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Models of chronic kidney disease

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Abstract

Chronic kidney diseases result from recurrent or progressive injuries in glomeruli, tubules, interstitium and/or vasculature. In order to study pathogenesis, mechanisms and effects of interventions, many animal models have been developed, including spontaneous, genetic and induced models. However, these models do not exactly simulate human diseases, and most of them are strain, gender or age dependent. We review key information on various rodent models of chronic kidney diseases.

Introduction

Chronic kidney disease (CKD) is a significant medical problem globally. A variety of etiologies (including genetic, autoimmune, infectious, environmental, dietary, medications) contribute to the diverse primary outcomes, but all can eventually lead to the same endpoint--chronic kidney disease. The primary process can involve glomerular, tubular, interstitial and/or vascular compartments. Animal models of CKD provide opportunity to investigate disease-specific mechanisms, to investigate molecular pathogenesis, and assess potential novel therapies. In this review we introduce a range of animal models that mirror various elements of human CKD.

In vitro models

Almost every intrinsic renal cell has been extensively investigated to assess potential causality of CKD, cell-specific mechanisms, and especially signaling pathways. However, the results are limited and can mainly be interpreted as individual and specific responses unique to only the cell type studied. Such approaches do not represent the crosstalk among the cells and the subsequent complex *in vivo* responses in CKD, and are thus of limited utility.

In vivo models

1. Spontaneous Models

1.1 Glomerular and interstitial injury models

● **Lupus nephritis:** Lupus nephritis is characterized by immune complex-mediated glomerulonephritis with consequent and various time and injury-dependent inflammatory

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and sclerosing reactions, accompanied by interstitial inflammation and late stage fibrosis. So far, at least four mouse models of lupus nephritis are available, including mice of NZB, (NZB x NZW) F1 hybrid (termed NZB/W), MRL/*lpr* and BXSB strains. Among these four, MRL/*lpr* and NZB/W spontaneously develop lupus nephritis that closely resembles human histological findings. Female NZB/W mice are more susceptible to renal lesions than male NZB/W. Females usually develop albuminuria at the age of 5–6 months and die as a result of renal failure by 10–12 months of age [1]. In comparison, both male and female MLR/*lpr* mice exhibit significant proteinuria at 16 weeks and about 50% die by 20–24 weeks [2]. Production of autoimmune antibodies against assorted nuclear antigens is closely related to the severity of kidney lesions. Interactions between the different susceptibility genes contribute to the genetic complexity of this disease [2,3].

● **Aging:** Humans develop progressive glomerulosclerosis, interstitial fibrosis, and tubular atrophy along with decreased glomerular filtration rate (GFR) with aging. Studies from naturally aging rat kidneys suggest that both gender and genetic background determine the rate and the scale of progression of age-related renal impairment and scarring. In general, age-related kidney scarring begins earlier and becomes more severe in male rats than in females. Sprague Dawley rats are more susceptible than other strains. 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 [4]. Compensatory hyperfiltration sustains GFR within normal range until rats are about 24 months of age. However, with advancing age, compensatory hemodynamic changes are insufficient to maintain GFR, and progressive decline manifests. The earliest renal morphologic changes, characterized by mesangial expansion and thickening of the glomerular basement membranes (GBM), begin at 3 months. By 2 years of age, GBM thickness and increased mesangial matrix are increased 2–3 fold vs. young adults and glomerulosclerosis and tubulointerstitial fibrosis ensue later [4]. Studies on aging mice also indicate that strain and gender affect the age-associated renal dysfunction and pathological changes [5,6]. In C57BL/6 mice, glomerular injury, including GBM thickening and mesangial matrix expansion, increase at 12 months of age in both genders and peak at 24 and 33 months of age in males and females, respectively [6]. Supplier-dependent differences in mice supposedly of same strain may explain the varied experimental results in renal aging studies [5].

1.2 Vascular injury models

● **Spontaneously hypertensive rats (SHR):** SHR is a good model for studying 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. The evolution of hypertension and age-related alterations in renal function differ between male and female SHR. Proteinuria begins to increase at 6 weeks of age in male SHR and increases linearly from 10 to 70 wk of age. In contrast, proteinuria in female SHR reaches a plateau at 6–8 weeks, is stable until 14 weeks and is approximately sixfold lower than in male SHR. 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 [7,8]. Starting between 40 and 50 weeks, SHR develop glomerulosclerosis and interstitial fibrosis.

● **Buffalo/mna rat:** The Buffalo/mna rat is a relevant model of human idiopathic nephrotic syndrome. By 2 months of age, Buffalo/mna rats spontaneously develop podocyte alterations including foot process effacement and vacuolization and manifest proteinuria and nephrotic syndrome. At 6 months, these rats present histological lesions similar to human

focal and segmental glomerulosclerosis (FSGS). By 22 months of age, more than 40% of the glomeruli became sclerotic [9]. Interestingly, the tip lesion found early in life in these rats extends to all parts of glomeruli later on. A kidney transplantation study in Buffalo/mna rat suggested that a circulating factor may play a causal role in the renal lesions [10].

● **Munich Wistar Frömter (MWF) rat:** The MWF rat is a genetic model relevant to the concept of human disease related to a congenital deficit in nephron number being predisposed to the development of hypertension and salt sensitivity in adulthood. MWF rats demonstrate an inborn reduction of nephron number on the order of 30–50% less than normal. By the early age of 10 weeks, MWF rats develop proteinuria and SBP ranges from 140 to 150 mmHg. By 9 months of age, SBP reaches 180 mmHg and the kidney exhibits significant glomerulosclerosis. Notably, these phenomena are more prominent in males than in females despite similar nephron deficit. Higher single nephron filtration rate and glomerular volume in males vs. females may contribute to this gender difference [11].

2. Genetically Engineered Models

● **Primary podocyte-specific genetic FSGS models:** Primary podocyte-specific genetic FSGS models, which allow elucidation of injuries relevant to human podocyte injury in general and specifically to so-called podocytopathies, are reviewed in detail elsewhere in this issue.

Briefly, such models allow genetically engineered podocytes to be selectively depleted by giving animals a specific toxin. We have studied chimeric mice where only some podocytes expressed a toxin receptor under the nephrin promoter (Nep 25 mice) and thus could be injured by immunotoxin administration. Interestingly, podocytes without the toxin receptor showed equally severe injury as those with the receptor, demonstrating that injury can spread from an initially injured podocyte to adjacent initially intact podocytes, setting up an intraglomerular vicious cycle of injury, culminating in sclerosis [12,13].

● **HIVAN:** The first HIV-associated nephropathy (HIVAN) transgenic mouse model was created using a replication-deficient version of HIV as the integrated transgene, so-called transgenic 26 (Tg26) mice. Proteinuria is first observed at 24 days of age. Around 20% of these mice die between 2 to 6 months with increased proteinuria, elevated blood urea nitrogen, edema, ascites, and hypoalbuminemia. Histological examination reveals mild and limited focal changes in mice younger than 2 months of age. Moribund mice with heavy proteinuria show diffuse segmental and global glomerulosclerosis of the collapsing variant, microcystic tubular changes, and monocytic interstitial infiltrate, which strikingly resembles the lesions seen in human HIVAN [14]. The genetic background modulates the severity of renal damage in Tg26 mice, with most severe injury on FVB/N strain.

Several single HIV gene transgenic and gene deletion HIVAN models have been generated to determine the role of specific HIV genes in the pathogenesis of HIVAN. We found that transgenic mice with podocyte-specific expression of a HIV gag/pol/env construct develop extensive HIVAN pathology [15]. Furthermore, HIV-1 genes *vpr* (**NC_001802.1 (5105..5396)**) and *nef* (**NC_001802.1 (8343..8963)**) synergistically damage podocytes leading to glomerulosclerosis [16]. Background strain modified the injury, with usual type sclerosis on C57BL/6 background, and collapsing glomerulopathy on mixed 129/Sv background. The same transgene structure used in the Tg26 mouse model has also been used to create a rat HIVAN model. Compared to the mouse model, this rat model presents prominent mesangial hyperplasia and although the HIV transgene appears to be more widely and efficiently expressed, collapsing glomerulopathy is not present [17].

● **Alport syndrome:** Mutations of the α3, α4, or α5 chains of type IV collagen (*COL4A3*, *COL4A4*, and *COL4A5*) cause Alport syndrome, an inherited disorder characterized by progressive glomerulosclerosis associated with hearing loss and lens abnormalities. Alport mice, which genetically lack the α3 (IV) collagen chain (**NC_000067.5 (82583551..82717843)**) on 129Sv background, thus show the same genetic defect as the autosomal form of human Alport syndrome. There is irregular thickening and splitting of GBM by 4 weeks of age, as in human Alport. However, these mice also show prominent extracapillary crescentic proliferation at this early stage, a lesion not seen in typical human Alport [18]. Proteinuria with mild hematuria occurs by 5 weeks [18,19]. Severe glomerular sclerotic lesions with subsequent tubulointerstitial fibrosis are found at 10 weeks. Renal function deteriorates rapidly around 14 weeks and only 5% survive longer than 4 months of age [20,21].

3. Acquired models

3.1 Immune-induced models

● **Thy-1 nephritis:** Thy-1 nephritis is an experimental rat model of mesangioproliferative glomerulonephritis (MsPGN), which mimics an antigen-triggered immune MsPGN in human, such as IgA nephropathy and Henoch–Schönlein purpura nephritis. It is induced by a single injection of rabbit anti-thymocyte serum or mouse anti-Thy 1 monoclonal antibody (OX-7 1 mg/kg body weight) through a tail vein [22]. In some studies, the combination of Thy-1 injection and uninephrectomy has been used to produce a progressive model [23]. The Thy-1 antigen is originally found on thymocytes, and also is present on rat glomerular mesangial cells. After injection of antibody, an immune attack is induced. However, no IgA or other immune complex deposits are found in this model. There is hematuria and proteinuria without hypertension in this model. There is mesangiolysis due to necrosis and fibrin deposition with monocyte/macrophage infiltration early on by day 2, followed by subsequent mesangial cell proliferation, mesangial matrix expansion and small crescent formation [24]. The mesangial cell proliferation peaks at about 1 week, and the nephritis spontaneously repairs after 3 weeks. Repeated injections of Thy-1 (OX-7 1.2 mg/kg body weight at 1 and 2 wk) can result in chronic sclerosis and proliferative lesions with interstitial fibrosis and progressive CKD [6].

● **Anti-GBM model:** Clinically Goodpasture's syndrome has lung hemorrhage and rapidly progressive glomerulonephritis, induced by autoantibody to the basement membrane of glomeruli (GBM) and alveoli. Models of anti-GBM nephritis have been developed in rodents. Mouse GBM was collected from isolated glomeruli, emulsified with complete Freund's adjuvant (CFA), and administered to rabbits by repeated immunization. Mice were then injected i.p. with this rabbit IgG emulsified with CFA, followed by a tail vein injection with anti-GBM antiserum five days later [25]. Within 2 to 3 weeks, mice exhibit pronounced glomerulonephritis with crescent formation, as well as tubulointerstitial disease. They develop severe proteinuria and azotemia in the following weeks. The principal targets are the NC domains of alpha-3 chain of type IV collagen [26]. Anti-GBM nephritis can be induced in both rats and mice, although great variation in susceptibility among strains has been reported. The Wistar Kyoto (WKY) rat is highly susceptible and develops crescentic glomerulonephritis, while the Lewis (LEW) rat is resistant [27]. In mice, BUB/BnJ, DBA/1J, and 129/svJ mice are more susceptible than A/J, AKR/J, C3H/HeJ, DBA/2J, MRL/MpJ, NOD/LtJ, P/J, SJL/J, and SWR/J mice [28]. Both the characteristics of the anti-GBM antibodies and factors related to the inflammatory response to antibody deposition are important in determining susceptibility to this model of experimental autoimmune glomerulonephritis.

3.2 Non-immune induced models

● **5/6 nephrectomy:** Sub-total 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 [29]. 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. The last approach is a combination of ligation and ablation model, which ties one or more branches of the mouse renal artery, and then cautery is 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. Approaches with infarction typically are associated with more severe proteinuria and hypertension than those with only excision. 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 glomerular sclerosis involves about 20% of glomeruli, accompanied by early interstitial fibrosis and tubular atrophy. By 12 weeks, widespread glomerulosclerosis and tubulointerstitial fibrosis are found [30]. Rats typically die of uremia starting at week 12. Although most rats 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 sclerosis [31].

● **Radiation nephropathy:** Radiation nephropathy occurs in about 20% of sufficiently irradiated subjects who have undergone therapeutic irradiation. Radiation nephropathy is characterized by acute endothelial injury, thrombotic microangiopathy and organization as a chronic progressive secondary sclerosis with proportional tubulointerstitial fibrosis. In animals, total-body irradiation (TBI) can induce an initial hyperemic response in GFR and effective renal plasma flow followed by a dose-dependent decline in GFR and effective renal plasma flow within 6 to 8 weeks [32]. Radiation nephropathy can be induced without systemic toxicities of bone marrow ablation or gastrointestinal toxicity by delivering a local dose (10 Gray) with shielding of the GI tract. Early lesions mirror the endothelial injury seen in human. In later stage, glomeruli show variable capillary loop thickening with subendothelial expansion, basement membrane duplication, mesangiolysis and sclerosis. Interstitial fibrosis with mild interstitial inflammation is a common feature of advanced disease. Radiation-induced injury involves complex and dynamic interactions between glomerular, tubular, and interstitial cells. Angiotensin II is clearly a predominant player in this process; however, other factors, including nitric oxide, transforming growth factor-β (TGF-β), and plasminogen activator inhibitor-1 (PAI-1) appear to be involved [33]. There is some evidence that mice are relatively resistant to radiation-induced renal injury and exhibit radiation nephropathy much later than rats. C57/BL6 mice fail to show an increase in blood urea nitrogen until approximately 1 year after TBI, while CBA mice exhibit dose-dependent decreases in renal function within 12 weeks of irradiation [34].

● **Unilateral ureteral obstruction (UUO):** Complete ureteral obstruction is not a usual cause of human renal disease. However, the UUO model is useful to examine mechanisms of tubulointerstitial fibrosis in vivo [35]. This model can be induced in either rats or mice and shows no specific strain dependence. Complete UUO initiates a rapid sequence of events in the obstructed kidney, leading within 24 h to reduced renal blood flow and glomerular filtration rate. The subsequent responses include interstitial inflammation (peak at 2–3 days), tubular dilation, tubular atrophy and fibrosis from 7 days. The obstructed

kidney reaches end stage by around 2 weeks [36]. Major pathways leading to the development of renal interstitial fibrosis are interstitial infiltration by macrophages, tubular cell death by apoptosis and necrosis, and phenotypic transition of resident renal cells. Because most cases of clinical congenital obstructive nephropathy involve partial, rather than complete obstruction, models of partial UUO have been developed in the neonatal rat and mouse. Partial or reversible UUO models are, however, technically very challenging to perfect, with frequent adhesions or fibrosis leading to failure of reversal and complete obstruction [37]. The advantage of the complete obstruction model is good reproducibility, short time-course, easy performance and the presence of the contralateral kidney as a control. Disadvantages include lack of functional readouts, in that serum creatinine is normal and no proteinuria because the injured kidney is completely obstructed and has no urine output. The model also has no hypertension.

● **Puromycin aminonucleoside nephrosis (PAN) and adriamycin nephropathy:** The nephrotoxic properties of adriamycin and puromycin aminonucleoside are frequently used to model nephrotic syndrome, and are discussed elsewhere in this issue.

● **Folic acid nephropathy:** Folic acid induces interstitial fibrosis. High dosages of folic acid (250ug/g BW) given i.p in mice induces folic acid crystals rapidly with tubular necrosis in the acute phase (1–14 days) and patchy interstitial fibrosis in the chronic phase (28–42 days). Co-administration of sodium bicarbonate with folic acid can increase the alkalinity of the urine and decrease crystal formation. However, tubular lesions still occur, suggesting that folic acid renal injury is induced both by crystal obstruction and direct toxic effect to tubular epithelial cells [36,38]. The advantage of this model, compared to UUO, is that renal function can be assessed as a measure of CKD. However, the model is somewhat variable, and some mice will regress spontaneously after 42 days.

● **CyA 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. These changes only develop, however, if accompanied by a very low salt diet. Cyclosporin A-induced nephropathy appears to involve the renin angiotensin system, endothelin, and overexpression of IL-6, TGF-β and activation of NAD(P)H oxidase in endothelial cells [39].

● **DOCA-salt nephropathy:** The administration of deoxycorticosterone acetate (DOCA), in combination with a high salt diet and unilateral nephrectomy, induces moderate to severe hypertension with renal injury and low renin levels [40]. In contrast, the two kidney-one clip model of hypertension has high renin levels. DOCA is administered weekly by subcutaneous injection. Salt is administered by substitution of 0.9% NaCl for drinking water. In order to produce progressive renal injury, the combination of uninephrectomy and angiotensin II infusion are also used. Renal changes include proteinuria and glomerulosclerosis, and impaired endothelium-dependent relaxation. Despite low renin, increasing evidence indicates that the local renin-angiotensin system (RAS) in the kidney contributes to renal injury of uninephrectomy and DOCA-salt hypertension, with increased TGF-β1 and extracellular matrix components. This model also mimics aldosterone overload, giving rise to a volume-dependent hypertension, and is thus also considered a model of human primary aldosteronism.

Model Comparisons

Choosing the correct model to address specific hypotheses is important for research. In general, the models with an unknown, mostly genetic etiology (SHR, Buffalo/mna, aging) provide the opportunity to search for new mechanisms and new genes in CKD. To investigate the morbidity associated with CKD, it seems reasonable to choose a model where the etiology is known to some extent, such as UUO, 5/6 nephrectomy, and podocyte-specific targeting-associated CKD. Further, different models represent different types of CKD, as described above in comparing e.g. glomerulosclerosis models (Buffalo, MWF, HIVAN, 5/6 Nx, etc.) to interstitial fibrosis models (UUO, CyA nephropathy, etc.).

As discussed above, 5/6 nephrectomy has been a widely used model for studying glomerulosclerosis. The advantages of this model include robust functional readouts (such as proteinuria, GFR and secondary hypertension), reliable induction in rodents, and comparison to the kidney removed at induction of injury. This model has elucidated mechanisms that translate to CKD secondary to nephron loss in humans. It has also been useful for study of mechanisms of glomerular disease. However, the surgery is difficult and it has a long time course. Further, the model is highly strain specific in mice. Additionally, hypertension is moderate to severe, and any interventions must adequately control for hypertensive *vs.* nonhypertensive mechanisms. For studying tubulointerstitial fibrosis, UUO is the most widely used model. It is easily and quickly induced, with a robust and reproducible phenotype. The intact nonobstructed kidney serves as an excellent control. However, this model lacks functional readouts in that serum creatinine is normal, and there is no proteinuria. Further, there is no significant glomerular injury, and the nonreversible injury limits its uses.

Model Translation to Humans

Clearly, animal models have been essential components of medical research to delineate mechanisms and test possible interventions in human disease including chronic kidney diseases. However, the efficacy demonstrated in animal models cannot always be translated into clinical success due to several limitations. One is the differences in physiology between animals and man. Another obstacle is that the genes that yield the phenotype in a given model in certain inbred strains may only represent a small subset of the genes that produce the phenotype in complex human diseases. Thus, judicious use of models of chronic kidney disease while considering the specifics of each model can aid in relevant interpretation and translation to clinical insights of mechanisms and potential therapeutic targets.

Conclusions

We have provided a brief overview of the most widely used animal models of CKD, and their characteristics. Differing models have differing strengths and weaknesses. The most important lesson is that no animal model can exactly simulate human disease expression or predict response in human CKD. Judicious choice of animal model can, however, offer valuable insights into mechanisms and pathogenesis, with appropriate caveats before translating results to possible parallels in human CKD.

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Pathology	Model	Etiology/Mechanism	Translation to human disease	References
Glomerulonephritis	MRL/*lpr* NZB/W nephritis	Spontaneous, immune complex LN	Partial	1,2,3
	Anti-GBM nephritis	Immune, necrosis	Partial	25,26,27,28
	Anti-Thy 1 nephritis	Immune, crescents, mesangiolysis	Partial	22,23,24
	Alport syndrome	Early crescentic, late sclerosis	Not a model of human Alport syndrome lesions	18,19,20,21
Glomerulosclerosis	Aging	Spontaneous	Good	4,5,6
	Buffalo/MWF	Spontaneous	Good	9,10,11
	Nep25/DT	Genetically engineered, podocyte toxin	Partial	12,13
	PAN/adriamycin nephropathies	Podocyte toxin	Excellent for MCD and FSGS	
	Radiation nephropathy	Radiation, direct cell injury	Good	32,33,34
	5/6 Nx	Surgical, decreasing nephron number	Excellent for secondary FSGS	29,30,31
	HIVAN	HIV transgenic systemically or podocyte specific	Good	14,15,16,17
Interstitial fibrosis	UUO	Surgical	Partial	35,36,37
	Folic acid nephropathy	Crystal and direct tubular toxin	Good	38
	CyA nephropathy	Vasoconstriction, ischemia	Good	39
Vascular	SHR	Spontaneous, hypertension	Good	7,8
	DOCA-salt	Vasoconstriction, hypertension	Good for primary aldosteronism, partial for usual hypertension-associated CKD	40

Abbreviations: LN, lupus nephritis; GBM, glomerular basement membrane; Nep25, nephrin-hCD25; DT, diphtheria toxin; PAN, puromycin aminonucleoside; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; Nx, nephrectomy; HIVAN, human immunodeficiency virus-associated nephropathy; UUO, unilateral ureteral obstruction; CyA, cyclosporine A; SHR, spontaneously hypertensive rat; DOCA, deoxycorticosterone acetate.