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Animal models of regression/progression of kidney disease

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Abstract

Current medical therapies may delay chronic kidney disease progression. However, increasing experimental evidence indicates remission or even regression can be achieved. In order to study mechanisms progression vs. regression by different interventions, appropriate animal models and research design must be implemented. We review key information of selected models, including etiology, pathogenesis, procedure, time course and assessment of potential regression.

Introduction

Some renal diseases, such as rapidly progressive glomerulonephritis, quickly lead to irreversible end stage renal disease (ESRD). Most common nephropathies progress less rapidly, but still show gradual decrease in glomerular filtration rate (GFR). When scarring is beyond a certain level, further progression ensues due to activation of compensatory, but ultimately profibrotic mechanisms. However, several clinical studies show the potential remission or regression of chronic kidney disease (CKD), as assessed by proteinuria and decreased stable GFR. These include diabetic nephropathy, lupus nephritis and IgA nephropathy [1-4]. To enhance potential of regression, it is imperative that progression/regression of renal injury is studied in depth experimentally [5-12]. Although progress has been made in the development and design of such animal models, not all kidney disease models reproduce the structural and functional changes in human kidney disease. In this article we review several rodent models, which have been studied for progression vs. regression of kidney diseases.

Definition and assessment of progression/regression in kidney disease

The kidney has partial regenerative ability. Many acute glomerular diseases are characterized by cell proliferation, necrosis and/or inflammatory processes that may be

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reversed by aggressive immunomodulatory therapy. However, when parenchyma is lost, the limited renal regeneration capacity results in organization of injury to sclerosed tissue with loss of parenchyma. Regression and progression of kidney disease must therefore be studied experimentally in the sclerosing phase to translate to human CKD.

Regression vs. progression is clinically defined by functional parameters. In terms of kidney function, Ruggenenti et al. defined progression of chronic nephropathies as increasing proteinuria and declining GFR, and regression as decreasing proteinuria and increasing GFR [13]. Morphologically, progression is defined by the development of glomerulosclerosis and ongoing tubular injury resulting in tubulointerstitial fibrosis. Regression is defined morphologically by a decrease of existing fibrosis. To prove regression, it is therefore imperative to assess results of intervention at a starting point of existing sclerotic injury. Comparison may be done by examining tissues from different groups over time, or by repeat examination of tissue from one animal, by e.g. renal biopsy.

Of note, functional changes in animal models do not necessarily reflect structural changes. Proteinuria, especially urine albumin:creatinine ratio (ACR), is a sensitive marker of glomerulopathy. However, in several animal models, changes in ACR are not parallel to glomerular morphological change. Serum creatinine is an insensitive indicator of function, and only starts to increase after 30% reduction in GFR. GFR, measured by creatinine clearance or inulin clearance, is the gold standard for glomerular function.

Of note, experimental models typically are followed for a relatively short time, e.g. 2-3 months, and functional changes over this interval may not accurately reflect long-term tissue remodeling. In particular in the remnant kidney model (see below), the surgically-induced remarkable acute decrease in GFR may make it difficult to detect any functional improvement after intervention in the few remaining nephrons. Additional biomarkers, such as Kim-1 and N-gal, may be useful for assessment of tubular function. Thus, morphologic assessment of scarring is also essential. In models of glomerulosclerosis, assessment of severity and extent of sclerosis, matrix accumulation within glomerular tufts and capillary tuft volume are useful measurements. Interstitial fibrosis is also a robust measure of parenchymal scarring.

Rodent models of progression *vs.* regression

Various kidney injury models have been developed in rodents. Some models have spontaneous remission, such as the single dose Thy-1 nephritis model. Some do not allow functional assessment, such as complete unilateral ureteral obstruction. Those suitable for studying progression *vs.* regression can be classified according to their initial injury site as models of glomerular, tubulointerstitial or vascular injury.

1. Glomerular injury models

Munich-Wistar-Frömter (MWF) rat—The MWF rat is a genetic model with a congenital deficit in nephron number by 30-50%, which predisposes to the development of hypertension and salt sensitivity in adulthood. By age 10 weeks, MWF rats develop proteinuria and hypertension with systolic blood pressure (SBP) ranging from 140 to 150

mmHg. By 50 weeks of age, SBP reaches 180 mmHg and the kidney exhibits significant glomerulosclerosis [14, 15]. Ten weeks treatment with ACE inhibition significantly reduced the volume of capillary tuft affected by sclerosis, indicating that some sclerotic lesions can be resolved by inhibition of ACE [5].

Aging—Progressive glomerulosclerosis, interstitial fibrosis, and tubular atrophy along with decreased glomerular filtration rate (GFR) develop with aging. Studies from naturally aging rat kidneys suggest that both genetic background and gender determine the rate and the severity of progression of age-related renal impairment and scarring. Sprague-Dawley rats are more susceptible than other strains. About 25% of male Sprague-Dawley rats become proteinuric with urinary protein excretion >10mg/day by 3 months of age, 38% by 6 months, 56% at 12 months, and 94% at 24 months [15, 16]. GFR is maintained within normal range until 24 months of age. However, with advancing age, compensatory changes are insufficient to maintain GFR, and progressive decline of GFR manifests. The earliest renal morphologic changes, characterized by mesangial expansion and thickening of the glomerular basement membranes (GBM), begin at 3 months. By 24 months of age, GBM thickness and increased mesangial matrix are increased 2-3 fold *vs.* young adults and glomerulosclerosis and tubulointerstitial fibrosis ensue later [16]. Rats treated with the angiotensin receptor blocker (ARB) losartan from age 18 months till 24 months showed decreased kidney collagen content and reduced aorta wall thickness ratio, to levels even lower than that of the baseline 18-month control rats, indicating ARB not only slows the progression of glomerulosclerosis in aging, but can also induce regression [17].

Diabetic nephropathy—Diabetic nephropathy (DN) models include those artificially induced, spontaneous, and genetically engineered. Streptozotocin (STZ) induces type 1 diabetes mellitus (T1DM) secondary to necrosis of pancreatic beta-cells, and is the most commonly used artificial DN model in rat. In one variant of this model, male rats at 8 weeks of age (200–250 g) were starved for 16 h and injected once into the tail vein with STZ (55 mg/kg) in sodium citrate buffer (1 mL/kg). Uninephrectomy has been added to STZ-induced diabetic nephropathy to accelerate the progression of renal injury [18]. These STZ-treated models develop a modest degree of proteinuria and serum creatinine increase, as well as mesangial expansion and varying nonspecific glomerulosclerosis, depending on the genetic background. At 8 months after STZ injection, urinary albumin excretion was moderately increased to approximately 60 mg/24 h, nearly three times higher than non-diabetic control rats at the same age. This model has been used to study regression of DN. STZ diabetic rats were treated with losartan for 2 months, and showed partial regression of mesangial expansion and less sclerotic lesions [12]. STZ rats treated with ACEI from 4 months till 8 months had amelioration of glomerulosclerosis, while regression was achieved by the addition of statin or endothelin (ET) A receptor antagonist [7, 19]. Regression of more advanced sclerosis was also observed by treatment for four weeks with hepatocyte growth factor gene therapy starting at 32 weeks after STZ injection [20]. Of note, STZ-induced diabetic rodents lack classic features of human DN, such as nodular sclerosis, and have little progression of tubulointerstitial fibrosis. These concerns have led to development of other rodent models to better capture human progressive DN.

The BTBR (black and tan brachyuric) mouse strain with the *ob/ob* leptin deficiency mutation (BTBR *ob/ob* mice) is a spontaneous DN model of type 2 diabetes mellitus (T2DM). This strain develops glomerular injury similar to human DN. Characteristics of early DN such as glomerular hypertrophy, accumulation of mesangial matrix, and loss of podocytes are detectable by 8 weeks of age. Glomerular lesions of progressive, advanced DN are present by 20 weeks. By 22 weeks, there was 20% increase in GBM thickness, 50% increase in mesangial matrix, mesangiolysis, diffuse mesangial sclerosis, focal arteriolar hyalinosis, and focal mild interstitial fibrosis lesions [21]. Leptin replacement, which led to normalization of diabetic state and weight loss, but not inhibition of the renin-angiotensin system (RAS), resulted in near-complete reversal of both structural (mesangial matrix expansion, mesangiolysis, basement membrane thickening, podocyte loss) and functional (proteinuria, accumulation of reactive oxygen species) measures of advanced diabetic nephropathy [22].

The *db/db*/eNOS$^{-/-}$ mouse is another DN model of T2DM. Addition of eNOS deficiency to *db/db* mice on the C57BLKS/J (BKS) background resulted in a robust model of nodular DN. The mice have obesity, hyperglycemia, hyperinsulinemia and mild to moderate hypertension. Hyperglycemia is first apparent at 6 to 8 wk of age, and mice exhibit full-blown functional and nephropathic changes by 16 to 20 wk. They develop significant albuminuria, decreased GFR, mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis, mesangiolysis, nodular glomerulosclerosis, and tubulointerstitial injury [23]. These features establish db/db/eNOS-/- and BTBR ob/ob as some of the very few to develop features of more advanced DN akin to human DN. ACEI treatment for 12 weeks, starting from 8 wk of age, significantly reduced albuminuria, glomerulosclerosis, and tubulointerstitial injury in the db/db/eNOS-/- mouse [24]. We also found that Apoptosis Signal-Regulating Kinase 1 (ASK1) inhibitor halted progressive glomerulosclerosis and preserved GFR reduction from 10 wk till 16 wk in this model (Yang HC *et al.*, SA-PO460, American Society of Nephrology Kidney Week 2012, San Diego, California, November 2012).

Puromycin aminonucleoside nephrosis (PAN)—Puromycin aminonucleoside inhibits protein synthesis with direct toxic damage to podocytes. It can be given by multiple intraperitoneal injections with initial administration of 10 mg/kg followed by 40 mg/kg every 4 weeks or as a single intravenous dose of 50 mg/kg to cause puromycin aminonucleoside-induced nephrosis (PAN). After injection, rats show an early nephrotic phase peaking at 10 days with complete foot process-effacement followed by apparent resolution. With multiple or higher doses, progressive lower-level proteinuria develops with early segmental sclerotic lesions develop from week 10-13, leading to well-defined segmental sclerosis at 18 weeks [25-27]. Regression was induced by ACEI or ARB, with less sclerosis at sacrifice at 28 weeks vs. biopsy at 16 wks at time of onset of therapy [28]. Combination of enalapril and low protein (from week 12 till 18) also reversed segmental glomerulosclerosis in the chronic PAN model [29].

5/6 nephrectomy—Subtotal nephrectomy, so called 5/6 nephrectomy, mimics the progressive renal failure after loss of renal mass in humans. There are different ways to

establish this model where one kidney is removed and 2/3 of the remaining kidney is ablated. One approach is the ligation model. Branches of the renal artery in the rat are ligated after contralateral uninephrectomy. This approach is not feasible in the mouse due to their limited renal artery branching. Another approach is the ablation model, which removes approximately 50% of the remaining kidney by polar excision 1–2 weeks after uninephrectomy. This approach can be used both in rat and mice. An additional approach is a combination of ligation and ablation model, which ties one or more branches of the mouse renal artery, with cautery performed as needed to remove additional renal mass, to achieve a total 5/6 nephrectomy. The natural history of this model depends on the methods used [15]. Approaches with infarction typically are associated with more severe proteinuria and hypertension than those with only excision of renal mass. The more severe hypertension with ligation is likely due to marked up-regulation of the renin angiotensin system in the peri-infarct zone. Proteinuria in the rat reaches 200-600 mg/24h, starting from week 2. There is early glomerular hypertrophy during the acute phase (0-4 weeks). By 8 weeks, glomeruli show mesangial expansion and focal and segmental glomerulosclerosis involves about 20% of glomeruli, accompanied by early interstitial fibrosis and tubular atrophy. By 12 weeks, widespread glomerulosclerosis and tubulointerstitial fibrosis are present [30]. Rats typically die of uremia starting at week 12. Although most rat strains are susceptible, C57BL/6 mice are highly resistant to development of sclerosis. 129/Sv and Swiss-Webster mice are among the few mouse strains susceptible to development of glomerulosclerosis with ablation [31]. Four weeks treatment with ACEI, ARB or spironolactone alone (from 8 wk till 12 wk) not only slowed development of glomerulosclerosis but also induced regression of existing glomerulosclerosis in some rats [10, 30, 32]. This was associated with a decrease in mean glomerular volume and mean glomerular tuft volume, a reduced number of capillaries per glomerulus, and reduced total length of capillaries per glomerulus, but without any significant change in the length of individual capillaries [10, 33]. Combining the ARB with nonhyperkalemic doses of spironolactone failed to further increase the regression of glomerulosclerosis [11]. Combining ARB with hydrochlorothiazide completely prevented progression of renal injury, even when it was initiated at advanced stages of the nephropathy (120 days after 5/6 nephrectomy) [34].

2. Tubulointerstitial injury models

Cyclosporine nephropathy—Cyclosporine A (CyA), an inhibitor of calcineurin, is used clinically as an immunosuppressant, but long-term CyA usage can induce renal fibrosis. In rats, administration of cyclosporin A (7.5 mg/kg/day and 15 mg/kg/day s.c.) for 28 days increases serum creatinine, BUN and decreases GFR with morphological changes including interstitial fibrosis, tubular atrophy, arteriolar injury and renal endothelial dysfunction. Mechanisms of cyclosporin A-induced nephropathy are multiple, including the renin angiotensin system, endothelin, and overexpression of IL-6, TGF-β and activation of NAD(P)H oxidase in endothelial cells [35]. Rats treated with high dose CyA for 28 days presented with advanced tubulointerstitial damage that progressed even after CyA withdrawal [36]. In contrast, rats treated with low dose CyA for 14 days had induced epithelial to mesenchymal transition (EMT) marker expression, and CyA withdrawal led to the gradual regression of histological lesions and decreased EMT markers after 6 weeks [37]. These findings suggest that injury stage determines progression or regression.

Aristolochic acid and folic acid nephropathies—Both aristolochic acid I (AAI) and folic acid can induce interstitial fibrosis. A single dose of AAI (4.7 mg/kg) results in moderate acute kidney failure in the early stage (4-10 days) and renal fibrosis later (>21 days) [38]. Multiple low doses of AAI (3 mg/kg, once every 3 days for 6 weeks) led to substantial tubulointerstitial fibrosis at 12 weeks [39]. High dosages of folic acid (250 ug/g BW) given i.p. in mice rapidly induces folic acid crystals with tubular necrosis in the acute phase (1-14 days) and patchy interstitial fibrosis in the chronic phase (28-42 days) [15]. Compared to the UUO model, both AAI and folic acid model provide functional data, and can be used in genetically modified mice. Thus, these models more closely model human tubulointerstitial nephritis resulting from toxic tubular necrosis.

Ischemia/reperfusion—Acute tubular necrosis induced by ischemia-reperfusion model (I/R) is usually a self-limited disease characterized by a remarkable ability of necrotic tubules to regenerate and for renal function to recover. Ischemia for 45 min followed by 24 h reperfusion is a commonly used animal model to simulate acute kidney injury in humans [40]. There are slight, yet detectable, increases in BUN between 6 and 12h of reperfusion and marked increases in BUN between 24 and 48h. During the time of peak injury, there is marked edema and matrix protein accumulation in the interstitium. In rats, at 40 weeks post I/R, dilated and shrunken tubules, thickened tubular basement membranes and interstitial fibrosis were detected [41]. After I/R, G2/M-arrested proximal tubular cells activate c-jun NH(2)-terminal kinase (JNK) signaling, which acts to upregulate profibrotic cytokine production. Treatment with a JNK inhibitor, or bypassing the G2/M arrest by administration of a p53 inhibitor, rescued fibrosis in the injured kidney [42].

***Ggt1* DTR transgenic mice—**The diphtheria toxin receptor (DTR) is encoded by human heparin-binding epidermal growth factor-like protein (hHB-EGF). Its mouse homolog, mHB-EGF, has very low affinity for DT because the amino acids critical for DT binding are missing. Transgenic expression of a construct containing the hHB-EGF cDNA with gamma glutamyl transferase (Ggt1), which is selectively expressed in the proximal tubule, has thus been used to develop a model of selective proximal tubule injury. After injection of DT, BUN and creatinine increase at day 2 with peak increases occurring at day 5. The alterations in renal function are accompanied by acute proximal tubular injury, with tubule dilation, loss of brush border, sloughing of individual epithelial cells, and distal cast formation [43]. Six weeks after DT injection, diffuse interstitial fibrosis develops, without proteinuria. This model thus also is suitable for study of regression of interstitial fibrosis and restoration of GFR.

3. Vascular injury models

Nitric oxide (NO) inhibition—Abrupt interruption of NO synthesis leads to hypertension and renal vasoconstriction. After treatment with nitro-L-arginine methyl ester (L-NAME, 20 or 50 mg/kg/day in drinking water), an inhibitor of NO synthesis, for 4 to 6 weeks, rats develop kidney injury, including glomerular ischemia, glomerular segmental necrosis, glomerulosclerosis, interstitial expansion and arteriolar wall thickening. These injuries are associated with progressive albuminuria, which can be amplified nearly to the nephrotic

range by concomitant salt overload [44]. Treating with losartan from week 4 to 8 completely normalized the renal functional and histologic parameters [45].

Spontaneously hypertensive rats (SHR)—SHR capture many elements of human essential hypertension. Abnormalities in the vascular smooth muscle, which lead to augmented vasoconstrictor ability, contribute to the hypertension. SHR develop hypertension around 5–6 weeks of age, with systolic blood pressure (SBP) reaching 180-200 mmHg in the adult age phase. Proteinuria begins to increase at 6 weeks of age in male SHR and increases linearly from 10 to 70 wk of age. GFR in male SHR decreases by 20% to 30% at 14 to 15 and 30 to 32 weeks of age, respectively, while there is no age-related GFR reduction in females. Starting between 40 and 50 weeks, SHR develop glomerulosclerosis and interstitial fibrosis [15, 46, 47]. Two weeks treatment with high dose ARB (at 16 weeks of age) causes regression of renal arteriolar hypertrophy in SHR, resulting in a sustained decrease in hypertension [48]. Treating younger (20 to 23 week old) SHR with L-NAME for 3 weeks induced all of the pathophysiological alterations associated with nephrosclerosis in the 73-week-old SHR. ACE inhibitor treatment for 3 weeks after L-NAME reversed these pathophysiological alterations [49].

Conclusions

We have provided a brief overview of the most widely used animal models for studying progression *vs.* regression in kidney disease. Optimal experimental study design must include appropriate choice of model, time course and assessments. However, many of these models do not exactly mirror human diseases. Further model development is thus necessary to optimize translational research.

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Table 1

Overview of Selected Models for Study of Regression/Progression of CKD

Model	Etiology/Mechanism	Method	Morphologic changes	Time course comparisons	Assessments reported	References
MWF rat	Nephron number reduction	Spontaneous, genetic	Glomerulosclerosis	50 wk-->60 wk	BP, Serum Cr, Proteinuria, Histology	5
Aging rat (Sprague-Dawley)	Aging	Spontaneous	Mesangial expansion, glomerulosclerosis, GBM thickening, tubulointerstitial fibrosis, arteriolar hyalinosis	18 mos-->24 mos	Proteinuria, Serum Cr, Histology	16, 17
Streptozotocin induced DM rat	Type I diabetes	Induced, STZ 55 mg/kg (i.v.)	Mesangial expansion, glomerulosclerosis, GBM thickening, tubulointerstitial fibrosis, arteriolar hyalinosis	10 mos-->12 mos, 4 mos-->8 mos	Proteinuria, Serum Cr, Histology	7, 12, 19, 20
BTBR *ob/ob* mouse	Type II diabetes	Spontaneous	Mesangial expansion, glomerulosclerosis, GBM thickening, tubulointerstitial fibrosis, arteriolar hyalinosis, rare nodules, mesangiolysis	18 wk-->24 wk	Proteinuria, BUN, Serum Cr, Histology	22
eNOS$^{-/-}$/*db/db* mouse	Type II diabetes	Genetic	Glomerulosclerosis, GBM thickening, tubulointerstitial fibrosis, arteriolar hyalinosis, rare nodules, mesangiolysis	10-->18wk-->24 wk	Proteinuria, GFR, Histology	
Puromycin aminonucleoside nephrosis rat	Podocyte injury	Induced, puromycin 10 mg/kg followed by 40 mg/kg every 4 weeks (i.p.)	Minimal change in acute phase, FSGS in chronic phase	16 wk -->28 wk, 12wk -->18wk	Proteinuria, GFR, Histology	28, 29
5/6 nephrectomy rat or mouse (strain dependent)	Renal mass reduction	Induced, UNX+ renal artery ligation± ablation	Glomerulosclerosis	8 wk-->12 wk	Protienuria, Serum Cr, Histology	10, 11, 30, 32, 33, 34
Cyclosporine A (rat or mouse)	Vascular and tubular injury due to vascular dysfunction/ toxicity	Induced, cyclosporin A (7.5 mg/kg/day and 15 mg/kg/day s.c.) for 28 days	Tubulointerstitial fibrosis, arteriolar hyaline	2-4 wk--> 8-10 wk	BUN, Serum Cr, GFR, Histology	36, 37
Aristolochic acid and folic acid nephropathies (rat or mouse)	Tubular injury due to toxic tubular necrosis (AA) or crystals (FA)	Induced, AAI (3 mg/kg, once every 3 days for 6 weeks) Folic acid (250 ug/g BW)	Tubulointerstitial fibrosis	6 wk after last dose	BUN, Serum Cr, GFR, Histology	
Ischemia-Reperfusion (rat or mouse)	Ischemia-reperfusion injury	Induced, variable times; e.g. 45 min ischemia + 24 h reperfusion	Acute tubular necrosis in acute phase, tubulointerstitial fibrosis in chronic phase	40 wk	BUN, Serum Cr, GFR, Histology	

Model	Etiology/Mechanism	Method	Morphologic changes	Time course comparisons	Assessments reported	References
Ggt1 DTR transgenic mice	Tubular injury due to toxic tubular necrosis	Genetic and induced, DT injection (100 mg/kg, i.p, day 0 and 5)	Acute tubular necrosis in acute phase, tubulointerstitial fibrosis in chronic phase	6 wk after last dose	BUN, Serum Cr, GFR, Histology	
NO inhibition (rat or mouse)	Hypertensive	Induced, L-NAME (50 mg/kg/day) for 4 weeks	Glomerulosclerosis and interstitial fibrosis	4 wk-->8 wk	BP, Proteinuria, Histology	45
SHR rat	Hypertensive	Spontaneous	Glomerulosclerosis and interstitial fibrosis	16-18 wk-->36 wk, 20 wk-->23 wk	BP, Proteinuria, Histology	48, 49