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The Rowett rat strain is resistant to renal fibrosis

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Abstract

Background. Genetic susceptibility to renal fibrosis may determine the individual rate of progression to renal failure. We aimed to study the progression in Rowett (RO) rats, a strain we found resistant to subtotal nephrectomy (SNX), comparing to Sprague–Dawley (SD) rats, a strain with established sensitivity in a radical ablation/infarction and diet-induced SNX model.

Methods. Eight-week-old male RO (RO-SNX) and SD (SD-SNX, n = 5/group) rats underwent SNX and were kept on high protein and salt diet. Kidney function was monitored and the kidneys were evaluated by histology and immunohistochemistry 5 weeks after SNX.

Results. RO-SNX rats had only mild proteinuria and less glomerulosclerosis, accompanied by less fibronectin and TGF-β staining as compared to SD-SNX rats. Glomerular nitrotyrosine staining was less intense in RO-SNX vs SD-SNX, accompanied by less podocyte damage as demonstrated by desmin staining.

Conclusion. Our results demonstrate the importance of podocyte damage in glomerulosclerosis and that Rowett rats are protected from renal fibrosis. To our knowledge, this is the first strain of rats with unknown genetic resistance, which makes the strain attractive for studying the genetic background of renal fibrosis.

Keywords: glomerulosclerosis; podocyte; progression; resistant strain

Introduction

Chronic kidney disease is a major healthcare problem worldwide. The key lesions are glomerular sclerosis and tubulointerstitial fibrosis, secondary to various renal diseases such as diabetes mellitus, hypertension, renal ischaemia, infection or systemic lupus erythematosus. However, there are significant interindividual differences in progression of chronic renal failure (CRF), which suggests the involvement of genetic factors [1,2].

The influence of gender and strain on glomerulosclerosis (GS) in rodents has been established [3,4]. Several studies demonstrated differences in susceptibility to CRF in rats using models of experimentally induced GS [5], nephrosis [6], mesangial injury [7] or hypertension [8,9]. In mouse strains, genetic background of susceptibility to glomerulosclerosis has been reported as well. In search for a genetically determined glomerular disease model, strain dependence was found to rely on a single gene defect in susceptible BALB/cJ and resistant C57BL/6J strains [10]. Furthermore, susceptibility to HIV nephropathy was demonstrated to depend on a network of podocyte-expressed genes [11].

Although several mechanisms have been demonstrated to participate in the development of GS, its pathogenesis is still incompletely understood. Nephron number, high intraglomerular capillary pressure [12,13], glomerular hypertrophy [14,15], podocyte damage, extracellular matrix (type IV collagen and fibronectin) accumulation [16,17], synthesis of profibrotic growth factors (TGF-β, CTGF) and albuminuria are characteristic determinants of progression [18,19].

Podocytes seem to play a central role in the pathogenesis of GS. During compensatory glomerular hypertrophy [12,16,20], effacement of podocyte foot processes leads to albuminuria and podocyte detachment from the basement membrane, further leading to tuft adhesion to the Bowman's capsule (focal sclerosis) [21,22]. Besides the mechanical injury of podocytes during glomerular hypertrophy, oxidative stress also contributes to podocyte damage [23,24].

In a pilot study, we detected resistance to subtotal nephrectomy (SNX) of Rowett black-hooded (RO) rats, an inbred strain with a 10% mortality compared to 60% of Sprague–Dawley (SD) rats 8 weeks after radical SNX. Thus, in the present study, we investigated the background of resistance by comparing resistant RO rats to the sensitive SD strain in an accelerated ablation–infarction (A/I) model. In this model, renal ablation is followed by high protein and salt intake leading to elevated plasma renin and rapid development of glomerulosclerosis [25], progressing to renal failure in SD rats.

Materials and methods

Animals and study protocol

Eight-week-old male SD and RO rats weighing 330–380 g were used (Charles River, Hungary). All animals were housed under standard conditions (light on 08:00–20:00 hr; 40–70% relative humidity, 22 ± 1°C) and had free access to water and chow (Altromin standard diet, Germany).

After 1 week of acclimatization, rats underwent SNX using the surgical A/I method (SD-SNX, RO-SNX, n = 5/group) [25]. The animals were anesthetized with diethyl ether, and then the right kidney was removed by median laparotomy. The left kidney was carefully decapsulated and

branches of the left renal artery were localized under a Zeiss operation microscope (Zeiss, Germany), and two branches were sequentially ligated using Prolene 6-0 (Johnson and Johnson, Hungary) sutures, leaving only one branch intact which supplied the lower frontal quadrant of the kidney. The area of ischaemia was macroscopically checked on both the frontal and rear sides of the kidney. As a result of the operation, ~75% of the left kidney mass was infarcted. In order to closely model the clinical situation of complex and ongoing renal injury and to accelerate kidney damage, operated rats received high protein diet (40% casein, Altromin special diet, Germany) and water supplemented with 0.25% NaCl [25].

Functional measurements

Twenty-four-hour urine was collected in metabolic cages (Techniplast, Italy) before the operation and at harvest. Simultaneously, blood samples were taken. Blood urea nitrogen and urine creatinine were evaluated using specific test stripes with a Reflotron IV analyzer (Roche Diagnostics, Hungary). Urinary protein was measured with the Bradford assay. Urinary protein excretion was then calculated as the urinary protein/creatinine ratio to normalize for the glomerular filtration rate. Also, urinary albumin excretion was determined using a microplate sandwich enzyme-linked immunosorbent assay (ELISA) [26] modified by using a rabbit anti-rat albumin peroxidase conjugate.

Renal tissue harvest

For basic histologic and immunohistochemical analysis, SNX animals were harvested 5 weeks after SNX. Upon harvest, blood was taken from the aorta, and kidneys were immersion-fixed in 4% buffered formaldehyde, embedded in paraffin and cut into 4-μm-thick sections. Slides were periodic acid Schiff (PAS)- or immunostained.

Glomerular damage indices

In SNX animals, the glomerulosclerosis index was assessed on PAS-stained paraffin sections according to the scoring system (scores 0–4) of El Nahas et al. [27]. Using light microscopy and a magnification of ×400, the glomerular score of each animal was derived as the arithmetic mean of 100 glomeruli. The tubular and interstitial damage scores were assessed on PAS-stained paraffin sections using a similar scoring system (scores 0–4) at a magnification of ×100 as described in detail elsewhere [28].

Immunohistochemistry

Paraffin sections of SNX animals were prepared and incubated with antibodies, using the avidin–biotin method [29], to detect fibronectin (anti-fibronectin rabbit polyclonal antibody, 1:1000, Sigma, Germany), TGF-β1 (anti-TGF-β1 rabbit polyclonal antibody, 1:100, Santa Cruz, USA), desmin (anti-desmin monoclonal mouse antibody, 1:50; DAKO, Germany) and nitrotyrosine (sheep polyclonal antibody, 1:400, Oxis Research, USA). Immunohistochemical reactivity was examined with light microscopy at a magnification of ×200. Semiquantitative scoring (scores 0–4; 0: no staining, 1: weak, 2: mild, 3: strong, 4: very strong staining) was performed as described elsewhere [30].

Statistics

Data are presented as mean ± SD. Non-parametric Mann–Whitney U test was performed to compare the groups. A P value of <0.05 was considered statistically significant.

Results

Animal data and kidney function following SNX

There was no difference in body weight between the groups either before the operations (SD-SNX: 368 ± 39 g vs RO-SNX: 351 ± 15 g, ns) or at the end of the study (SD-SNX: 373 ± 38 g vs RO-SNX: 362 ± 34 g, ns). Blood urea concentrations at the end of the study were significantly elevated in SD-SNX vs age-matched SD rats (Table 1). Blood urea was significantly lower in RO-SNX rats. The urinary protein/creatinine ratio was equally normal in both groups before SNX. Five weeks after SNX (at the time of harvest), SD-SNX rats developed significant proteinuria vs during the start of the study. Proteinuria did not develop in RO-SNX rats. Urinary albumin ELISA confirmed the proteinuria data: urinary albumin excretion progressively increased in SD-SNX but stayed normal in RO-SNX rats.

Histological indices of renal damage and immunohistochemical evaluation of SNX animals

On PAS-stained slides (Figure 1A–B), several glomeruli were sclerotic to some extent in SD-SNX rats (Tables 2 and 3; Figure 1). Glomeruli had dilated capillaries in both groups; however, glomerular damage was significantly milder in the RO-SNX group. Tubulointerstitial damage was characterized as interstitial infiltration and tubular dilatation and/or atrophy. In SD-SNX kidneys, severe tubulointerstitial damage was observed. Tubulointerstitial damage was significantly alleviated in RO-SNX rats.

Fibronectin accumulation observed both in the glomeruli and the tubulointerstitial space of SD-SNX was significantly ameliorated in RO-SNX. Strong staining for TGF-β1 (Figure 1C, D) was observed in SD-SNX kidneys vs significantly less intense staining in the glomeruli of RO-SNX. Staining for desmin (Figure 1E, F), a marker of podocyte damage, was strong in glomeruli of SD-SNX rats, but desmin staining was significantly reduced in RO-SNX animals. Nitrotyrosine staining was localized to glomerular capillaries and podocytes. Intense staining was observed in SD-SNX but not in RO-SNX rats.

Discussion

Different susceptibility to GS is well known in humans. Individual rate of progression to end stage can be very different despite a similar etiology.

Table 1. Renal function

Group	Blood urea (μmol/l)	Urine protein/creatinine ratio		Albuminuria (g)	
Time	Harvest	Initial	Harvest	Initial	Harvest
SD-NX	24.3 ± 8.6	1.5 ± 0.3	22.7 ± 11	32.5 ± 17.8	247.7 ± 136
RO-NX	11.4 ± 2.3	1.3 ± 0.4	3.5 ± 1.7	13.1 ± 3.8	45.4 ± 32.6
Significance	P < 0.05	NS	P < 0.05	NS	P < 0.05

Mean ± SD, n = 5/group. Statistics: SD-SNX vs RO-SNX. Blood urea in age-matched healthy SD rats is 5 ± 1 μmol/l.

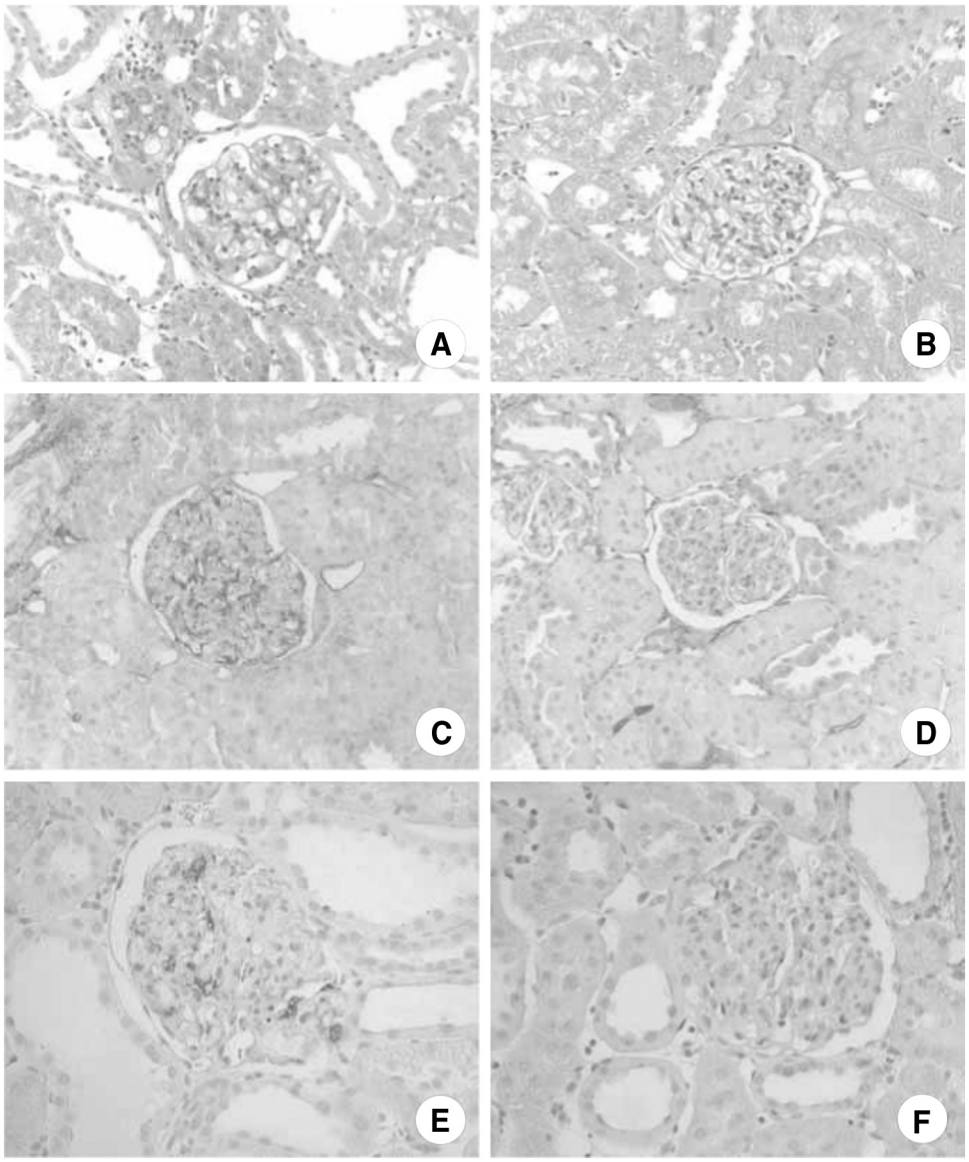

Fig. 1. Kidney samples of subtotally nephrectomized (SNX) rats from Sprague–Dawley (SD; right column: SD-SNX) and Rowett (RO; left column: RO-SNX) rats: (**A,B**) PAS staining; (**C,D**) TGF-β staining; (**E,F**) desmin staining (magnification ×400).

The present study demonstrates a new rat strain with genetic resistance to a complex model of renal scarring with significantly reduced oxidative damage to podocytes.

Rat strains resistant to progression of renal damage have been previously demonstrated. A central role of the renin–angiotensin–aldosterone system in renal fibrosis is supported by the resistance of Wistar–Furth rats to remnant nephropathy [3]; however, aldosterone levels were similar and not elevated (data not shown) in our study 5 weeks after SNX. Another previous study has demonstrated reduced sensitivity of Lewis rats vs Fischer (F344) rats to renal mass reduction-induced chronic renal failure. In the background, 30% less glomeruli/kidney was demonstrated in F344 rats [31]. A difference in glomerular number was

Table 2. Evaluation of histology and immunohistochemical staining of fibrosis markers

Group	GSI	TDI	Fibronectin		TGF-β1 in glomeruli
			Glomeruli	Tubulointerstitium	
SD-SNX	2.1 ± 0.1	2.7 ± 0.4	0.6 ± 0.1	1.1 ± 0.2	1.5 ± 0.2
RO-SNX	1.5 ± 0.1	1.2 ± 0.5	0.1 ± 0.1	0.6 ± 0.1	0.9 ± 0.3
Significance	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$

GSI, glomerulosclerosis index; TDI, tubulointerstitial damage index, PAS staining. Mean ± SD, n = 5/group.

Table 3. Immunohistochemical evaluation of staining for desmin (marker of podocyte damage) and nitrotyrosine (nitroxidative stress marker)

Group	Desmin	Nitrotyrosine in glomeruli
D-SNX	1.0 ± 0.1	0.8 ± 0.1
RO-SNX	0.4 ± 0.1	0.3 ± 0.1
Significance	$P < 0.05$	$P < 0.05$

Mean ± SD, n = 5/group.

not responsible for the resistance in the Rowett strain according to our histomorphometric study, as glomerular number was similar in naïve animals of the studied strains (data not shown).

We used a complex model of progressive renal failure with the A/I method in SD rats leading to a more rapid progression of kidney disease [32] presumably caused by the early upregulation of renin [33]. High salt accelerates CRF as it increases renal angiotensin-converting enzyme activity [34], and both angiotensin II and aldosterone induce profibrotic factors and consequent renal scarring [35,36]. Protein overload leads to tubulointerstitial damage [37]. Thus, salt and protein loading was included in the study protocol in order to model an ongoing injury to the kidney and to induce renal failure.

Five weeks after SNX, both blood urea levels and urinary protein/albumin loss were lower in Rowett rats. Although differences in blood urea levels could be the influence of the catabolic state of the animals, body weights were similar in the two groups throughout the study; thus, lower blood urea was probably due to better renal function in Rowett rats.

It has been described in the rat remnant kidney model that glomerular hypertrophy and structural changes in podocytes appear early following SNX, accompanied by increased desmin expression in podocytes [20], supporting the hypothesis that podocyte injury may be the central event initiating GS. Podocytes are usually attached to several capillaries; therefore, hypertrophy of the glomerular tuft itself increases the mechanical stress to podocytes. Because of the lack of cell proliferation, podocytes adapt to the decrease in cell number and glomerular growth by cell hypertrophy [12,13]. Under physiological conditions, desmin staining in podocytes cannot be detected in vivo [38]. The expression of desmin is enhanced in response to mechanical injury to stabilize the cytoskeleton of podocytes during hypertrophy [39]. Therefore, enhanced staining for desmin in podocytes is a reliable marker of podocyte injury and can be observed in a variety of experimental models of CRF [40,41]. Less glomerulosclerosis in RO rats could be a consequence of less podocyte damage as demonstrated by a reduced glomerular desmin and nitrotyrosine staining. The background of less nitroxidative stress and podocyte injury in RO rats needs further clarification. Less tubulointerstitial fibrosis is also possibly due to less podocyte damage and protection from albuminuria in RO animals. Podocyte damage was reduced in RO animals as demonstrated by desmin and nitrotyrosine staining, invoking the hypothesis that podocyte-expressed genes may be responsible for protection that is similar to the recent study in mouse HIV nephropathy model [11].

In conclusion, we demonstrate a new rat strain that is genetically resistant to a complex model of glomerulosclerosis and renal fibrosis. Resistant Rowett rats had reduced oxidative damage of podocytes, shedding light on the etiologic role of podocyte oxidative damage in glomerulosclerosis. This strain could be a valuable tool for the identification of genetic resistance factors against renal fibrosis.

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Conflict of interest statement. None declared.

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Inhibition of nuclear factor kappa B attenuates tumour progression in an animal model of renal cell carcinoma

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Abstract

Background. Renal cell carcinoma (RCC) is a highly metastatic and lethal disease with few efficacious treatments. Many studies have shown that the ubiquitous transcription factor nuclear factor kappa B (NF-κB) plays a key role in the development and progression of many cancers including RCC. The aim of this investigation was to evaluate the anti-cancer effect of pyrrolidine dithiocarbamate