Inflammopharmacology

REVIEW

Rodent animal models: from mild to advanced stages of diabetic nephropathy

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Abstract Diabetic nephropathy (DN) is a secondary complication of both type 1 and type 2 diabetes, resulting from uncontrolled high blood sugar. 30–40 % of diabetic patients develop DN associated with a poor life expectancy and end-stage renal disease, causing serious socioeconomic problems. Although an exact pathogenesis of DN is still unknown, several factors such as hyperglycemia, hyperlipidemia, hypertension and proteinuria may contribute to the progression of renal damage in diabetic nephropathy. DN is confirmed by measuring blood urea nitrogen, serum creatinine, creatinine clearance and proteinuria. Clinical studies show that intensive control of hyperglycemia and blood pressure could successfully reduce proteinuria, which is the main sign of glomerular lesions in DN, and improve the renal prognosis in patients with DN. Diabetic rodent models have traditionally been used for doing research on pathogenesis and developing novel therapeutic strategies, but have limitations for translational research. Diabetes in animal models such as rodents are induced either spontaneously or by using chemical, surgical, genetic, or other techniques and depicts many clinical features or related phenotypes of the disease. This review discusses the merits and demerits of the models, which are used for many reasons in the research of diabetes and diabetic complications.

Keywords Diabetes mellitus · Diabetic nephropathy · Rodent models · Streptozotocin · Genetic models · Non-obese models

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Introduction

Diabetes mellitus (DM) is a complex metabolic disorder of the endocrine system resulting from a defect in insulin secretion, insulin action, or a mixture of both (Lachin and Reza 2012). DM is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the industrialized world. The secondary complications of DM are neuropathy, retinopathy and nephropathy (Bhatti et al. 2013). Diabetic nephropathy (DN), a long-term major microvascular complication of DM type 1 and type 2, affects a large population worldwide (Kong et al. 2013). Glomerular endothelia, mesangial cells, podocytes and tubular epithelia are the cellular elements of the kidney which are targets of hyperglycemic injury (Arora and Singh 2013). DN is characterized by glomerulosclerosis, thickening of the glomerular basement membrane, glomerular and renal cell, mesangial cell expansion, podocyte loss and tubulointerstitial fibrosis, which ultimately result in progressive albuminuria, reduction in glomerular filtration rate, elevation of arterial blood pressure and fluid retention (Mason and Wahab 2003; Arora and Singh 2013). DN is also characterized by an increased urinary albumin excretion (UAE) and is categorized into stages: microalbuminuria (UAE >20 and ≤99 µg/min) and macroalbuminuria (UAE ≥200 µg/min) (Gross et al. 2005). The exact pathogenesis of DN is still not clear (Kong et al. 2013). Furthermore, risk factors for the development of DN include older age, overweight, smoking, non-Caucasian race, male sex and poor glycemic, lipid and blood pressure controls (Ritz and Orth 1999).

DN has since metamorphosed from a clinical rarity to a single major cause of kidney failure in the industrialized world. Clinical evidence has reported that intensive control of glycemia and blood pressure could successfully reduce

proteinuria, which is the main sign of glomerular lesions in DN, and improve the renal prognosis in patients with DN (Kume et al. 2014).

However, the impact of these interventions will fail to stem the increased prevalence of renal failure projected over the next decade (Gilbertson et al. 2005). As the total number of people with diabetes is projected to increase substantially by 2050, the prevalence of DN will rise dramatically (Reutens and Atkins 2011).

Diabetes is a complex metabolic disorder; it involves many pathways which ultimately lead to β-cell destruction or insulin resistance to receptors. Till date, scientists have tried to study the exact pathogenesis or down-regulatory pathways involved in disease progression. Therefore, to study the exact pathogenesis of DM there is a need to develop animal models, in which pathological changes are produced as observed in humans. In scientific literature, there are a number of models available for DN. In the present review, we have tried to collect all the models and discussed the mechanism, merits and demerits of each model.

Rodent animal models for DN

Rodents are most frequently used as animal models for understanding the complex pathogenesis of DN (Wolf et al. 2014). They provide opportunities to the researchers to explore the genetic and environmental factors that may influence the development of the disease (Chatzigeorgiou et al. 2009). There are a number of rodent models available which are classified as in Table 1.

STZ-induced type-1 diabetic nephropathy in rats

Chemical constitution

Streptozotocin (2-deoxy-2-(3-methyl-3-nitrosoureido)-ᴅ-glucopyranose ($C_{18}H_{15}N_3O_7$) was discovered from the strain of soil microbes, *Streptomyces Achromogens*, as a new antibiotic in 1956 and developed as a therapeutic agent for the treatment of metastatic insulin-producing islet cell tumor (Szkudelski 2001). STZ has been determined to be the nitrosoamide methylnitrosourea (MNU) linked to the C2 position of ᴅ-glucose (Bennett and Pegg 1981). The nitrosamide MNU contributes to its alkylation properties, and glucose moiety directs its selective pancreatic β-cell uptake via the glucose transporter (GLUT-2) (Elsner et al. 2000). Once STZ enters the β-cells, it is then cleaved between the 2′-carbon and methyl nitrogen to form carbamoylating and alkylating reactive species (Schnedl et al. 1994; Thulesen et al. 1997; Elsner et al. 2000).

Table 1 Classification of models

Category of diabetic nephropathy	Models
Chemically induced	
	STZ-induced type-1 DN
	STZ-induced type 1 DN in rats
	STZ-induced type-1 DN in mice
	Low-dose STZ-induced type 2 DN in high-fat diet (HFD)-fed heminephrectomized rats
	STZ-induced advanced DN in 5/6 nephrectomized rats
	STZ-induced DN in uninephrectomized animals
	Alloxan-induced DN
Surgically induced	
	Renal ischemia-induced advanced DN in rats
Genetically induced	
	Insulin-2 Akita mice
	Non-obese diabetic mouse
	LepRdb/LepRdb(db/db) mouse
	C57BL6
	ROP mouse
	FVB mouse
	KK mice
Transgenically induced	
	Inducible cAMP early repressor transgenic (ICER 1γ Tg) mouse model of DN
	Human RAGE gene overexpressed mouse for advanced DN
	MafA−/-MafK+ overexpressing hybrid transgenic mouse model of severe DN

Dose

Streptozotocin-induced DM in rats produces all the secondary complications in rodents including DN (Wei et al. 2003). A single dose administration of STZ (40, 50, 55, 60 and 65 mg/kg i.p.) in Sprague–Dawley (SD), Wistar–Kyoto (WKY) or spontaneously hypertensive (SHR) rats has been shown to induce DN after 4–8 weeks, as assessed in terms of serum creatinine (SC), blood urea nitrogen (BUN), proteinuria, creatinine clearance (CC), which is often associated with extracellular matrix deposition, dyslipidemia and development of glomerulosclerosis and tubulointerstitial fibrosis (Casey et al. 2005; Shah and Singh 2006; Gojo et al. 2007; Budhiraja and Singh 2008; Haidara et al. 2009). Following the STZ injection, rats should be given drinking water with glucose to limit early mortality due to hypoglycemia. Generally, 3 days or 1 week after STZ, animal should be screened and those with fasting blood glucose above 240 mg/dL are generally included in the studies of DN (Casey et al. 2005; Gojo et
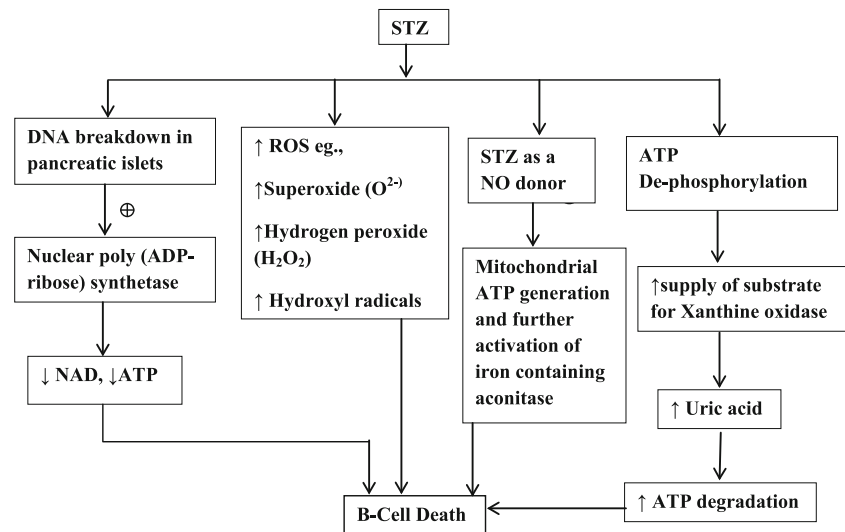
2007). It has been demonstrated that animals showing excessive hyperglycemia are vulnerable to the development of ketonuria and mortality. Thus, in long-term studies of DN, the blood glucose levels are maintained in a desirable range (16–33, 300–600 mg/dL) by a daily subcutaneous injection of long-acting insulin (2–4 U/rat) (Davis and Alonso 2004). Further, it is generally supposed that STZ may induce pancreatic damage selectively due to specific expression of GLUT-2 in the pancreas. However, it has been observed that STZ causes direct DNA damage and cell proliferation in rat kidney, which last for at least for 3 weeks. Therefore, drug treatment should not be started at least 3 weeks after STZ administration to allow kidneys to recover from the acute and mild nephrotoxic effects of STZ (Kraynak et al. 1995).

Mechanism of action

The underlying mechanisms of STZ-induced DM is the following: (a) DNA strand breakage in pancreatic islets and consequent activation of nuclear poly (ADP-ribose) synthetase, which results in the depletion of intracellular nicotinamide adenine dinucleotide (NAD) and adenosine triphosphate (ATP) levels; (b) excessive generation of reactive oxygen species (ROS), such as superoxide (O^{2-}), hydrogen peroxide and hydroxyl radicals (Takasu et al. 1991); (c) STZ being a nitric oxide (NO) donor partially mediates restriction of mitochondrial ATP generation. Further, NO also binds and inhibits the activation of iron-containing aconitase (Welsh et al. 1994); (d) augmented ATP dephosphorylation increases the supply of substrate for xanthine oxidase and enhances the production of uric acid, the final product of ATP degradation (Nukatsuka et al. 1988; Nukatsuka et al. 1990a; Nukatsuka et al. 1990b). The overactivation of protein kinase C (PKC) and

increased renal RAAS have been well implicated in the pathogenesis of STZ-induced DN (Brownlee et al. 1988; Chang et al. 2003; Chung and Chung 2003; Asaba et al. 2005; Navaneethan et al. 2005; Tojo et al. 2005) (Fig. 1).

It has been revealed that altered dynamic changes in gene expression of CD-1 (ICR) mouse kidney in early phases of DN are related to glucose and lipid metabolism, protein synthesis and degradation, signal transduction, ion transport and extracellular matrix and ultimately leads to glomerulosclerosis, mesangial cell expansion and glomerular hypertrophy (Wada and Yagihashi 2010). Further, reports proposed that mice that received high-dose STZ developed more albuminuria than mice that received a low-dose STZ regimen, although they showed similar levels of hyperglycemia (Hackbarth et al. 1981; Hackbarth and Hackbarth 1981).

To exclude the nonspecific cytotoxicity of high-dose STZ, multiple injections of sub-diabetogenic doses of STZ (40–50 mg/kg) daily i.p. were given for five consecutive days in CD-1 mice. The mice had mild initial hyperglycemia during the initial 5–6 days with a subsequent complete diabetic syndrome observed on the 8th and 11th day, which was accompanied by pronounced insulinitis with infiltrating lymphocytes and macrophages and pancreatic β-cell necrosis (Rossini et al. 1977; Leiter 1982, 1985). The lower levels of albuminuria with low-dose STZ than with high-dose STZ showed reduced direct renal toxicity (Hackbarth et al. 1981; Hackbarth and Hackbarth 1981; Susztak et al. 2004).

Low-dose STZ-induced type 2 diabetic nephropathy in high-fat diet (HFD)-fed heminephrectomized rats

Unlike high-dose STZ, which induces type 1 DM (T1DM) by causing severe pancreatic damage, an administration of

low-dose STZ has been shown to produce partial pancreatic damage and mild glucose intolerance which are important characteristics of the late stage of type 2 DM (Kelly et al. 2003). Further, administration of STZ (40 mg/kg, i.v.) to heminephrectomized rats followed by feeding with a high-fat diet presented a significant increase in plasma glucose levels after 15 weeks and decreased plasma insulin levels, increased plasma total cholesterol and triglyceride levels and increased blood pressure at 25 weeks (Kelly et al. 2003). These animals displayed microalbuminuria and increased creatinine clearance at the age of 15 weeks, subsequently followed by overt proteinuria and mesangial expansion after the age of 25 weeks (Sugano et al. 2006). In this model, either by manipulating dietary formula or by pharmacological intervention, it would be possible to normalize blood pressure, hyperlipidemia and hyperglycemia to analyze how different treatment modalities retard the progression of DN.

STZ-induced advanced diabetic nephropathy in 5/6 nephrectomized rats

It has been investigated that a single injection of STZ (35 mg/Kg, i.p.) in five/six nephrectomized rats results in the development of hyperglycemia, hypoinsulinemia, hypertriglyceridemia and hypercholesterolemia along with increased serum glycosylated proteins, a metabolic abnormality resembling DN in humans (Yokozawa et al. 2001). Increased levels of serum creatinine, urinary protein and decreased creatinine clearance were also observed, leading to the development of advanced DN and overt albuminuria within 80 days, as this animal model was associated with severe lesions of the glomerular capillary loops, mesangial area and Bowman's capsule, coagulation in the glomerular capillary loops and azotemia (Yokozawa et al. 2001). The major limitation of this animal model is that the development of glomerulopathy was not purely due to hyperglycemia. The development of elevated blood pressure and hyperlipidemia may independently influence the progression of DN. Further, the bilateral surgical manipulation in STZ-treated nephrectomies rats may produce artifacts in histological analyses (Yokozawa et al. 2001).

STZ-induced diabetic nephropathy in uninephrectomized animals

Uninephrectomy was reported to accelerate the progression of renal injury observed in STZ-induced DN in different rat strains including SD rats, Wistar and SHR, which may be a consequence of increased glomerular capillary pressure (Kang et al. 2000; Utimura et al. 2003). Utimura et al. (2003) showed that if Wistar rats were first uninephrectomized and 3 weeks after surgery made diabetic by a single injection of STZ (65 mg/kg i.v.), the blood glucose was then maintained between 16 and 22 mmol/L (300–400 mg/dL) for the next 8 months with partial insulin treatment. These uninephrectomized diabetic rats achieved a urine albumin excretion rate (UAER) of 60 mg/24 h at 8 months, which was nearly three times higher than non-diabetic control rats (Utimura et al. 2003). The uninephrectomy (UNX) per se produced elevated levels of serum creatinine and urinary total protein, along with uremia in rats (Zhao et al. 2008). In addition, UNX rats shows increased serum total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol 10 months after uninephrectomy. Further, fat redistribution and increased renal accumulation of fats and lipid peroxides were observed in UNX rats. Pharmacological treatment with ACE inhibitors such as lisinopril and enalapril prevents the development of chronic renal dysfunction by reducing hypercholesterolemia, fat redistribution or transformation and lipid peroxidation in UNX rats (Zhao et al. 2008).

Merits and demerits

STZ is mostly used to induce experimental DM, since it has some advantages over alloxan such as prolonged hyperglycemia, longer half-life (15 min) and the development of well-characterized diabetic complications such as DN with fewer incidences of ketosis as well as mortality. Both alloxan and STZ diabetic animals are commonly used for screening the compounds including natural products for their insulinomimetic, insulinotropic and other hypoglycemic/antihyperglycemic activities (Young et al. 1990; Katovitch et al. 1991). But nowadays, alloxan is almost replaced by STZ for induction of diabetes in laboratory animals (Ozturk et al. 1996).

Alloxan-induced diabetic nephropathy

Chemical constitution

Alloxan (2,4,5,6-tetraoxypyrimidine;2,4,5,6-pyrimidinetetrone) is an oxygenated pyrimidine derivative and also a barbituric acid derivative that can induce diabetes in animals due to the specific necrosis of pancreatic β-cells (Peschke et al. 2000; Szkudelski 2001). Brugnatelli originally isolated alloxan in 1818 (McLetchie 1982). Alloxan was firstly produced by the oxidation of uric acid by nitric acid (Bailley et al. 1946). Alloxan is considered a strong oxidizing agent in the form of dialuric acid. Dialuric acid, a reduction product of alloxan, has also been shown to be diabetogenic in animals (Bailley et al. 1946; Brückmann and Wertheimer 1947) and cause ultrastructural changes

similar to those observed in response to alloxan (Szkudelski 2001). This drug can be administered parenterally, i.e., intravenously, intraperitoneally or subcutaneously to exert its diabetogenic action. The induction of insulinopenia due to alloxan causes a state of experimental DM called 'alloxan diabetes' (Dunn and Letchie 1943; Goldner 1945; McLetchie 1982).

Dose

The dose of alloxan needed for developing diabetes depends on the animal species, route of administration and nutritional status (Federiuk et al. 2004). Single-dose administration of alloxan 120 mg/kg body weight i.p. results in the development of diabetes in rats after 72 h. Alloxan induced diabetes characterized by a significant increase in plasma glucose, enhanced levels of renal damage markers, plasma creatinine, urea nitrogen and urinary albumin. Diabetic renal injury is associated with increased kidney weight to body weight ratio and glomerular hypertrophy (Da and Sil 2012).

Mechanism of action

Alloxan shows two distinct pathological effects: selective inhibition of glucose-induced insulin secretion through specific inhibition of glucokinase, the glucose sensor of the beta cell, and it causes a state of insulin-dependent diabetes through its ability to induce ROS formation, resulting in the selective necrosis of β-cells. These two effects are due to specific chemical properties of alloxan-like selective cellular uptake and accumulation of alloxan in pancreas. Alloxan is an unstable chemical compound having molecular shape similar to glucose (Weaver et al. 1979; Lenzen and Munday 1991; Gorus et al. 1982). Both alloxan and glucose are hydrophilic and do not penetrate the lipid bilayer of the plasma membrane. Due to structural similarity of alloxan to glucose molecule, the GLUT2 glucose transporter in the beta cell plasma membrane accepts this glucomimetic and transports it into the cytosol (Weaver et al. 1978; Gorus et al. 1982). Alloxan does not inhibit the function of GLUT2 transporter (Elsner et al. 2002), and therefore selectively enters beta cells in an unrestricted manner (Boquist et al. 1983; Malaisse et al. 2001). It is not toxic to insulin-producing cells that do not express this GLUT2 transporter (Elsner et al. 2002; Bloch et al. 2003).

Alloxan generates reactive oxygen species (ROS) in a cyclic reaction with its reduction product, dialuric acid (Winterbourn and Munday 1989). In beta cells, the toxic effect of alloxan is initiated by free radicals formed during cyclic redox reaction. Autoxidation of dialuric acid generates free radicals such as superoxide radicals and hydrogen peroxide, hydroxyl radicals as well as

intermediate of the alloxan radical (Munday 1988; Winterbourn et al. 1989; Winterbourn and Munday 1989). Alloxan generates ROS by reacting with thiol groups on proteins such as enzymes and albumin (Sakurai and Miura 1989; Lenzen and Mirzaie-Petri 1992) (Fig. 2).
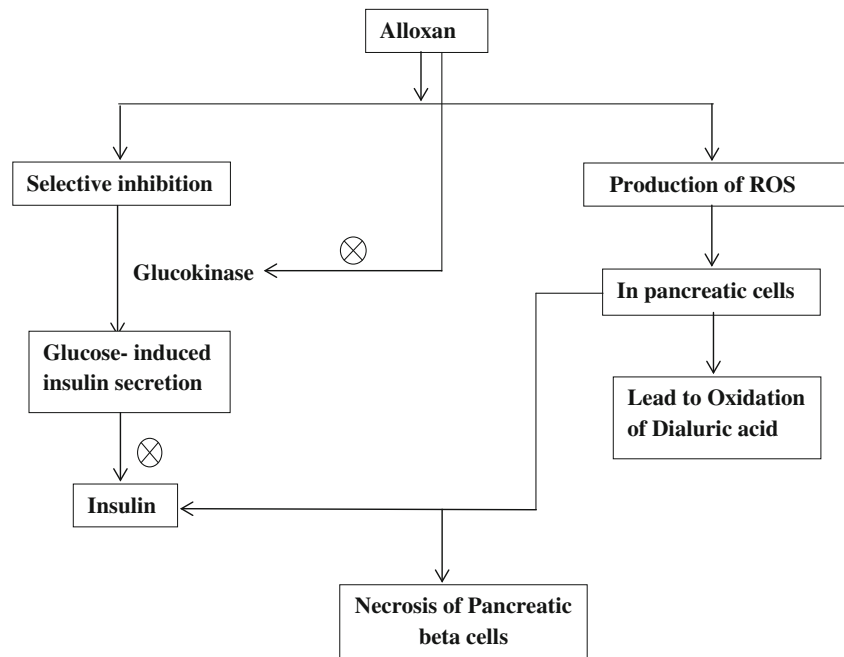
Merits and demerits

Alloxan has low stability and very short half-life (<1 min). Because of the acidic nature of the solution, intravenous route of its administration is preferred. The hypoglycemic phase is severe, due to this alloxan should not be given to fasted animals. Alloxan-treated animals show severe polydipsia, hyperglycemia, glucosuria, hyperlipidemia, polyphagia and also develop various complications of uncontrolled diabetes such as DN, neuropathy, cardiomyopathy, well-marked retinopathy and others. Alloxan is disadvantageous as the percentage incidence of diabetes is quite variable. Further, the incidence of ketosis and mortality is very high. Alloxan-treated animals show reversal of hyperglycemia in which pancreatic regeneration is early and common. Because of these limitations, Alloxan is less commonly used as compared with the STZ (Bailey and Day 1989; Pelé-Tounian et al. 1998; Young et al. 1990; Katovitch et al. 1991).

Renal ischemia-induced advanced diabetic nephropathy in rats

It has been reported that unilateral renal ischemia of 30 min in T1DM rats causes a severe progressive renal injury leading to ESRD, whereas in non-DM rats ischemia of the same duration causes a reversible injury (Melin et al. 1997). Ischemia–reperfusion (I/R) with hyperglycemia leads to the development of DN (Ziyadeh 2004). It is also reported that in diabetic rats, renal ischemia produces progressive kidney damage which resembles DN in humans. Animals exhibit early signs of diabetic renal injury, such as mesangial cell expansion and basement membrane thickening (Hirose et al. 1982; Evan et al. 1984; Evan and Tanner 1986; Yong and Bleasel 1986; Steffes et al. 1989).

Renal fibrosis and tubulointerstitial inflammation, the prominent pathological features of human DN, have been proposed as a consequence of renal ischemia (Ziyadeh 2004). Recently, it has been demonstrated that apoptosis in tubular cells, especially in outer medulla, is induced by renal I/R injury (Daemen et al. 1999; Chien et al. 2001). Insulin-like growth factor 1 (IGF-1) shows some structural homologies with insulin and is known as an anti-apoptotic agent that decreases the injury after renal I/R (Goes et al. 1996; Daemen et al. 1999). Insulin has anti-apoptotic effects on epithelial cells from mammary glands (Farrelly

Fig. 2 Mechanism of action of alloxan

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                                    │ Alloxan  │
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                  ┌──────────────────────┴───────────────────────┐
                  ▼                                               ▼
        ┌──────────────────┐                          ┌────────────────────┐
        │ Selective        │                          │ Production of ROS  │
        │ inhibition       │                          └────────────────────┘
        └──────────────────┘                                    │
                  │         Glucokinase  ◄─── ⊗                  ▼
                  │                                   ┌────────────────────┐
                  ▼                                   │ In pancreatic cells│
        ┌──────────────────┐                          └────────────────────┘
        │ Glucose- induced │                                    │
        │ insulin secretion│                                    ▼
        └──────────────────┘                          ┌────────────────────┐
                  │  ⊗                                 │ Lead to Oxidation  │
                  ▼                                     │ of Dialuric acid   │
            ┌──────────┐                               └────────────────────┘
            │ Insulin  │  ◄────────────────────────────────────┘
            └──────────┘
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        ┌────────────────────┐
        │ Necrosis of        │
        │ Pancreatic         │
        │ beta cells         │
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et al. 1999). Treatment with insulin for 1 week before renal I/R decreases the structural and functional damage to the kidney caused by 30 min of arterial clamping in the DM rat associated with renal lactate accumulation (Podrazik et al. 1989). There is elevation of reactive oxygen species (ROS) in rat kidneys subjected to I/R, and treatment with superoxide dismutase decreases apoptosis in proximal tubular cells (Chien et al. 2001). Hyperglycemia also induces oxidative stress and increases lipid peroxidation in cultured tubular cells (Kuramochi and Homma 1993; Han et al. 2000). In DM rats, treatment with anti-oxidants such as vitamin C and E decreases renal expression of TGF-β, and vitamin C inhibits renal hypertrophy (Craven et al. 1997). Like other chronic renal diseases, DN is associated with an infiltration of inflammatory cells. Bohle and co-workers found T lymphocytes, fibroblasts, monocytes/macrophages and a few B-cells in kidneys with DN (Bohle et al. 1991). Mostly, renal I/R injury in non-DM rats describes a transient inflammation (Forbes et al. 2000). Combination of I/R with DM resulted in a severe inflammatory response that persisted for at least 8 weeks (Melin et al. 1997). However, good glycemic control before and during I/R prevented deterioration of renal function despite uncontrolled hyperglycemia during the first 4 weeks (Melin et al. 1997).

Diabetic kidney has also been associated with an increased ratio of free NADH/NAD$^+$, similar to that found in hypoxia. This is called ''pseudohypoxic state'' (Williamson et al. 1993). It has been shown that TNF-α expression in kidney mediates neutrophil infiltration and injury after renal I/R (Donnahoo et al. 1999). Also, it is

well known that renal I/R induces inflammatory response, which is exacerbated in the diabetic kidney (Eddy and Giachelli 1995: Panés et al. 1996) and concern with the degree of arterial obliteration (Ziyadeh 2004). Further, an impaired response to nitric oxide might be responsible for the more pronounced decrease in renal function in the early post-ischemic phase in DM rats. It has been found that diabetic rats subjected to 1 h of bilateral renal artery clamping died within 48 h, while most non-diabetic animals survived after the ischemic injury (Wald et al. 1990). In addition, renal ischemia of 30 min duration only produces transient reversible renal injury, but the same extent of renal ischemia causes a rapidly progressive DN and end-stage renal failure, along with severe tubulointerstitial inflammation and renal fibrosis within 8 weeks in the diabetic rat (Melin et al. 1997; Mu et al. 1999; Melin et al. 2002; Mills et al. 2004).

Merits and demerits

This model is widely used to induce DN in diabetic rats. It is reported that unilateral renal ischemia of 30 min produces progressive kidney damage which resembles DN in humans (Evan and Tanner 1986; Steffes et al. 1989). But still this model is not fully established, because the pathophysiology of I/R injury is multifactorial and the exact sequence of events in I/R injury remains unknown. However, the role of inflammation has clear and several other important events resulting in tissue damage and kidney failure (De Vries et al. 2012).

Genetic model of diabetic nephropathy

Chemical or surgical maneuvers for diabetes induction might, however, cause some diversity among individual animals in terms of the extent of severity and the onset of diabetes. Accordingly, by use of a genetic approach, a diabetic state and particular pathogenic molecular culprit would be most stably induced. Thus, genetic models serve as an essential experimental tool for investigating the molecular mechanisms and genetic susceptibility in the development of DN. There are numerous genetic models that mimic human diseases.

Insulin-2 Akita mice

Insulin-2 Akita (Ins2Akita) is a mouse mutant model of type 1 diabetes. It has been reported that this model is insulin responsive and represents a model of maturity-onset diabetes of the young with insulin resistance. These mice are commercially available through the Jackson Laboratories (Mathews 2002). The Ins2 gene is the mouse homolog of human preproinsulin gene that causes misfolding of the insulin protein. Mice possess another active insulin gene, Ins1, which lacks an intron present in the C-polypeptide-encoding region. The Akita (Ins2Akita) spontaneous mutation (commonly referred as Mody) is an autosomal dominant mutation in the insulin II gene (Ins2). Mice heterozygous for the Akita spontaneous mutation (Ins2Akita) are viable and fertile, whereas mice homozygous for the Ins2Akita allele die within 1–2 months (Ron 2002; Srinivasan and Ramarao 2007). Ins2Akita mutation disrupts normal insulin processing and causes a failure in secretion of mature insulin, which results in early development of hyperglycemia, characterized by hyperglycemia, hypoinsulinemia, polydipsia and polyuria, beginning at approximately 3–4 weeks of age. Obesity or insulitis does not accompany diabetes. Histologically, there is a reduction in active pancreatic β-cell density without insulitis and islets release very little mature insulin at 4–35 weeks of age. These mutant mice respond well to exogenously administered insulin. Thus, Insulin-2 Akita (Ins2Akita) mouse shows development of pancreatic β-cell damage, with little release of mature insulin from viable β-cells as a result of β-cell-selective proteotoxicity resulting from misfolding of insulin 2 (Ron 2002).

It has been demonstrated that there is a twofold increase in the urinary albumin excretion rate in $Ace2^{-/y}$ $Ins2^{WT/C96Y}$ mice as compared to $Ace2^{+/y}$ $Ins2^{WT/C96Y}$ mice [both produced when $Ace2^{-/-}$ mice crossed with Akita mice $(Ins2^{WT/C96Y})$] due to similar blood glucose level (Haseyama et al. 2002). $Ace2^{-/y}$ $Ins2^{WT/C96Y}$ mice reveal increased mesangial matrix scores and glomerular basement membrane thickness as compared to $Ace2^{+/y}$ $Ins2^{WT/}$ ^{C96Y} mice. Kidney levels of angiotensin II were not increased in the diabetic mice and treatment with an Ang II receptor blocker decreased urinary albumin excretion rate in $Ace2^{-/y}$ $Ins2^{WT/C96Y}$ mice, suggesting that the acceleration of kidney injury in mice is Ang II mediated (Wang and Li 2008). Renal immunopathologic studies demonstrated significant deposition of IgA in the glomeruli of Akita mice (Haseyama et al. 2002). The severity of DN in the C57BL/6J Ins2Akita (hybrid strain of C57BL/6J and Ins2Akita) mouse does not seem to be robust.

Meanwhile, the Ace-2/Ang-(1-7)/Mas axis functions as a negative regulator of the RAS. It was demonstrated that Ace2 knockout (ACE2-/y) mice show impaired glucose tolerance. Now, it has been proven that the Ace2/Ang-(1-7)/Mas axis can ameliorate insulin resistance in the liver. Activation of the Ace2/Ang-(1-7)/Mas axis increases glucose uptake and decreases glycogen synthesis in the liver by increased expression of glucose transporters and insulin receptor substrates and decreased expression of enzymes for glycogen synthesis. Ace2 knockout mice presented elevated levels of oxidative stress; exposure to Ang-(1-7) reduced the stress in hepatic cells, and activation of the Ace2/Ang-(1-7)/Mas axis led to improved hepatic insulin resistance through the Akt/PI3 K/IRS-1/JNK insulin signaling pathway. It has been documented for the first time that the Ace2/Ang-(1-7)/Mas axis can ameliorate insulin resistance in the liver, which is considered to be the primary cause of the development of T2DM (Cao et al. 2014).

Merits and demerits

This model is insulin responsive, causing severe DN. It also shows histological changes at 4–35 weeks (Mathews 2002). Ins2Akita mice could be used as a substitute for mice that are rendered insulin-dependent diabetic by treatment with alloxan or STZ (Ron 2002). This model is also considered as a new diabetes target (Cao et al. 2014) and has rarely any disadvantages, but even then it is not used commonly.

Non-obese diabetic mouse

The non-obese diabetic (NOD) mouse was obtained by selectively breeding offspring from the cataract-prone ICL-ICR mouse. Insulinitis is present at the age of 4–5 weeks followed by partial β-cell destruction and decreased insulin level in circulation in these mice. Frank diabetes typically appears at the age between the 12th and 30th week. These animals can survive for weeks without administration of insulin, since keto acidosis is mild in these for any extended time after the onset of hyperglycemia, indicating more complete insulin deficiency.

In addition, the inheritance of specific MHC class II alleles and many non-MHC loci as polygenic susceptibility loci, transmission of the disease by hematopoietic stem cells, the development of an intra-islet inflammatory infiltrate (insulinitis) with anti-islet cell antibodies and a strict dependence of disease on T cells showed that autoimmune disease would lead to β-cell failure in NOD mice. The model presents a number of similarities with the features of human type 1 diabetes (Leiter et al. 1987; Atkinson and Leiter 1999; Cameron et al. 2008). Furthermore, studies of DN using this model also have supported roles for TGF-β and advanced glycosylation end products (AGE) in the pathogenesis of mesangial proliferation and sclerosis (Sakurai and Miura 1989; Ritz and Orth 1999).

LepRdb/LepRdb(db/db)mouse

The db/db mutation on the C57BLKS background has been examined intensively and shows features similar to human DN. The diabetic gene (db) is transmitted as an autosomal recessive trait, and it has been reported that long intracellular domain form of OB-R is crucial for initiating intracellular signal transduction. As a corollary, the inability to produce this form of OB-R, which leads to the severely obese phenotype found in db/db mice, and weight-reducing effects of leptin being mediated by signal transduction through a leptin receptor in the hypothalamus showed that the db gene encodes for a G-to-T point mutation of the leptin receptor, leading to abnormal splicing and defective signaling of the adipocyte-derived hormone leptin (Stephens and Caro 1998). This obese and diabetic mutant (db) was recognized in the C57BLKS/J strain and was subsequently also backcrossed to a pure C57BL/6J background. The C57BLKS/J mouse shares 84 % of its alleles with the common C57BL/6 strain and 16 % with DBA/2 J strain (Naggert et al. 1995). The C57BLKS/J db/db mouse exhibits hyperinsulinemia by 10 days of age, and blood glucose levels are elevated at $(7.2 \pm 2.3$ mM) 1 month of age (Lee and Bressler 1981), while the db/db mouse develops frank hyperglycemia with glucose values of 9.7 ± 1.6 and 15.7 ± 4.3 mM by 8 week and at 10 week of age. Progressive hyperglycemia $(28.6 \pm 13.2$ mM) is noted at 16 weeks of age (Like et al. 1972; Lee and Bressler 1981).

Besides this, increased level of urinary collagen IV excretion, glomerular mesangial cell expansion and increased albumin secretion also occur in diabetic db/db mice that showed similarities to the changes found in human DN (Gartner 1978; Cohen et al. 2001). After 16 weeks of age, there is a very consistent threefold increase in mesangial matrix expansion based on several independent studies (Sharma et al. 2003). However, the degree of albuminuria does not consistently increase with

the duration of diabetes, as there are similar levels of albuminuria between 8 and 25 weeks (Koya et al. 2000; Cohen et al. 2001; Sharma et al. 2003). The severity of diabetes in db/db mice depends on the C57BL/6 background in the diabetic phenotype and is less severe than that in C57BLKS/J; as these mice age, plasma glucose seems to normalize (Koenig et al. 1976; Leiter et al. 1981; Meade et al. 1981; Leiter et al. 1987, 1989).

More recently, some investigators have investigated that a subset of approximately 50 % of C57BL/6J db/db mice developed persistent hyperglycemia (Chow et al. 2004; Zheng et al. 2004). In these mice, more robust albuminuria, glomerular lesion and mesangial cell expansion have been described (Chow et al. 2004).

Susceptibility of inbred mice strain to diabetic nephropathy

Studies have identified certain strains (e.g., 129, ROP, NON, KK/HIJ) as more prone to glomerulosclerosis than other commonly studied strains (e.g., C57BL/6, FVB/NJ) that seem relatively resistant to renal disease. It is noteworthy that studies of DN have been performed in fewer than 5 % of the available mouse strains.

C57bl/6

C57BL/6 is a widely used inbred strain; it has been reported that urine protein excretion in C57BL/6 mice increased at 4 weeks after five/six nephrectomies and was back to normal at 8 and 12 weeks in remnant kidney model, which proposed that kidney disease in this strain is resistant to renal injury (Zheng et al. 1998; Ma and Fogo 2003).

It has been revealed that infusion of DOCA salt and angiotensin II leads to hypertensive glomerular damage, increased expression of profibrotic and inflammatory genes, albuminuria, tubular casts, increased plasma cholesterol, cardiac hypertrophy and fibrosis in C57BL/6 mice (Kirchhoff et al. 2007). Further, studies indicate that on the C57BLKS background, type 2 diabetic db/db mice have lesions consistent with DN (thickened basement membrane, mesangial expansion), whereas they are resistant to DN on a C57Bl/6 background. Moreover, these models have not been completely designated; this difference proposed two possibilities: either the worse severity of hyperglycemia that develops in C57BLKS causes this (111) (a combination of peripheral insulin resistance and insulin deficiency develops in C57BLKSLepr db, whereas C57BL/6Lepr db have peripheral insulin resistance) or C57BLKS expresses modifier genes that predispose to DN (Noonan and Banks 2000; Tikellis et al. 2008).

ROP mouse

The ROP [Ra/$^+$ (ragged), Os/$^+$ (oligosyndactyly) and Pt/$^+$ (pintail)] strain of mouse obtained from a heterogeneous stock were heterozygous for three mutant alleles, viz. Ra/$^+$ (ragged), Os/$^+$ (osteosyndactylism) and Pt/$^+$ (pintail). Estimation of reduced renal mass in kidney of Os/$^+$ ROP mice showed approximately 50 % fewer nephrons in the Os/$^+$ mice than in the $^{+/+}$mice (Zalups 1993). Further, decreased renal mass was responsible for more glomerulosclerosis in wild-type mice (Os$^{+/+}$, Ra$^{+/+}$, and Pt$^{+/+}$) of ROP background than C57BL/6 mice (Esposito et al. 1999; Cornacchia et al. 2001; Fornoni et al. 2003). Mice on the ROP background, in the absence of Os, Ra, or Pt mutant alleles, may show increased propensity for glomerulosclerosis and hyperglycemia after combined nephron mass reduction and diabetes (Zheng et al. 1998).

FVB mouse

FVB/NJ was obtained from outbred Swiss mice at NIH inbred for the *fv1b* allele and shows sensitivity to the Friend leukemia virus B strain. FVB/NJ is commonly used for transgenic injection because of the prominent pronuclei in the fertilized eggs and the large litter size. FVB/N mice are transgenic for a calmodulin mini gene regulated by the rat insulin II promoter, which has shown fivefold increase in calmodulin and its mRNA in beta cells and insulin secretory defect in mice leading to the development of T1DM (Epstein et al. 1989, 1992). They develop glomerular capillary basement membrane thickening, not albuminuria (Carlson et al. 1997). The LepRdb mutation has been backcrossed onto the FVB/NJ strain, and the kidneys from these mice show mesangial sclerosis, but not albuminuria, and GFR has been described (Chua et al. 2002).

KK mice

These mice were originally established from inbreeding a Japanese mouse (Kondo et al. 1957). KK mice exhibit only mild insulin resistance and seem to be predisposed to the development of renal lesions, very reminiscent of DN (Reddi et al. 1977; Reddi and Camerini-Davalos 1989). The severity of hyperglycemia, insulin resistance and impaired glucose tolerance is exacerbated further by initiation of the agouti (Ay) allele into the KK (Suto et al. 1998). Pharmacological treatment with candesartan has been shown to reduce urinary type IV collagen and albumin excretion and attenuate glomerular hypertrophy and mesangial matrix accumulation possibly by suppression of TGF-betaS/Smad signaling pathway in KK/Ta mice with DN (Liao et al. 2003). Further, glipizide treatment has been demonstrated to improve glucose intolerance, decrease kidney size, reduce kidney glycoprotein and mesangial matrix accumulation, and proteinuria in type II diabetic KK mice (Reddi et al. 1990).

Merits and demerits The NOD mouse model of T1DM has contributed greatly to our understanding of disease pathogenesis and has facilitated the development and testing of therapeutic strategies to battle the diseases in humans. In LepRdb/LepRdb(db/db) mouse, the db/db mutation on the C57BLKS background has been examined intensively and shows features similar to human DN (Stephens and Caro 1998). Approximately, 50 % of C57BL/6J db/db mice developed more persistent hyperglycemia (Chow et al. 2004; Zheng et al. 2004). C57BL/6, ROP, FVB and KK are commonly used strains of mouse to induce complications of DM such as DN, retinopathy, neuropathy and cardiomyopathy. Moreover, these models have not been completely designated; due to this, these models are less commonly used as compared to the chemical models.

Inducible cAMP early repressor transgenic (ICER 1γ Tg) mouse model of diabetic nephropathy

ICER 1γ Tg mouse has been reported to exhibit persistent hyperglycemia due to low production of insulin and insulin-producing β-cells (Inada et al. 1999). ICER Iγ is a transcriptional repressor transcribed from an alternative intronic promoter of the CRAM gene and competes with transcriptional activators activated by insulin for binding to the DNA and cyclineA gene transcription (Foulkes et al. 1991; Inada et al. 1998, 2008). This results in suppression of insulin synthesis, β-cell proliferation and development of severe diabetes as early as 2 weeks of age, but with an excellent survival rate without insulin therapy (Inada et al. 1999; Kajihara et al. 2003).

Human RAGE gene overexpressed mouse for advanced diabetic nephropathy

When transgenic mice with overexpressed human RAGE in vascular cells (RAGETg) are cross bred with another transgenic mouse deficient in the islet production of insulin, the resultant double transgenic animals develop exhibiting renal insufficiency and advanced glomerulosclerosis that resemble human DN, implicating the functional importance of AGE-RAGE system in the development of DN (Takamura et al. 1998). The RAGE-overexpressing IDDM mice are the first animal model in which the process of diabetes-induced kidney changes lead to ESRD. The administration of AGE formation inhibitors
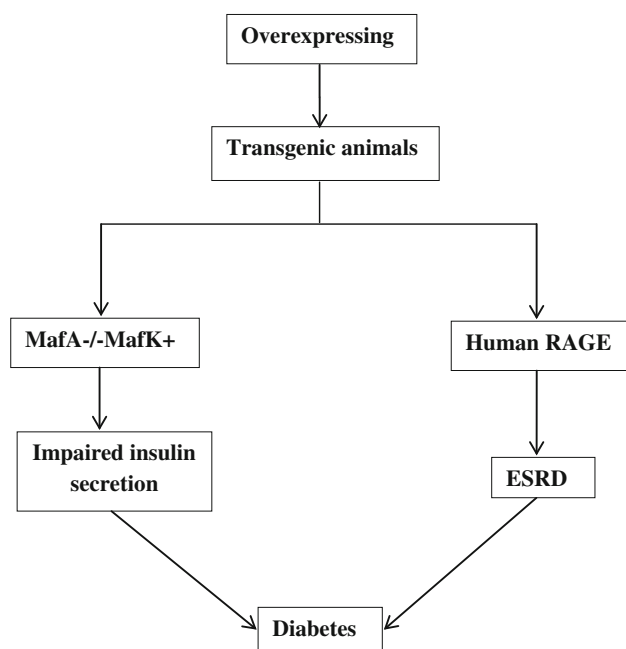
Fig. 3 Mechanism of action of human RAGE and MafA−/-MafK+

such as (±)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide (OPB-9195) has been shown to produce beneficial effects in this model (Takamura et al. 1997).

MafA$^{-/-}$MafK$^+$ overexpressing hybrid transgenic mouse model of severe diabetic nephropathy

MafA is a transcription factor belonging to Maf family and contains a C-terminal basic leucine zipper domain that binds to specific DNA sequences that are named Maf recognition elements (MAREs). They are divided into two subgroups, i.e., large and small Maf proteins. Small Maf protein family includes MafK, MafF and MafG, which do not possess the transactivation domain (Kataoka et al. 2002), whereas the large Maf proteins possess an N-terminal activation domain and stimulate the transcription of target genes. MafA plays an important role in insulin gene transcription and MafA-deficient (MafA$^{-/-}$) mice develop diabetes mellitus due to decrease in insulin gene transcription, impaired glucose-stimulated insulin secretion and mild abnormalities of the pancreatic islets (Zhang et al. 2005). This mild diabetic phenotype, due to the presence of other large Maf proteins, MafB and/or c-Maf can stimulate the expression of insulin genes and other MafA target genes (Kataoka et al. 1995; Inada et al. 1998; Olbrot et al. 2002; Kajihara et al. 2003; Matsuoka et al. 2003; Kataoka et al. 2004). Therefore, MafA$^{-/-}$ transgenic mice that overexpressed MafK, specifically MafK$^+$ mice in pancreatic beta cells, had impairment of glucose-stimulated insulin secretion. MafK is another small Maf protein that acts as a dominant negative protein to suppress the effect of large Maf proteins in pancreatic beta cells (Kataoka et al. 1995, 2004). MafK$^+$ mice has been shown to exhibit reversible hyperglycemia, which appears at younger age and spontaneously disappears at older age without development of overt diabetes, due to compensatory upregulation of endogenous Maf A. Further, transgenic mice with MafA$^{-/-}$ knockout and overexpression of MafK$^+$ in pancreatic beta cells overexpressed MafK in pancreatic β-cells. (MafA$^-$/-MafK$^+$) mice in order to

Table 2 Some animal models of types 1 and 2 diabetes mellitus studied for experimental DN

Type of model	Type of DM	Advantages	Limitations
STZ-induced DN	Type 1	Well established, reproducible, easily done in the laboratory	Insulin resistance does not occur
High-fat diet, low-dose STZ heminephrectomized rats	Type 2	Occurrence of overt DB, hypertension, hyperlipidemia	Developed mesangial cell expansion after 25 weeks, thus time consuming
STZ-induced advanced DN in 5/6 nephrectomized rats	Type1	Occurrence of azotemia, hyperglycemia and glomerular lesions, thus advanced DN	Development of glomerulopathy was not due to hyperglycemia
STZ-induced DN in uninephrectomized rats	Type 1	Well established	Not characterized
Renal ischemia-induced DN in STZ-treated rats	Type 1	Advanced DN occurrence in 6–8 weeks, occurrence of renal fibrosis, tubular inflammation and DN is similar to human DN	Not fully characterized
Genetic model of DN	Types 1 and 2	Animals are commercially available, spontaneous development of β-cell failure may mimic disease	Biohazard, strain-dependent dosing, potential for non-specific renal effects, autosomal recessive, mutation in gene

depress MafA protein and transcriptional activity of other large Maf proteins in mice have been evaluated. The resultant transgenic (MafA$^-$/-MafK$^+$) mice developed overt severe diabetes mellitus at the age of 5 weeks (Shimohata et al. 2006, 2009) (Fig. 3; Table 2).

Merits and demerits

Transgenic mice are useful as animal models for human disease. They are also useful in cases where we are unsure of the role of a particular protein product. ICER 1γ Tg mouse shows sustained hyperglycemia (Inada et al. 1999). RAGE-overexpressing IDDM mice exhibit renal insufficiency and advanced glomerulosclerosis seen in human DN (Takamura et al. 1998), whereas MafK$^+$ mice display reversible hyperglycemia, which appears at younger age and disappears at older age without overt diabetes (Shimohata et al. 2009). It is a costly exercise to produce transgenic animals and a special animal license must be applied before making transgenic and also time consuming, 2 generation times are required before results are known. In some countries transgenic animals are banned since the techniques involved germline gene therapy. Animal rights activists argue that to produce and breed animals manipulated to suffer from disease is painful and unwarranted.

Conclusion

Nowadays, a number of rodent animal models are being developed to better understand disease pathogenesis and develop new drugs for DN. The therapeutic agents currently available are limited; morbidity and mortality due to nephropathy are continuously increasing worldwide. Most experiments are carried out on rodents, even though other species with human-like biological characteristics are also used. But there is a long tradition of using these rodent animals as models of human DN, in which diabetes is developed either spontaneously or by using chemical, surgical, genetic or other techniques, to depict many clinical features or related phenotypes of the disease.

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