for urine collection, and urine protein and serum creatinine were measured with a Hitachi 912 analyzer. Animals were killed at week 2, and the kidneys were harvested for analysis of sclerosis, apoptosis and immunohistochemical studies.

Morphological analyses. Kidney tissue was fixed in 4% formalin (for light microscopy) or 4% paraformaldehyde solution (for detection of apoptosis and immunohistochemistry) and routinely processed. Four-μm sections were stained with hematoxylin-eosin and periodic acid-Schiff. A semiquantitative score was used to evaluate the degree of focal segmental glomerulosclerosis (FSGS). Sclerosis was defined as a collapse of glomerular capillary tuft accompanied by hyaline material. The severity of sclerosis for each glomerulus was graded for the presence of FSGS according to the following scale: 0, no evidence of focal segmental glomerulosclerosis; I, <25% involvement; II, 25–50% involvement; III, >50% involvement of the glomerulus, respectively. Two independent observers in a blinded fashion performed the evaluations. An Olympus BX-50 microscope was used for viewing and photographing.

Immunohistochemistry. Proliferating cells were identified by the expression of proliferating cell nuclear antigen (PCNA). Three-μm cryostat sections were incubated with the purified hamster antimouse monoclonal antibodies to PCNA (BD, PharMingen, USA), diluted in phosphate-buffered saline pH 7.4 (PBS) 1:50, for 30 min at room temperature. Slices were washed in PBS (3 times) and incubated with FITC-conjugated antihamster IgG monoclonal antibodies (diluted 1:50, BD, PharMingen, USA) for 30 min at room temperature. Negative controls with nonspecific antisera instead of primary antibody were done at the same time and showed no staining. For immunofluorescence, sections were examined at a magnification of ×100, ×368 with a Zeiss Axiophot 2 microscope. The results were evaluated according to the following scale: 0, none; 1+, isolated staining in less than 25% of the glomeruli; 2+, staining in 25 to 50% of the glomeruli; 3+, staining in 50 to 75% of the glomeruli; 4+, staining present in more than 75% of the glomeruli. Two independent observers in a blinded fashion performed the evaluations.

Detection of apoptosis. Apoptotic cells were detected by the transferase-mediated dUTP nick-end labeling (TUNEL) method using in situ cell death detection kit (POD Cat No. 1684817 Roche Diagnostics, Roche, Germany). Briefly, 4-μm paraformaldehyde-fixed sections were deparaffinized and rehydrated in graded ethanol and PBS. Samples were pretreated by incubation with proteinase K (2 μg/mL; Roche Diagnostics GmbH, Mannheim, Germany) for 15 min at room temperature. Endogenous peroxidase was inactivated by 3% H_2O_2 (Merck, Germany) in PBS for 30 min, and sections were rinsed with PBS, immersed in citrate buffer pH 6.0, and then incubated with TdT and digoxigenin dUTP (diluted 1:1) at 37°C for 60 min. Then the reaction was stopped with buffer, and antidigoxigenin peroxidase conjugate was applied and incubated for 30 min. The slides were developed by using diaminobenzidine substrate. For negative control, slides were incubated with TdT buffer without TdT. As a positive control, slides were treated with DNase (1 μg/mL; Sigma, St. Louis, USA) for 10 min. Cell apoptosis in the cortex of the kidney was assessed by scoring the TUNEL-positive cells in the glomeruli at ×100 magnification in all glomeruli in each section. TUNEL-positive staining was graded from 0

to 4: 0, none; 1+, isolated staining in less than 25% of the TUNEL-positive cells; 2+, staining in 25 to 50% of the TUNEL-positive cells; 3+, staining in 50 to 75% of the TUNEL-positive cells; 4+, staining present in more than 75% TUNEL-positive cells. Two independent observers in a blinded fashion performed the evaluations. Sections were examined at a magnification of ×100, ×368 with a Zeiss Axiophot 2 microscope.

Statistical analysis. Data are presented as mean values ± SEM. Data were analyzed by one-way ANOVA.

Results

SBP and renal function. At week 1, SBP was increased in 5/6 NPX + 3 Gy group rats, but not in rats of the 5/6 NPX group. At week 2, SBP was clearly increased in the 5/6 NPX group, while in the 5/6 NPX + 3 Gy group, SBP increase was lower (Table 1).

To assess renal function, the levels of proteinuria and serum creatinine were determined. Twenty-four-hour urinary protein excretion was increased in both the operated groups. Maximal effects on proteinuria were seen in the 5/6 NPX group animals, but rats irradiated with 3 Gy showed lower levels of proteinuria (Table 1). Serum creatinine at week 2 was significantly higher in the 5/6 NPX group as compared to the 5/6 NPX + 3 Gy group (Table 1).

Morphological analyses. Morphological studies demonstrate that glomerular changes were associated with renal mass ablation. The FSGS increased significantly in the 5/6 NPX group (Table 2; Fig. A) as compared to the control group. In the 5/6 NPX + 3 Gy group, FSGS was decreased as compared to the 5/6 NPX group (Table 2; Fig. B).

Immunohistochemistry. The 5/6 nephrectomized rats showed a dramatic increase of PCNA-positive cells in glomeruli at week 2 (Table 2; Fig. C). The mean number of positive cells per glomerular cross section was determined by evaluating 15–20 glomeruli. PCNA positivity was present in the glomerular epithelial cells, mesangial area, and also in tubules (Table 2). In contrast, all irradiated rats showed significantly fewer PCNA-positive cells at week 2 than the 5/6 NPX group (Table 2; Fig. D). Glomerular cell proliferation was negative in the glomeruli and distal tubules of healthy rats (Table 2).

Apoptosis. Apoptotic cells were detected in the glomerular and epithelial cells of the remnant kidneys by the TUNEL method. The number of apoptotic cells was significantly increased in the 5/6

Table 1. Systolic blood pressure, proteinuria, and serum creatinine in the experimental groups

Group	SBP (mm Hg) week 1	SBP (mm Hg) week 2	Proteinuria (g/24 h) week 1	Proteinuria (g/24 h) week 2	Serum creatinine (μmol/L)
5/6 NPX	106.8±1.41[a,b]	146.5±4.17[b]	12.9±1.96	36.1±3.4[a]	103.3±2.6[a]
5/6 NPX + 3 Gy	128.9±1.71[c]	139.4±2.99[c]	12.6±5.9	17.7±3.2	73.6±1.9
Control	113.1±2.7	116.0±2.63	0	0	0

Values are given as mean±SEM. Statistically significant differences (at $P \leq 0.05$) are shown as folows: [a]5/6 NPX group vs. 5/6 NPX + 3 Gy group; [b]5/6 NPX vs. control; [c]5/6 NPX + 3 Gy group vs. control. ANOVA was used for intergroup comparison among groups (Tukey and Dunnett tests).

Control, healthy animals (rats without surgery and irradiation); 5/6 NPX, nephrectomized rats; 5/6 NPX + 3 G, nephrectomized rats with irradiation.

Table 2. Effects of focal segmental glomerulosclerosis, cells proliferation, and apoptosis two weeks after experiment

Group	PCNA-G	PCNA-T	TUNEL-G	TUNEL-T	FSGS
5/6 NPX	3.8±0.3[a]	2.9±0.2[a]	3.9±0.2[a]	3.4±0.3[a]	23.3±2.5
5/6 NPX + 3 Gy	1.5±0.2	1.3±0.2	2.6±0.3	2.0±0.4	20.1±4.0
Control	0	0	0	0	0

Values are given as mean±SEM. Statistically significant differences (at $P \leq 0.05$) are shown as follows: [a]5/6 NPX group vs. 5/6 NPX + 3 Gy group. ANOVA was used for intergroup comparison among groups (Tukey and Dunnett tests).

Control, healthy animals (rats without surgery and irradiation); 5/6 NPX, nephrectomized rats; 5/6 NPX + 3 Gy, nephrectomized rats with irradiation.

PCNA-G, proliferation cell nuclear antigen detected in the glomerulus; PCNA-T, proliferation cell nuclear antigen detected in the tubules; TUNEL-G, apoptosis detected in the glomerulus; TUNEL-T, apoptosis detected in the tubules; FSGS, focal segmental glomerulosclerosis.

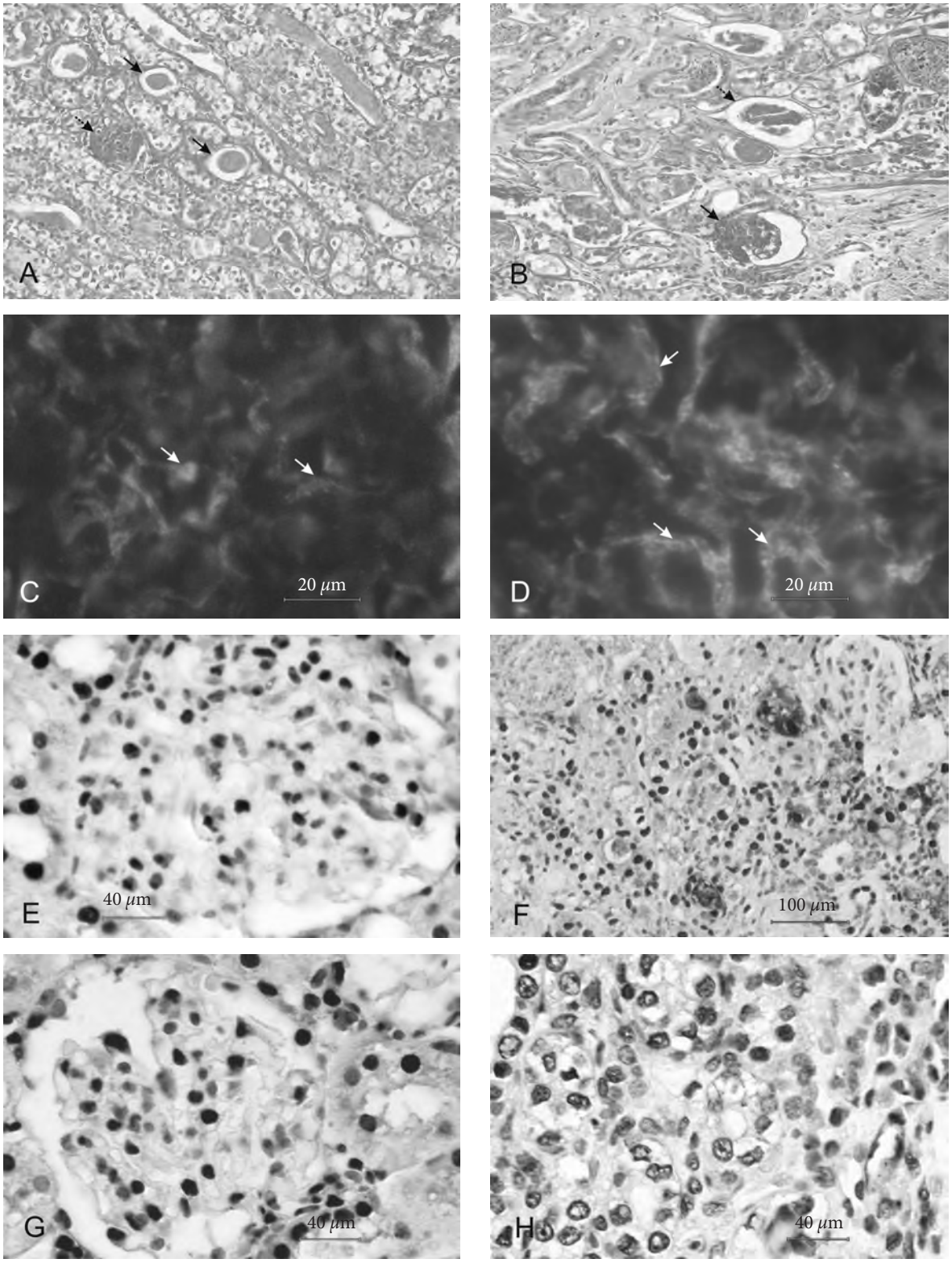

Fig. A, 5/6 NPX group. Focal segmental glomerulosclerosis in the kidney cortex. Damaged renal corpuscles (arrows). Periodic acid-Schiff (magnification, ×100); B, focal segmental glomerulosclerosis in the irradiated rats group. Sclerotic renal corpuscles (arrows). Periodic acid-Schiff (magnification, ×100); C, immunofluorescence study for the proliferation cell nuclear antigen in renal sections of 5/6 NPX rat group. Proliferation cell nuclear antigen-positive cells are stained green (arrows) (magnification, ×368); D, immunofluorescence study for the PCNA in renal sections of rat with 5/6 NPX and 3-Gy irradiation. Proliferation cell nuclear antigen-positive cells are stained green (arrows) (magnification, ×368); E, 5/6 NPX rats showed progressive focal segmental glomerulosclerosis associated with increased TUNEL staining in the glomerulus (magnification, ×400); F, 5/6 NPX rats showed increased TUNEL staining in the tubules (magnification, ×200); G, 5/6 NPX + 3 Gy irradiated rats showed moderate TUNEL staining in the glomerulus (magnification, ×400); H, 5/6 NPX + 3 Gy irradiated rats showed moderate TUNEL staining in the tubules (magnification, ×400).

NPX rats at week 2 (Table 2; Fig. E, F), but decreased after low-dose irradiation (Table 2; Fig. G, H). Combination of 5/6 NPX + low-dose irradiation reduces glomerular apoptosis. Maximal number of positive apoptotic cells was detected in the epithelial cells of sclerotic glomeruli and distal tubules in the 5/6 nephrectomized rat group. The ratio of PCNA/TUNEL-positive cells in the glomeruli showed a decreasing trend in response to low-dose irradiation.

Discussion

We have previously shown that low-dose irradiation has a beneficial effect on the course of experimental renal disease employing the renal mass ablation model. Irradiation of 3 Gy in the 5/6 nephrectomized rats diminished proteinuria and hypertension as well decreased serum creatinine, FSGS, and PCNA at week 2 (17). Having reproduced these findings in the current study (see Table 1 and 2), we aimed to investigate how the effect of low-dose irradiation is related to the number of apoptotic cells in the glomeruli and tubules after renal mass ablation. Apoptosis has been proposed to play an important role in the regulation of renal cell number in both healthy and diseased kidneys (19). An efficient deletion of excessive, damaged, or nonfunctioning renal cells and infiltrating inflammatory cells by apoptosis seems to be beneficial (19). During the progression of experimental glomerulonephritis to end-stage renal failure, apoptosis also seems to play an essential role in the resolution of intra- and extraglomerular inflammation (20). However, the loss of resident renal cells by uncontrolled apoptosis is detrimental as it may induce a reduction of functional renal mass and lead to renal insufficiency. Thomas et al. (21) have reported a progressive and sustained increase in the number of apoptotic cells in the glomeruli, tubules, and interstitium of the remnant rat kidneys, with maximal areas of apoptosis detected in the sclerotic glomeruli, atrophied tubules, and expanded interstitium, which indicate that apoptosis of renal cells might contribute to the progression of tubular atrophy and chronic renal fibrosis.

Our study and studies by other authors (22) have shown that low-dose irradiation of the remnant kidneys provokes a beneficial change in the course of renal disease. Many factors may contribute to this favorable feature including lower levels of systemic arterial pressure, as hypertension can be one of the causes of chronic renal insufficiency. As a result of hypertension, the different segments of the nephron are damaged first due to the high hydraulic pressure and sclerosis of the glomeruli. In the case of chronic renal insufficiency, renal tissue and tubules are destroyed, and because of that, the speed of glomerular filtration decreases. Concurrent to the destruction of the tubules, compensatory changes also occur. Undamaged tubules hypertrophy in order to retain a possibly high speed of glomerular filtration. High blood pressure, first of all, damages the glomeruli and leads to the development of glomerular sclerosis. Glomeruli become hypertrophied; mesangial cells show a tendency to proliferation, and their number and size increase. Therefore, it is not surprising that tight blood pressure control can decrease apoptosis of tubular and glomerular cells during renal damage. Soto et al. have reported that renal mass reduction and hypertension caused severe renal lesions associated to an increment of apoptosis rate in glomerular and especially in tubular cells, but tight blood pressure control decreased the apoptosis rate and morphologic lesions (23). Furthermore, the authors suggest that changes in the expression of apoptosis-regulatory genes contribute to the progressive damage in hypertensive rats with renal mass reduction. Decreased apoptosis of tubular and glomerular epithelial cells found in the 5/6 NPX+3 Gy group in our study (Table 2) thus represents one of the mechanisms of beneficial actions of low-dose irradiation.

Another beneficial effect of low-dose irradiation on the course of renal disease in our study was a reduction of proteinuria. Proteinuria is not only a sign of renal insufficiency but it is also important in the development of chronic renal insufficiency (17). Epithelial cells of nephrons are damaged because of excessive protein content in urine (20). Our previous experiments (24) showed that a modest thickening of the glomerular basement membrane after the 5/6 NPX and changes in the filtration pores made the penetration of the barrier possible also for proteins with a large molecular mass. Another factor contributing to the permeation of proteins was hemodynamic, because with the slowing of blood circulation after the ligation of blood vessels, factors contributing to the permeation of proteins appeared. Probably the changes in the glomerular basement membrane are affected by the developing proteinuria, which is accompanied by changes in the filtration of proteins. In our experiment, changes in kidney function were expressed by a significant increase in systolic blood pressure in nephrectomized animals by the end of week 2. The NPX group animals had a significantly increased proteinuria and an increased amount of serum creatinine in urine (Table 1), which are indicators of the above-mentioned damages in the filtration barrier.

Recently, in connection with the introduction of new immunological, molecular biological, and histological methods, the understanding of the mechanism of progression of renal damage has significantly improved (1, 8). In the progression of chronic

kidney disease (5), an important role is played by hemodynamic as well as nonhemodynamic factors. In the case of chronic renal failure, as mentioned above, cell proliferation and apoptosis develop in the damaged glomeruli and tubules, in particular the distal ones. With the progression of FSGS, the sclerotic process involves occasional capillaries of the glomeruli, and at the same time, regular proliferation of mesangial cells is noted. Due to the hypertrophy of the glomeruli, also mesangial cells, which show a tendency of proliferation, are damaged. Glomerulosclerosis is characterized by increased extracellular matrix formation and cell proliferation (25). Treatment of nephrectomized animals with irradiation significantly lowered the FSGS, and therefore it is speculated about a possible influence of resident mesangial cells on the early events following renal mass ablation and maintenance of subsequent pathophysiological changes (25).

Conclusions

The presented results demonstrate that low-dose irradiation is a factor slowing the process of chronic renal injury. We also found that glomerular cell proliferation and programmed cell death were decreased after treatment with low-dose radiation.

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Ląstelių proliferacija ir apoptozė Wistar žiurkių inkstuose po inksto dalies pašalinimo ir švitinimo maža doze

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Raktažodžiai: liekamasis inkstų kiekis, žiurkė, švitinimas maža doze, ląstelių proliferacija, apoptozė.

Santrauka. Tirta ląstelių proliferacija ir apoptozė liekamajame žiurkių inkstų kiekyje po švitinimo maža doze.

Medžiaga ir metodai. Pirmąją grupę sudarė vyriškosios lyties suaugusios Wistar žiurkės (n=9) po 5/6 dalies inksto nefrektomijos, o antrosios grupės žiurkėms (n=9) taikyta nefrektomija kartu su švitinimu maža doze. Kontrolinę grupę sudarė žiurkės, kurioms nedaryta nei operacija, nei taikytas švitinimas (n=9).

Rezultatai. Hipertenzija ir proteinurija, sąlygota nefrektomijos, sumažėjo po švitinimo 3 Gy doze. Žiurkėms po 5/6 dalies inksto nefrektomijos nustatytas žymus proliferuojančių ir apoptozinių ląstelių skaičiaus padidėjimas inkstų kamuolėliuose ir distaliniuose inkstų kanalėliuose po dviejų savaičių, o po švitinimo maža doze šie rodikliai sumažėjo statistiškai reikšmingai.

Išvada. Tyrimo duomenimis, švitinimas maža doze yra veiksnys, stabdantis lėtinės inkstų pažaidos procesą.

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