·Commentary·

Spontaneous rodent models of diabetes and diabetic retinopathy

Cai-Rui Li [1,2], Shu-Guang Sun [2]

[1]Lions Eye Institute, Molecular Ophthalmology Department, Nedlands, Australia
[2]Department of Ophthalmology, the Hospital of Dali University, Dali 671000, Yunnan Province, China
Correspondence to: Cai-Rui Li.[1]Lions Eye Institute, Molecular Ophthalmology Department, Nedlands, Australia; [2]Department of Ophthalmology, the Hospital of Dali University, Dali 671000, Yunnan Province, China. lcrbrett@hotmail.com
Received:2009-12-28 Accepted:2010-02-25

Abstract

• Diabetes is a complex and heterogeneous disorder presently affecting more than 100 million people worldwide and causing serious socio-economic problems. Spontaneous rodent models of diabetes mellitus have proved invaluable in understanding the pathogenesis, complications, and genetic or environmental influences that increase the risks of diabetes. We have reviewed here in the development and characterization of spontaneous rodent models that displayed most features commonly associated with diabetic retinopathy.

• KEYWORDS: rodent model; diabetes mellitus; diabetic retinopathy
DOI:10.3980/j.issn.2222-3959.2010.01.01

Li CR, Sun SG. Spontaneous rodent models of diabetes and diabetic retinopathy. *Int J Ophthalmol* 2010;3(1):1-4

INTRODUCTION

Diabetes mellitus is a term that is used loosely to describe a complex and heterogeneous disorder simply characterized by hyperglycemia (elevated blood sugar levels). Diabetes mellitus has occurred in humans at least 4000 years. In 1966, it was proposed that the same may be true in animals, particularly those living in association with humans, whether as domestic animals or as animals bred in the laboratory[1].

An animal model is defined as "a living organism with an inherited, naturally acquired, or induced pathological process that in one or more respects closely resembles the same phenomenon occurring in man". Animal models of diabetes mellitus can be caused by anti-insulin serum, pancreatectomy, glucose infusion, β-cytotoxic agents, and viruses; or caused by diabetogenic nutritional and hormonal factors. Some models spontaneously develop non-insulin-dependent or insulin-dependent diabetes [2]. Selective inbreeding has produced several strains of animal that are considered reasonable models of type 1 diabetes(T1D), type 2 diabetes (T2D) and related phenotypes such as obesity and insulin resistance. Apart from their use in studying the pathogenesis of the disease and its complications, all new treatments for diabetes, including islet cell transplantation and preventative strategies, are initially investigated in animals[3]. Here we review the spontaneous rodent models of diabetes and their application on retinal research.

SPONTANEOUS MODELS OF TYPE 1 DIABETES

There are several spontaneous rodent models of type 1 diabetes, two of which have been extensively studied: the Bio-Breeding (BB) rat and the non-obese diabetic (NOD) mouse[4].

NOD Mouse The NOD mouse was developed by selectively breeding offspring from a laboratory strain that in fact was first used in the study of cataract development[5,6]. Insulitis is present when the mice are 4-5 weeks old, followed by subclinical β-cell destruction and decreasing circulating insulin concentrations. Frank diabetes typically presents between 12 and 30 weeks of age. An autoimmune lesion involving lymphocytic infiltration and destruction of the pancreatic β-cells leads to hypoinsulinemia, hyperglycemia, ketoacidosis, and death. There is a larger gender difference with 90% of females and 20% of males developing diabetes in NOD mice[7].

Type 1 diabetes is a polygenic disease. Both in human and in NOD mouse type 1 diabetes, the primary susceptibility gene is located within the MHC [8]. NOD mouse represents probably the best spontaneous model used in genetic and immunologic studies and seems particularly analogous to human Type 1 diabetes. It has provided not only essential information on type 1 diabetes pathogenesis, but also valuable insights into mechanisms of immunoregulation and tolerance. Importantly, it allows testing of immuno-intervention strategies potentially applicable to man[9,10].

Type 1 Bio-Breeding Rat Models The Bio-Breeding (BB) rat was first recognized in the Bio Breeding

Laboratories in 1974 [11]. It is extremely useful for studying both spontaneous diabetic-prone (BBDP) and induced diabetic-resistant (BBDR) diabetes and associated diabetic complications[12]. As in human type 1 diabetes, the syndrome in BB rats is characterized by hyperglycemia, lymphocytic insulitis, and the presence of antibodies to islet cell surface molecules. In common with the NOD mouse, the pancreatic islets are subjected to an immune attack with T cells, B cells, macrophages and natural killer cells being recruited to the insulitis[13,14]; the susceptibility gene is located within the MHC [15]. A variety of auto-antibodies, including glutamic acid decarboxylase (GAD), have been reported in both BB rats and the NOD mouse, although it remains far from clear which, if any, of these are primary autoantigens[16-18].

It is believed that the development of diabetes in the model is secondary to a cell-mediated autoimmune process and may have implications for the pathophysiology of type 1 diabetes in humans. BBDP rats are prone to the long-term complications of diabetes such as neuropathy and retinopathy that occur in this model are very similar to complications in human diabetics[19].

SPONTANEOUS MODELS OF TYPE 2 DIABETES

Numerous spontaneous rodent models have been used to model various defects of human type 2 diabetes, such as Otsuka Long Evans Tokushima fatty (OLETF), Goto-Kakizaki (GK), Akita mice and Akimba mice that showed the some characteristics of these animal models same as human.

OLETF Rat Selective breeding for more than 20 generations has led to the generation of a spontaneously diabetic strain of Long-Evans rats that displays polyuria, polydipsia, and slight obesity [1,20]. The OLETF rat develops hyperphagia and insulin resistance between 12 and 24 weeks of age, and mild obesity, hyperglycemia, and hyperinsulinemia between 20 and 28 weeks of age. By 40 weeks of age, the diabetic rats are hypoinsulinemic and exhibit defects in insulin secretion[21]. Obese OLETF rats are unable to control individual meal size due to the loss of cholecystokinin-A receptors [22,23]. These rats have proven useful in studying the effects of exercise and diet on the development of type 2 diabetes, to test the efficacy of antidiabetic agents, and to study the complications of diabetes[24-26].

GK Rat The GK rat is a widely accepted model for research in type 2 diabetes. The GK rat was created by selective breeding of Wistar rats for oral glucose intolerance[27]. There are at least two loci responsible for high blood glucose in GK rats [28]. Males and females become diabetic at weaning age, most likely due to an over all inherent lack of normal beta cell mass. Diabetes in the GK rat is characterized by fasting hyperglycemia, impaired secretion of insulin in response to glucose, and hepatic and peripheral insulin resistance. Late onset complications such as retinopathy, microangiopathy, neuropathy, and peripheral nephropathy have been described in the literature[29,30].

Type 2 Bio-Breeding Rat Models This model has been extremely useful for studying both spontaneous diabetic-prone (BBDP) and induced diabetic-resistant (BBDR) diabetes and associated diabetic complications [12]. In this strain, diabetes is manifested by lymphopenia, obesity, hyperinsulinemia, and auto immune diabetes. Islets from obese rats reveal beta-cell hyperplasia, and diabetes develops due to a combination of insulin resistance and autoimmune insulitis. So the BBZDP/Wor rat is often complicated by the presence of both type 1 and type 2 diabetes characteristics[31,32].

Akita Mice Akita mice, a model of spontaneous early-onset diabetes mellitus, are from the C57BL/6 background with a dominant mutation in the Ins2 gene, which results in a loss of beta cell function and failed insulin secretion 4-6 weeks postpartum. Symptoms in Akita mice include hyperglycemia, hypoinsulinemia, polydipsia, and polyuria, beginning around 3-4 weeks of age. The diabetic phenotype is more severe and progressive in the male than in the female. Obesity or insulitis does not accompany diabetes [33]. The mean lifespan of diabetic male mice on the C57BL/NJcl background (305 days) was significantly shorter than that of nondiabetic males in another colony of the same strain (690 days). Akita mice will serve as an excellent substitute for mice made insulin dependent diabetic by treatment with alloxan or streptozotocin[34,35].

AKimba Mice The AKimba mice have been produced through crossing homozygous Kimba mice with Akita mice in Lions Eye institutes (LEI) in Australia. Kimba is a transgenic mouse model of retinal neovascularization. The AKimba mouse demonstrates features exhibited by the Akita as well as the Kimba mice[36].

DIABETIC RETINOPATHY

The frequency of diabetic retinopathy increases proportionally to the duration of diabetes and blood glucose control. Microaneurysms are the earliest clinically visible manifestation of background retinopathy. Additional microvascular abnormalities result from significant vascular occlusion and characterize the preproliferative retinopathy stage. Approximately 50% of patients who reach the preproliferative stage will progress to proliferative retinopathy within 15 months[37].

Most present diabetic rodent models can be used to study the initial or latent phase diabetic retinopathy. Matsuura showed that the peak latency of oscillatory potential (OP), the earliest electroretinographic manifestation of diabetic

retina, was prolonged and retinal acellular capillaries and pericyte ghosts, the characteristic morphological changes in early diabetic retinopathy were not accelerated in OLETF rat[38]. Thinning of inner nuclear layers and outer retina were observed [35,39]. These observations suggested that retinal neuronal changes takes place prior to the angiopathic diabetic changes in diabetic rodents. Retinal complications including increased vascular permeability, thicker basement membranes, caliber irregularity, narrowing, tortuosity and loop formations of capillaries in these animals were similar to those seen in diabetic patients[35,40].

It was reported that apoptosis of retinal microvascular cells (RMC) was increased and oxidative stress promoted the apoptosis of RMC in diabetic GK rats, similar to that in diabetic patients. Furthermore, a combination of vitamins C and E and an advanced glycation end-products inhibitor mostly inhibited this increased apoptosis and ameliorated diabetic retinopathy. It indicated that apoptosis of RMC was a good marker of the progression of diabetic retinopathy in GK rats[41]. Vascular endothelial growth factor (VEGF) and hypoxia inducible factor-1 (HIF-1) levels in ocular tissue of GK rats[42] and NOD mice[43] were evaluated by ELISA and immunohistochemical studies. Increased VEGF and HIF-1 production in certain ocular tissue, similar to that in humans, are observed quite early. Lower levels of glutathione and normal endothelial/ pericyte ratio in GK rat retina indicated that impaired glucose metabolism may influence one of the defense mechanisms for oxidative stress and that decreased glutathione levels occur prior to morphological signs of pericyte loss and/or endothelial cell proliferation in this diabetic animal model[44].

Few diabetic rodent models can present features of the advanced diabetic retinopathy. BBZDR/Wor rats progress to late stages of preproliferative retinopathy (PPDR) but do not demonstrate proliferative (PDR) aspects of the disease[45,46]. The AKimba mouse was hyperglycemic and developed retinopathy resembled the late stages of PPDR and the stage of PDR. The retinopathy includes increased permeability, capillary dropout, retinal non-perfusion, vein beading, hemorrhage, neovascularisation and retinal detachment.

In a word, spontaneous rodent models of diabetes mellitus have proved invaluable in understanding diabetes and diabetic retinopathy. The work comparing and contrasting type 1 and type 2 diabetic rodent models should help elucidate detailed molecular mechanisms behind diabetic complications, and help lead to the development of better therapeutics to treat diabetes and diabetic retinopathy.

REFERENCES

1 Willy JM, Abdullah S. Animal models of diabetes. In: Conn PM, ed. Sourcebook of models for biomedical research, Humana Press. Vol 1. ed. Totowa, New Jersey, US, 2008:651-656

2 Frederick ES, Richard JT. Ethical issues involved in the development of animal models for type I diabetes. *ILAR J* 1993;35(1):1-2

3 Rees DA, Alcolado JC. Animal models of diabetes mellitus. *Diabet Med* 2005;22 (4):359-370

4 Sai P, Gouin E. Spontaneous animal models for insulin-dependent diabetes (type 1 diabetes). *Vet Res* 1997;28(3):223-229

5 Li ZG, Zhang W, Anders AA. Alzheimer-like changes in rat models of spontaneous diabetes. *Diabetes* 2007; 56(7):1817-1824

6 Makino S, Kunimoto K, Muraoka Y, Mizushima Y, Katagiri K, Tochino Y. Breeding of a non-obese diabetic strain of mice. *Exp Anim* 1980;29(1):1-13

7 Atkinson M, Leiter EH. The NOD mouse model of insulin dependent diabetes: as good as it gets? *Nat Med* 1999;5(6):601-604

8 Todd JA. Genetic analysis of type 1 diabetes using whole genome approaches. *Proc Natl Acad Sci USA* 1995;92(19):8560-8565

9 Meagher C, Sharif S, Hussain S, Cameron MJ, Arreaza GA, Delovitch TL. Cytokines and chemokines in the pathogenesis of murine type 1 diabetes. *Adv Exp Med Biol* 2003;520:133-138

10 Yoon JW, Jun HS. Cellular and molecular pathogenic mechanisms of insulin-dependent diabetes mellitus. *Ann N Y Acad Sci* 2001;928:200-211

11 Eizirik DL, Mandrup PT. A choice of death the signal-transduction of immune-mediated β-cell apoptosis. *Diabetologia* 2001;44(12):2115-2133

12 Eiselein L, Schwartz HJ, Rutledge JC. The challenge of type 1 diabetes mellitus. *ILAR J* 2004;45(3):231-236

13 Bone AJ, Hitchcock PR, Gwilliam DJ, Cunningham JM, Barley J. Insulitis and mechanisms of disease resistance: studies in an animal model of insulin dependent diabetes mellitus. *J Mol Med* 1999;77(1):57-61

14 Lally FJ, Ratcliff H, Bone AJ. Apoptosis and disease progression in the spontaneously diabetic BB/S rat. *Diabetologia* 2001;44(3):320-324

15 Ramanathan S, Poussier P. BB rat lyp mutation and type 1 diabetes. *Immunol Rev* 2001;184:161-171

16 Yoon JW, Yoon CS, Lim HW, Huang QQ, Kang Y, Pyun KH, Hirasawa K, Sherwin RS, Jun HS. Control of autoimmune diabetes in NOD mice by GAD expression or suppression in β cells. *Science* 1999;284(5417):1183-1187

17 Bortel R, Waite DJ, Whalen BJ, Todd D, Leif JH, Lesma E, Moss J, Mordes JP, Rossini AA, Greiner DL. Levels of Art2+ cells but not soluble Art2 protein correlate with expression of autoimmune diabetes in the BB rat. *Autoimmunity* 2001;33(3):199-211

18 Mackay IR, Bone A, Tuomi T, Elliott R, Mandel T, Karopoulos C, Rowley MJ. Lack of autoimmune serological reactions in rodent models of insulin dependent diabetes mellitus. *J Autoimmun* 1996;9(6):705-711

19 Hänninen A, Hamilton WE, Kurts C. Development of new strategies to prevent type 1 diabetes: the role of animal models. *Ann Med* 2003;35(8):546-563

20 Shima K, Zhu M, Mizuno A. Pathoetiology and prevention of NIDDM lessons from the OLETF rat. *J Med Invest* 1999;46(3-4):121-129

21 Kawano K, Hirashima T, Mori S, Saitoh Y, Kurosumi M, Natori T. Spontaneous long-term hyperglycemic rat with diabetic complications. Otsuka Long-Evans Tokushima Fatty (OLETF) strain. *Diabetes* 1992;41(11):1422-1428

22 Bi S, Moran TH. Actions of CCK in the controls of food in take and body weight: Lessons from the CCK-A receptor deficient OLETF rat. *Neuropeptides* 2002;36: 171-181

23 Bi S, Moran TH. Response to acute food deprivation in OLETF rats lacking CCK-A receptors. *Physiol Behav* 2003;79(4-5):655-661

24 Yamamoto M, Jia DM, Fukumitsu KI, Imoto I, Kihara Y, Hirohata Y, Otsuki M. Metabolic abnormalities in the genetically obese and diabetic Otsuka Long-Evans Tokushima Fatty rat can be prevented and reversed by alpha-glucosidase inhibitor. *Metabolism* 1999;48(3):347-354

25 Sima AA, Sugimoto K. Experimental diabetic neuropathy: An update. *Diabetologia* 1999;42(7):773-788

26 Ziegler D. Treatment of diabetic polyneuropathy: Update 2006. *Ann N Y Acad*

*Sci*2006;1084(11):250-266

27 Kim CS, Sohn EJ, Kim YS, Jung DH, Jang DS, Lee YM, Kim DH, Kim JS. Effects of KIOM-79 on hyperglycemia and diabetic nephropathy in type 2 diabetic Goto-Kakizaki rats. *J Ethnopharmacol*2007;111(2):240-247

28 Fakhrai-Rad H, Nikoshkov A, Kamel A, Fernström M, Zierath JR, Norgren S, Luthman H, Galli J. Insulin-degrading enzyme identified as a candidate diabetes susceptibility gene in GK rats. *Hum Mol Genet*2000;9(14):2149-2158

29 Sato N, Komatsu K, Kurumatani H. Late onset of diabetic nephropathy in spontaneously diabetic GK rats. *Am J Nephrol*2003;23(5):334-342

30 Nobrega MA, Fleming S, Roman RJ, Shiozawa M, Schlick N, Lazar J, Jacob HJ. Initial characterization of a rat model of diabetic nephropathy. *Diabetes*2004;53(3):735-742

31 Mordes JP, Bortell R, Blankenhorn EP, Rossini AA, Greiner DL. Rat models of type 1 diabetes: genetics, environment and autoimmunity. *ILARJ* 2004;45 (3):278-291

32 Vernet D, Cai L, Garban H, Babbitt ML, Murray FT, Rajfer J, Gonzalez-Cadavid NF. Reduction of penile nitric oxide synthase in diabetic BB/WORdp (type I) and BBZ/WORdp (type II) rats with erectile dysfunction. *Endocrinology*1995;136(12):5709-5717

33 Choeiri C, Hewitt K, Durkin J, Simard CJ, Renaud JM, Messier C. Longitudinal evaluation of memory performance and peripheral neuropathy in the Ins2C96Y Akita mice. *Behav Brain Res*2005;157(1):31-38

34 Gastinger MJ, Singh RS, Barber AJ. Loss of cholinergic and dopaminergic amacrine cells in streptozotocin-diabetic rat and Ins2Akita- diabetic mouse retinas. *Invest Ophthalmol Vis Sci*2006;47(7):3143-3150

35 Barber AJ, Antonetti DA, Kern TS, Reiter CE, Soans RS, Krady JK, Levison SW, Gardner TW, Bronson SK.The Ins2Akita mouse as a model of early retinal complications in diabetes. *Invest Ophthalmol Vis Sci*2005;46(6):2210-2218

36 Tee LB, Penrose MA, O'Shea JE, Lai CM, Rakoczy EP, Dunlop SA. VEGF-induced choroidal damage in a murine model of retinal neovascularisation. *Br J Ophthalmol*2008;92(6):832-838

37 Aiello LM. Perspectives on diabetic retinopathy. *Am J Ophthalmol*2003;136(1):122-135

38 Matsuura T, Yamagishi S, Kodama Y, Shibata R, Ueda S, Narama I. Otsuka long-evans tokushima fatty (OLETF) rat is not a suitable animal model for the study of angiopathic diabetic retinopathy. *Int J Tissue React*2005;27(2):59-62

39 Lu ZY, Bhutto IA, Amemiya T. Retinal changes in Otsuka long-evans Tokushima Fatty rats (spontaneously diabetic rat): possibility of a new experimental model for diabetic retinopathy. *Jpn J Ophthalmol*2003;47(1):28-35

40 Noritake M, Imran AB, Tsugio A. Retinal capillary changes in Otsuka long-evans tokushima fatty rats (spontaneously diabetic strain). *Ophthalmic Res* 1999;31(5):358-366

41 Yatoh S, Mizutani M, Yokoo T, Kozawa T, Sone H, Toyoshima H, Suzuki S, Shimano H, Kawakami Y, Okuda Y, Yamada N. Antioxidants and an inhibitor of advanced glycation ameliorate death of retinal microvascular cells in diabetic retinopathy. *Diabetes Metab Res Rev*2006;22(1):38-45

42 Sone H, Kawakami Y, Okuda Y, Sekine Y, Honmura S, Matsuo K, Segawa T, Suzuki H, Yamashita K. Ocular vascular endothelial growth factor levels in diabetic rats are elevated before observable retinal proliferative changes. *Diabetologia*1997;40(6):726-730

43 Li C, Xu Y, Jiang D, Hong W, Guo X, Wang P, Li W. The expression of HIF-1 in the early diabetic NOD mice. *Yanke Xuebao*2006;22(2):107-111

44 Agardh CD, Agardh E, Hultberg B, Qian Y, Ostenson CG. The glutathione levels are reduced in Goto-Kakizaki rat retina, but are not influenced by aminoguanidine treatment. *Current Eye Research*1998;17(3):251-256

45 Ellis EA, Guberski DL, Hutson B, Grant MB. Time course of NADH oxidase, inducible nitric oxide synthase and peroxynitrite in diabetic retinopathy in the BBZ/WOR rat. *Nitric Oxide*2003;6(3):295-304

46 Frank RN, Schulz L, Abe K, Iezzi R. Temporal variation in diabetic macular edema measured by optical coherence tomography. *Ophthalmology* 2004;111 (2):211-217