Chapter 2

Animal Models of Renal Pathophysiology and Disease

Adam Hosszu, Tamas Kaucsar, Erdmann Seeliger, and Andrea Fekete

Abstract

Renal diseases remain devastating illnesses with unacceptably high rates of mortality and morbidity worldwide. Animal models are essential tools to better understand the pathomechanisms of kidney-related illnesses and to develop new, successful therapeutic strategies. Magnetic resonance imaging (MRI) has been actively explored in the last decades for assessing renal function, perfusion, tissue oxygenation as well as the degree of fibrosis and inflammation. This chapter aims to provide a comprehensive overview of animal models of acute and chronic kidney diseases, highlighting MRI-specific considerations, advantages, and pitfalls, and thus assisting the researcher in experiment planning.

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Key words Kidney disease, Magnetic resonance imaging (MRI), Animal models, Rodents

1 Introduction

Renal diseases remain devastating illnesses with unacceptably high rates of mortality and morbidity worldwide. The prevalence of end stage kidney disease is currently between 8% and 16% and is rapidly increasing; the number of patients increased tenfold in the last four decades [1].

Kidney diseases generate a major drain on health and productivity-related resources for healthcare systems; thus, prevention and early treatment would have an enormous social and economic impact.

Understanding the pathologic mechanisms of renal injury is essential for finding new targets for intervention and developing effective treatments for patients with kidney disease [2]. Landmark publications have outlined key areas in which progress is necessary, specifically highlighting the need for superior diagnostic tools [3].

At present, diagnosis of kidney disease is difficult and often involves invasive procedures such as biopsy. Conventional markers of renal function such as serum creatinine and blood urea nitrogen

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are poorly sensitive and poorly selective. The levels of these biomarkers can take several hours or days to reach a new steady state and thus represent a delayed indication of functional change that lags behind structural deterioration during the early stage of acute kidney injury (AKI). In addition, the imbalance between oxygen supply and demand in kidney tissue is the initiating step in the pathophysiology of renal ischemia–reperfusion injury (IRI), and a pivotal early element in the pathophysiology of AKI of other origins. Currently kidney biopsy is the only available method to assess renal microstructure, but it has several disadvantages, including its invasive nature and susceptibility to sampling bias. Thus, noninvasive, in vivo imaging methods such as MRI are indispensable for the adequate assessment of kidney function, oxygenation, and structure in both preclinical and clinical setups. Importantly, several novel techniques are available to generate MRI data by measuring tissue properties linked to filtration, tissue oxygenation, perfusion, fibrosis, inflammation, or tissue edema that can be used as biomarkers of renal disease [4]. MRI affords full kidney coverage, soft tissue contrast that helps to differentiate the renal layers, second-to-minute temporal resolution, support of longitudinal studies, and high anatomical detail without the use of ionizing radiation [5, 6].

Drug discovery is a time-consuming, expensive, and high-risk process. In order to develop one FDA approved drug in the preclinical phase thousands of compounds have to be tested from which only dozens end up in clinical trials [7]. Conducting studies on animal models is a valuable strategy in the preparation for clinical trials because of the high similarity between some animals and humans in their genetics, physiology, diseases, and diagnostic tools. Without doubt the translatability of results obtained in animal models to humans has numerous limitations, but often they represent an indispensable approach for trying to predict the effects of a drug in the complex human system, and also for deciding on an appropriate dose regime for the clinical trial(s) that balances efficacy and safety. Many mechanistic questions can be answered only through invasive procedures or extreme exposures possible only in animals. Moreover, due to the fact that decades may elapse between the onset and clinical manifestations of renal diseases in humans (e.g., diabetic kidney disease), rodent models offer a more feasible means of experimentation because the timeline of pathogeneses are typically much shorter (either naturally or due to tailored disease induction).

An ideal disease model accurately mimics the human condition genetically, experimentally and/or physiologically, but unfortunately such models do not exist. One reason for the poor outcomes in clinical trials is that most animal models do not fully recapitulate the pathological mechanisms underlying human diseases. Human diseases are very complex, but specific factors of a disease are relatively easy to model, which is an advantage and disadvantage

at the same time. All of the widely used animal models have their particular limitations; therefore, the model used should be appropriate for the question being addressed [8].

The present chapter summarizes animal models of renal diseases highlighting MRI-specific considerations, advantages, and pitfalls with an aim to assist the researcher in planning an experiment and choosing the best species/strain/model to address the question being asked.

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2 Ethical Issues

A wide range of positions exist on the debate over the ethics of animal experiments. On one end of the spectrum people argue that an animal should have as much right to live out a full life, free of suffering as a human and thus all animal experimentation should end. Others argue that while the unnecessary abuse of animals is clearly wrong, animal experimentation must continue because of the enormous scientific resource that animal models provide. A detailed discussion of the growing scholarly literature in animal research ethics is beyond the scope of this chapter; however, the authors feel obliged to provide some fundamental guidelines for conduct of ethical research. The authors of this chapter believe that biomedical animal research is founded on a pivotal ethical principle: "*It is among the most noble and indeed imperative of human endeavors to employ scientific research to prevent, alleviate, and cure the pain, suffering, distress, fear, anxiety, disability, infirmity and death associated with human disease*" [9]. Because the use of animal models to understand human disease is motivated by such a high ethical ideal, we must aim to adhere to the highest ethical standards when conducting research.

When designing a study applying the principles of 3Rs: replacement, reduction, and refinement is advised to provide a framework for performing the most humane animal research possible. *Replacement* means the substitution of animals with alternative techniques or avoid the use of animals altogether. Alternative methods such as cell cultures or novel approaches such as stem cell technologies, tissue engineering, or modeling using artificial intelligence show promise for replacing animals in many areas of research but often give limited information about what happens in the whole living animal. *Reduction* means to obtain information of given amount and precision from fewer animals or more information from the same number of animals. Proper experimental design and statistical analysis of the proposed project is pivotal in using the optimal number of animals. If more animals are used than is necessary for

obtaining reliable results, then animal lives are wasted. On the other hand, if too few animals are used then the results can be unreliable and the experiment has to be repeated, using more animals in total. *Refinement* means minimizing the incidence or severity of procedures that result in distress or suffering of animals which still have to be used. Refinement can also improve the quality of research by reducing stress in animals. By law, any suffering or pain to an animal must be minimized. Animals must be anaesthetized for surgery, and, if necessary, analgesics must be administered afterward, which will be discussed in detail in the chapter by Kaucsar T et al. "Preparation and Monitoring of Small Animals in Renal MRI."

3 General Guidelines for Choosing an Animal Model

3.1 Rat or Mouse?

The first major decision when designing a study using an animal model is to choose the most suitable species. Rodent models are the most popular to resemble human disease for a number of reasons: 90% of genes are orthologous in the rat, murine, and human genomes, small size and fast reproduction of rodents facilitates high-throughput studies, and a very good genetic/molecular tool box is available.

Differences within rodents must not be underestimated when designing experiments. Inbred mouse strains are more stable, uniform, repeatable, and better defined than outbred rat strains such as Wistar or Sprague-Dawley where the exact genetic background of each animal is unknown [10].

While rats used to be the preferred rodent in kidney research, this changed with the advent of murine transgenic and knockout technologies in the past decades. Genetically modified mice provide unique opportunities for targeted research of the impact of individual proteins on phenotype and responsiveness to therapeutic interventions. Gene deletion or overexpression generally results in very predictable and precise phenotypes in mice. Furthermore, due to their small size many more mice can be housed in a small space than rats and are therefore cheaper to maintain; they have a short reproductive cycle and accelerated life span.

Murine models of kidney disease do have some limitations and disadvantages that are worth considering. Surgical procedures such as ureteric obstruction, renal ischemia, or kidney transplantation are widely used to model human disease. Surgical manipulations and micropuncture studies are technically much easier to perform in larger animals such as rats.

Moreover, the pathophysiology in rat models is often not replicated in mice. For example, while humans and rats have only one copy of the renin gene, mice either have a single gene or two copies at the renin locus. This may be an important confounding variable considering the central role of the renin–angiotensin–aldosterone system in renal disease and that the plasma renin activity of mice

with two renin genes is tenfold higher than their single-gene counterparts [11].

Hypertension is a leading cause of kidney failure; thus, noninvasive blood pressure measurements are a crucial component of studies in the field. While the technique is fairly routine in rats, it has been proven to be rather challenging in mice [12].

Finally, the smaller size of mice means smaller amounts of experimental material to work with. The fundamental limitation in MRI is signal-to-noise ratio, which is in direct correlation with the volume of the subject. Acquiring high-resolution images of relatively small mouse kidneys could be challenging using lower field strength MRI machines. Furthermore, concurrent measurement of multiple variables such as RNA expression, protein levels, histology, and metabolic processes from individual animals can be challenging.

3.2 Which Strain?

The choice of the right strain is essential since disease phenotypes in rodents are strongly influenced by species and strain. For example, there are distinct differences in the susceptibility to ischemic AKI among various mouse strains or even different colonies of the same strain. 129/Sv and National Institute of Health Swiss mice have been shown to be less sensitive to ischemic injury than C57BL/6 or BALB/c mice [13, 14]. Most transgenic models are described to have comparable genetic background with wild-type strains such as C57BL/6 after at least five generations of backcross; however, the wild-type mice from the same transgenic models may differ significantly from ordinary C57BL/6 mice. Similarly, Brown-Norway rats have been found to be almost completely protected against several manifestations of IRI when compared with the commonly used Sprague-Dawley rat model [15]. In conclusion, pilot experiments always have to be performed to determine the appropriate duration of ischemia for a new strain to be studied.

The C57BL/6 mouse strain is also relatively resistant to the development of diabetic kidney disease (DKD). C57BL/6 mice develop significantly less albuminuria and renal histopathological changes than DBA/2J and KK/HIJ mice [16]. Sprague-Dawley rats are far more sensitive to streptozotocin-induced diabetes than nude rats [17].

The remnant kidney model or 5/6 nephrectomy model has been used extensively in rats to study the pathogenesis of glomerulosclerosis. In contrast, mouse strains such as C57BL/6 and C57BLX Swiss-Webster mice do not develop significant glomerulosclerosis or increased systolic blood pressure and proteinuria in this model. C57BL/6 mice and Wistar rats are less susceptible to deoxycorticosterone acetate (DOCA) salt-induced hypertension than 129/Sv mice or Sprague-Dawley rats respectively [18, 19]. Thus, the more susceptible 129/Sv strain is

recommended to study hypertension-associated glomerulosclerosis in mice [20].

3.3 Sex

The anatomical structure of the healthy kidney is different in the two sexes. Females have more glomeruli in the kidneys, higher renovascular resistance, lower absolute GFR, and lower renal plasma flow. There are differences on the cellular level as well: males have larger mitochondria and more lysosomes and ribosomes in their proximal tubular cells. Although estrogen and androgen receptors are found in renal tissue in both sexes, animal experimental models (e.g., castration, ovariectomy) suggest that sex hormones are involved in the sexual dimorphism of the kidney [21].

Female sex is a protective factor in several renal diseases which disappear after menopause. Not only the outcome of AKI is better in females [22, 23], but the progression of renal function deterioration during the aging process [24] as well as other chronic renal diseases [25] is also slower in females compared to males. Some studies support the protective role of female hormones (17-β-estradiol, progesterone) [26–28]. Others highlight the negative effect of testosterone: Park et al. found more severe renal injury after testosterone therapy in female, ovariectomized, and castrated male mice [29].

For the aforementioned reasons the use of female rodents is only advised if the study specifically aims to investigate sex differences or the role of sex hormones. Duration of the estrous cycle is 4–5 days in both rats and mice; a vaginal smear has to be obtained and stages of the estrous cycle have to be identified before starting an experiment. C. Caligioni provides a detailed description of assessing the reproductive status of mice [30].

3.4 Other Species

Some nonrodent species are also used, although less frequently. In theory, nonhuman primates are the most similar to human biology, but the heterogeneity is huge among species. Close approximation of genetic, structural, and functional features of nonhuman primates to humans make them ideal experimental models; however, specific ethical considerations are essential [31]. These animals are likely to sense pain, distress, and social relationships in the same way as humans. Moreover, they are expensive to obtain and house, may transmit diseases to humans, and can be difficult to handle due to their strength and intelligence. Experiments with nonhuman primates are limited to a very small number of animals compared to rodents; thus, their statistical value can be doubtful.

Work using dogs played an enormous role in the early advancement of dialysis and transplantation techniques, or the use of azathioprine in immunosuppression, and others [32]. However, ethical considerations and strong feelings of the public have substantially limited the use of companion animals for research purposes.

Farm animals such as pigs are fairly similar to humans in renal anatomy, size, and metabolism. Pigs are the subject of extensive research especially as a potential source of kidneys for xenotransplantation [33]. The size of fully grown pigs limits routine laboratory use; moreover, potential virus or prion transmission from pigs to humans will possibly reduce their use as xenograft sources.

4 Models of AKI

4.1 Ischemia–Reperfusion Injury

Renal IRI is the most common cause of AKI in patients and temporary occlusion of renal blood flow is unavoidable during kidney transplantation. Therefore, models that accurately and reproducibly replicate renal IRI are indispensable for investigating the pathomechanism of AKI and for the development of novel therapeutic agents. There are three commonly used models of IRI: (1) bilateral clamping of renal arteries and veins; (2) unilateral clamping; and (3) unilateral clamping with contralateral nephrectomy [34]. The bilateral model is regularly used because it is considered most relevant to human pathology where blood supply is typically affected in both kidneys. Some studies performed decapsulation prior to renal ischemia that may have renoprotective effects, as reported earlier [35]. However, decapsulation was not conducted in the majority of published studies. Unilateral IRI models without contralateral nephrectomy leave animals with a healthy kidney which takes over the excretory function. Consequently, this model allows for the study of the effect of prolonged ischemia times without excessive postprocedure lethal outcomes. On the other hand, this model does not allow the study of filtration and excretory function of the affected kidney after IRI because of the compensation achieved by the unaffected healthy kidney. In the third model right nephrectomy is performed at the time of left kidney IRI. Tissue from the removed right kidney can be used as highly valuable control in studies where pretreatment that induces or suppresses specific gene or protein expression is involved. Thus, changes in the molecule of interest can be confirmed and quantified in each individual animal used in the experiment. This model is most useful when the researcher aims to test the effect of drugs or compounds administered prior to the induction of IRI, furthermore overall survival is more reliable than with bilateral clamping and this model closely mimics the situation occurring in renal transplantation. Several studies suggest the protective potential of contralateral nephrectomy against IRI by increasing blood flow and other beneficial pleotropic effects (e.g., antiapoptotic, proliferative, vasodilatory) in the remaining kidney [36], which should be taken into consideration when designing an experiment.

The pathological consequences of renal IRI are proportional to the period of ischemia which has to be determined for the

individual species, strain, sex, and age. Shorter ischemia causes subclinical AKI, with minor histologic change and without any functional deterioration as assessed by serum creatinine and BUN [37]. As ischemia duration increases clinical AKI develops with moderate renal damage accompanied by renal failure. If the extent of injury is mild, then the full recovery of renal function can be expected. However, longer ischemia generally leads to lethal kidney damage, with continuously deteriorating kidney function and the animals die due to uremia [38]. As a guide, 30–50 min and 20–35 min of occlusion respectively is generally used in rats and mice. Clamping time, maintenance of body temperature, and the type of anesthesia are key parameters to be standardized for reproducibility.

4.2 Renal Transplantation

Renal transplantation is predominantly performed in rats due to the challenging microsurgical techniques involved. Depending on the aim of the study various combinations of inbred and outbred strains model various complications of kidney transplantation such as IRI, acute rejection, or chronic allograft nephropathy [39]. Autotransplantation models are ideal for the study of alloantigen-independent mechanisms such as IRI or the effect of cold storage on the organ. Fisher and Lewis rat strains differ at the major histocompatibility loci I and II which results in chronic allograft nephropathy if no immunosuppression is applied. Thus, transplantation from a Fisher donor to a Lewis recipient is the most commonly used model of chronic allograft nephropathy [40]. Other strains—both as donor and recipient—include outbred strains: Sprague-Dawley, Wistar, and Long-Evans; or inbred strains: Lewis, Brown-Norway, and Dark Agouti [41–43].

A large number of different surgical techniques have been reported, probably due to the technical difficulties associated with rat renal transplantation. Detailed procedures are available in an excellent review by Schumacher et al. which describes all technical aspects, different techniques of vascular anastomosis, strain selection, and more [44].

4.3 Sepsis-Induced AKI

Sepsis is a complex disease that involves at least two stages, which should ideally be reproduced in animal models. An initial proinflammatory burst resulting in hypodynamic circulation with hypotension and organ dysfunction is followed by compensatory immune depression, with hyperdynamic circulation, but these can overlap. There are three types of sepsis animal models: exogenous toxin (e.g., LPS)-induced; alteration of endogenous protective barriers (e.g., cecal ligation and puncture (CLP) or colon ascendens stent peritonitis (CASP)); or exogenous bacteria-induced. The LPS model is predominantly used in rodents as the standard CLP model does not develop AKI, while bacterial infusion models are established mainly in larger animals such as dogs and sheep. C. N. May's

group established a model of hyperdynamic sepsis in conscious sheep. In this model sepsis is induced by intravenous infusion of live *Escherichia coli* and is characterized by hypotension, tachycardia, peripheral vasodilation, and AKI [45].

Advantages of LPS injection are that its simple, sterile, and induces systemic inflammation that has many similarities with hypodynamic sepsis pathophysiology in humans. The disadvantage is that early and transient proinflammatory mediator production is more intense than in humans. LPS causes decreased GFR, increased BUN levels, and neutrophil infiltration in the kidney [46]. LPS dose can be titrated to mimic different aspects of sepsis: typical LPS doses cause systemic hypotension and decreased glomerular perfusion, while lower doses do not cause systemic hypotension but decrease glomerular perfusion [47].

4.4 Toxin-Induced AKI

4.4.1 Cisplatin

Cisplatin is a widely used anticancer drug; however, high doses have significant toxic effects on proximal tubules. Cisplatin treatment leads to inflammation and interstitial fibrosis, moreover renal blood flow is also altered. Most studies use a single *i.p.* injection of 6–20 mg/kg cisplatin in rats, which induces AKI within 72 h and both pathology and recovery phase are comparable to those of humans [48]. Higher doses are also used, albeit less frequently [49, 50].

4.4.2 Contrast-Induced AKI (CIAKI)

Intravascular administration of iodinated X-ray contrast media (CM) for computer tomography, MRI or angiography can induce AKI characterized by renal tissue hypoxia due to reduced renal blood flow and consequent oxidative stress [51]. Incidence varies between 3% and 25% depending on several factors. Firstly, the potential to cause CIAKI is less when CM are given intravenously (typically in lower doses, e.g., for computed tomography or urography) than intra-arterially (often in higher doses, e.g., for cardiac procedures), because the renal first-pass concentration is higher for the latter route of administration. Secondly, physicochemical properties of CM solutions such as osmolality and viscosity impinge on their different safety profiles. Thirdly, hydration status of the patient plays an important role. Finally, preexisting conditions such as endothelial dysfunction, for example related to diabetes mellitus, and impaired renal function increase the risk of CIAKI [51].

There are a number of models that reliably induce CIAKI in otherwise healthy animals. The clinical setting of cardiac procedures is emulated by a model, in which a 1.5 mL bolus of a high viscous CM (iodixanol 320 mg iodine/mL) is injected into the thoracic aorta of naïve rats [52–54]. A high dose of intravenously administered iodixanol (rat: 4 g iodine/kg body weight; rabbit: 5 g iodine/kg body weight) also induces CIAKI [55, 56].

In order to emulate conditions of patients who are at increased risk for CIAKI, several animal models employing a combination of contrast agent injection and other injuries (e.g., vasodilator inhibition, dehydration, IRI, diabetes) have been studied. Vasoconstriction induced by inhibition of nitric oxide synthase (e.g., L-NAME, 10 mg/kg body weight) combined with prostaglandin synthesis inhibition (indomethacin, 10 mg/kg body weight) prior to CM administration (iohexol, 1 g iodine/kg body weight) has been employed in rats and mice [57]. Another reliable murine model of CIAKI includes 30 min bilateral renal ischemia and CM administration 24 h after reperfusion [58].

4.4.3 Aristolochic Acid and Folic Acid

Both models are useful to study AKI to chronic kidney disease (CKD) transition. Aristolochic acid nephropathy is characterized by proximal tubular injury, necrosis and oxidative stress resulting in progressive interstitial fibrosis [59]. Aristolochic acid is the underlying cause of Balkan nephropathy and Chinese Herb nephropathy [60].

In folic acid nephropathy folic acid crystal deposits appear in the tubular lumen resulting in obstruction and subsequent acute tubular necrosis, tubular dilatation and cast formation. Mitochondrial dysfunction and early renal fibrosis are typical features of folic acid nephropathy as well.

4.4.4 Glycerol

In rhabdomyolysis skeletal muscle breakdown leads to the release of intracellular proteins and toxic compounds into circulation. AKI is a recurrent complication of rhabdomyolysis, mainly caused by inflammation and oxidative stress. Human symptoms are reproduced in rodents by water deprivation for 24 h followed by glycerol administration into the hindlimb muscle [61]. Elevated BUN and serum creatinine levels in this model are not exclusively the result of declined renal function, but rhabdomyolysis as well, thus GFR or creatinine clearance measurement should be preferred.

5 Models of CKD

5.1 Unilateral Ureteral Obstruction (UUO)

Renal fibrosis is the hallmark of progressive kidney disease that involves glomerular sclerosis tubulointerstitial fibrosis and atherosclerosis. UUO in rodents can be experimentally manipulated with respect to timing, severity and duration, while reversal of the obstruction allows the study of recovery. Complete UUO results in reduced renal blood flow and GFR within 24 h, followed by hydronephrosis, inflammation and tubular cell death within days. In 1–2 weeks severe hydronephrosis and severe fibrosis develops. The surgical procedure is relatively straightforward. Animals undergo a midline incision, the left ureter is located and then ligated [62]. Because clinical congenital obstructive nephropathy involves

only partial obstruction, models of partial UUO have been developed in neonatal mice or rats. These models are, however, technically challenging and meticulous technique is essential. In one method a piece of silicone tubing is slit and longitudinally fitted around the ureter forming a sleeve. Another recommended technique involves placement of a fine stainless-steel wire parallel to the ureter. After ligation the wire is pulled out leaving a partial obstruction. The ligature can then be removed at various time points to study recovery mechanisms. Due to functional and cellular compensatory mechanisms we recommend using sham-operated animals as controls instead of the contralateral kidney (unless comparing a therapeutic intervention on the obstructed kidney).

5.2 5/6 Nephrectomy

The 5/6 nephrectomy model mimics progressive renal failure after loss of renal mass in humans. The recommended approach is removal of the right kidney and resection of the upper and lower poles of the left kidney (2/3 of the kidney) [63]. The approach where branches of the renal artery are ligated is not feasible in mice due to their limited renal artery branching. Remnant kidneys develop glomerulosclerosis, tubulointerstitial fibrosis, renal atrophy and proteinuria. Susceptibility to renal injury in the 5/6 nephrectomy model is highly variable between different strains. C57BL/6 mice are resistant compared to 129/Sv or Swiss Webster mice.

5.3 Models of DKD

DKD is the leading cause of end-stage kidney disease worldwide. Unfortunately, animal models that replicate all important functional, structural and molecular features of human DKD are lacking. In both mice and rats, type 1 diabetes mellitus (T1DM) can be induced by streptozotocin, which is transported by GLUT2 transporter and destroys pancreatic beta cells. Renal and hepatic cells also express GLUT2, thus streptozotocin has additional direct nephrotoxic and hepatotoxic effects apart from the injury induced by diabetes [64]. Genetic models of T1DM such as Akita and OVE26 mice are also available [65]. T1DM can be induced by streptozotocin injection in DBA/2J mice, which are susceptible to nephropathy [16]. Streptozotocin induces T1DM with hyperlipidemia in ApoE$^{-/-}$ mice [66].

Models of type 2 diabetes mellitus (T2DM) utilize genetically obese rodents such as ob/ob mice, db/db mice, or Zucker rats [67, 68]. These animals are either leptin deficient or have inactivating mutations in the leptin receptor. High-fat diet can be useful to investigate the mechanisms of insulin resistance, even though the animals do not exhibit classical features of human DKD, they rarely become hyperglycemic and high-fat diet alone may cause renal injury. MKR mice can be used in a nonobese model of T2DM because the insulin receptor is dysfunctional resulting in insulin resistance, hyperglycemia and hyperlipidemia [69].

5.4 Models of Polycystic Kidney Disease

Polycystic kidney disease (PKD) is a genetic disorder associated with cystic bile ducts, bile duct proliferation, and cystic pancreatic ducts. There are two types of PKD in humans: the autosomal dominant PKD (ADPKD) caused by mutations in the PKD1 or PKD2 gene, and autosomal recessive PKD (ARPKD) caused by a mutation in the PKHD1 gene. In ADPKD the renal parenchyma is replaced by cysts originating from all segments of the nephron, collecting tubules, and ducts. In ARPKD cysts originate only from dilated collecting tubules and ducts.

In spontaneous hereditary models of PKD animals have obvious PKD phenotypes, but the responsible genes are not necessarily orthologous with the human genes. Examples of such models are Han:SPRD-Cy rats [70], PCK rats [71], Pcy mice [72], and Jck mice [73].

Transgenic mouse models have also been developed. Thivierge et al. produced a model with a bacterial artificial chromosome in which PKD1 gene expression is increased in the kidney, heart and liver, and the gene product PC1 is overexpressed in renal cysts [74]. Several transgenic models have been developed by deletion of human orthologous genes *Pkd1* [75], *Pkd2* [76] or *Pkhd1* [77]. Nagao et al. published a detailed review of PKD models [78].

5.5 Models of Hypertension

5.5.1 Spontaneously Hypertensive Rats (SHR)

The SHR rat strain was generated by protracted rounds of breeding and selection for high blood pressure. SHR rats develop hypertension at 5–6 weeks of age and systolic blood pressure of 180–200 mmHg by adulthood with high renin levels. Proteinuria increases from 6 weeks of age, GFR decreases by 20% by 15 weeks of age and glomerulosclerosis and tubulointerstitial fibrosis develops at around 50 weeks of age. Progression of hypertensive renal damage in this model mirrors that seen in human hypertension [79]. Unilateral nephrectomy may be required to induce significant renal injury [80].

5.5.2 Deoxycorticosterone Acetate (DOCA)–Salt Hypertension

The subcutaneous implantation of a DOCA pellet, uninephrectomy, and supplementation of 1% NaCl in drinking water or high-salt diet induces moderate-to-severe hypertension with renal injury and low renin levels [81]. Angiotensin II administration can aggravate renal injury. Renal pathological changes include proteinuria, fibrotic alterations, and impaired endothelium-dependent relaxation.

5.6 Podocyte Injury Models

Focal segmental glomerulosclerosis (FSGS) is the primary cause of glomerular diseases, characterized by proteinuria or nephrotic syndrome. Fibrotic lesions in some glomeruli (focal) or in specific parts of a single glomerulus (segmental) are the histological features of the disease.

In animal models FSGS can be induced by podocyte toxins such as puromycin, aminonucleoside or adriamycin [82]. The main disadvantage of drug-induced models is the uncertainty of

their similarity to human pathology of the disease as well as a robust variability between rodent strains in susceptibility (e.g., C57BL/6 mice are far more resistant than BALB/c) [83].

Spontaneous FSGS models include the Buffalo/MWF and Munich Wistar Fromter rat models [84, 85]. Excellent transgenic models include the Nep25 mouse model [86], the diphtheria toxin rat model, the Thy-1.1 mouse model [87], and others. Genetically engineered mouse models give valuable insight to protein–protein interactions and their role in the prognosis of FSGS. Yang et al. provide a comprehensive review of FSGS rodent models [88].

6 Humanized Mouse Models

Many elements of mouse biological systems are different from those of humans, especially their immune system. Humanized mice have become important preclinical tools to accurately recapitulate human biological systems. Presently there are three widely used strains of immunodeficient mice: NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl} (NSG), NODShi.Cg-Prkdc^{scid}Il2rg^{tm1Sug} (NOG) and C;129S4-Rag2^{tm1Flv}Il2rg^{tm1Flv} (BRG), which lack T, B, and NK cells and have functionally impaired dendritic cells and macrophages. These mice are engrafted with human transplants including peripheral blood mononuclear cells, a combination of bone marrow, liver, and thymus, or hematopoietic stem cells [89]. Humanized mouse models have tremendous potential in the study of the mechanisms of allograft rejection during transplantation or immune-mediated renal diseases such as T1DM [90, 91].

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