—Review—

The Oikawa-Nagao Mouse: A Polygenic Animal Model for Unraveling the Pathophysiology of Type 2 Diabetes and Obesity

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The Oikawa-Nagao (ON) mouse is a polygenic animal model of type 2 diabetes and obesity developed by selective breeding of mice with inferior glucose tolerance [diabetes-prone (ON mouse DP®; ON-DP) strain] and superior glucose tolerance [diabetes-resistant (ON mouse DR®; ON-DR) strain]. Hybrid mice of three different inbred strains (C57BL/6, AKR, and AKR) were fed a high-fat diet and then selectively bred for higher and lower post-challenge blood glucose levels in oral glucose tolerance tests over 20 generations. Compared to ON-DR mice, ON-DP mice were found to be predisposed to develop obesity and diabetes after being fed a high-fat diet. Our recent studies suggest that the emergence of these phenotypes is associated with novel pathophysiology of type 2 diabetes and obesity, such as low insulin secretion capacity associated with high CD36 expression in pancreatic β-cells and hypoleptinemia preceding obesity due to low leptin secretion capacity in adipocytes. In addition, it has been suggested that ON-DP mice fed an atherogenic diet are a suitable model to reproduce atherosclerotic lesion formation due to fluctuations in blood glucose levels. This may facilitate the elucidation of mechanisms underlying diabetic macrovascular complications. This review will present the development strategy of the ON mouse strain, representative metabolic phenotypes and their underlying mechanisms. Furthermore, their relevance to the pathophysiology of type 2 diabetes and obesity in humans will be discussed.
(J Nippon Med Sch 2025; 92: 2–9)

Key words: CD36, leptin, obesity, Oikawa-Nagao mouse, type 2 diabetes

Introduction

The escalating prevalence of diabetes has become a global concern today. The steep rise in the number of type 2 diabetes (T2D) cases, particularly in the East Asian region, including Japan, is believed to be due to a combination of genetic factors, such as race-specific low insulin secretion capacity, and environmental changes, such as the westernization of diets and decreased physical activity[1,2]. Dietary patterns in the East Asian region have approximately tripled over the past half century[3–5], suggesting that an increase in fat intake may contribute to the increased risk of T2D. Experimental and epidemiological studies have shown that high-fat diets (HFD) cause excessive weight gain and obesity, leading to insulin resistance, one of the two major pathologies in the development of T2D[6].

However, individual differences in susceptibility to obesity and T2D are observed even in the modern fat-rich environment, and disappointingly, little progress has been made in basic research to understand the origins of these differences. One reason for this may be that most basic research on HFD has been conducted in animal strains that are predisposed to develop obesity and diabetes under HFD, such as Wistar rats, Sprague-Dawley (SD) rats, and C57BL/6 mice[7–9]. To address this issue, the authors developed a novel mouse model comprising two strains with genetically distinct susceptibility to HFD-induced diabetes (**Fig. 1**).

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https://doi.org/10.1272/jnms.JNMS.2025_92-104
Journal Website (https://www.nms.ac.jp/sh/jnms/)

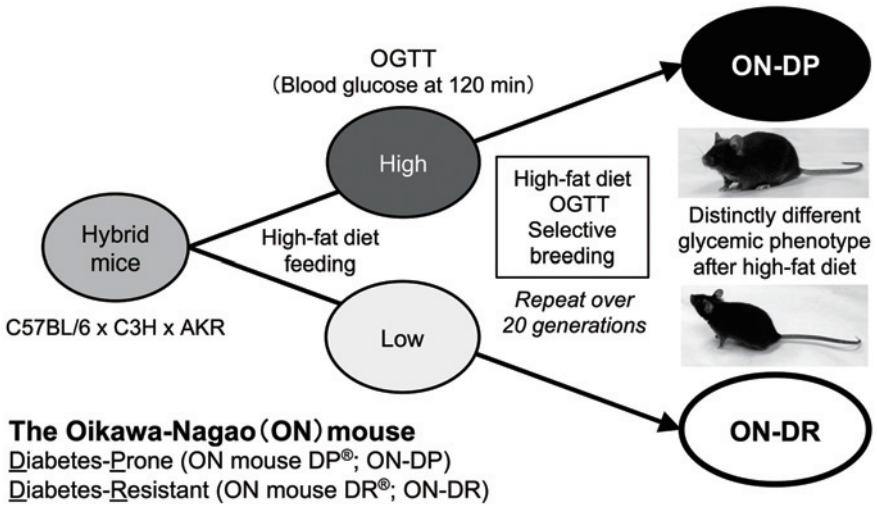

Fig. 1 Brief summary of selective breeding for the Oikawa-Nagao (ON) mouse Diabetes-Prone (ON mouse DP®; ON-DP) and Diabetes-Resistant (ON mouse DR®; ON-DR) strains.
OGTT, oral glucose tolerance test.

Development of the Oikawa-Nagao Mouse

In 2001, a mouse selective breeding study was initiated using glucose tolerance after HFD as a selection index[10]. The parental mouse population consisted of hybrids of three inbred strains, C57BL/6, AKR, and C3H, to expand the genetic diversity to allow extraction of the set of genes involved in susceptibility to HFD-induced diabetes. The parental mice were first fed an HFD, followed by oral glucose tolerance tests (OGTT). Mice with high blood glucose levels after 120 minutes of OGTT (BG_{120min}) were selected and bred. Their offspring were then subjected to a similar process of HFD feeding, OGTT, selection, and breeding over several generations. Eventually, it was found that some mice in the same litter maintained normal glucose tolerance (NGT) even after HFD. Therefore, since 2005, mice with high BG_{120min} (males with 200 mg/dL or higher, and females in descending order) and mice with low BG_{120min} (both males and females around 100 mg/dL) were selectively bred for more than 20 generations until the BG_{120min} distribution was completely segregated between the male mice of the two lines. At the end of the selective breeding, both lines were named Oikawa-Nagao (ON) mice, and in 2019, each line was officially registered as Diabetes-Prone (ON mouse-DP®; ON-DP) and Diabetes-Resistant (ON mouse-DR®; ON-DR)[11].

Glucose Metabolism Phenotype

First, glucose metabolism phenotypes were evaluated in ON mouse strains[12]. When OGTT was performed in both strains of male ON mice before HFD (on normal chow, 5 weeks old), ON-DP mice did not show an increase in fasting blood glucose (FBG) compared to ON-DR mice, but their post-challenge blood glucose levels were higher, like impaired glucose tolerance (IGT) in humans (**Fig. 2 A**). After 5 weeks of HFD, FBG increased and BG_{120min} exceeded 400 mg/dL only in ON-DP mice, which progressed to diabetes (**Fig. 2B**). In contrast, in ON-DR mice, neither FBG nor BG_{120min} increased ever after HFD and maintained NGT. This means that following the phenotype of male ON-DP mice during HFD allows us to observe the developmental process from IGT to diabetes, and also allows us to compare them with NGT of ON-DR mice. Furthermore, there is a clear sexual dimorphism in the development of glucose intolerance after HFD in ON-DP mice, with BG_{120min} remaining around 400 mg/dL in males but around 200 mg/dL in females[11].

Characterization of Pancreatic Islets

Before HFD, ON-DP mice had higher post-challenge blood glucose levels accompanied by a smaller increase in plasma insulin levels in OGTT compared to ON-DR mice. This resulted in a low insulinogenic index of ON-DP mice (**Fig. 2C**), indicating β-cell dysfunction. Accordingly, pancreatic islets of Langerhans were isolated from ON mice before HFD for the following analyses[12]. When glucose-stimulated insulin secretion (GSIS) was measured, islets from ON-DP mice showed significantly lower GSIS compared to those from ON-DR mice (**Fig. 2D**). Similar results were obtained with islets isolated from

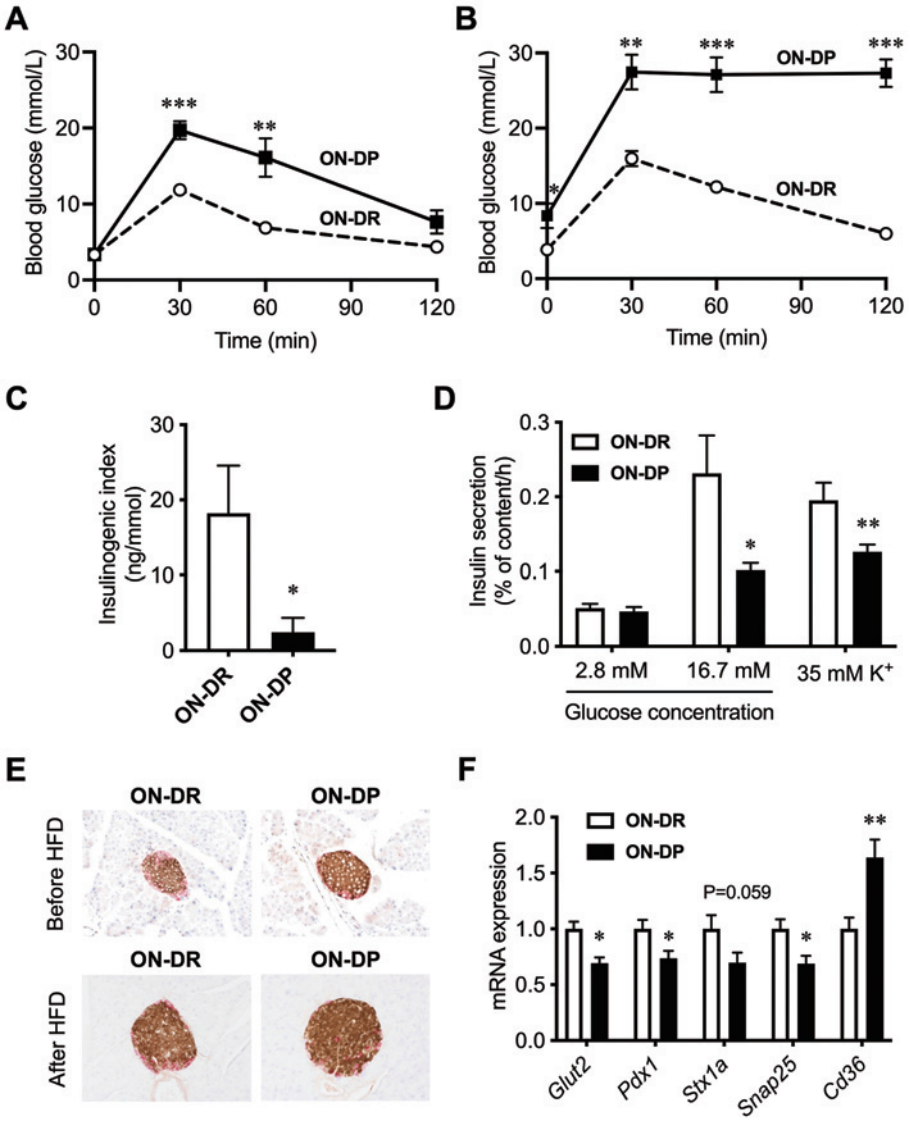

Fig. 2 Glucose metabolism phenotypes and pancreatic islet characteristics of the Oikawa-Nagao (ON) mouse Diabetes-Prone (ON-DP) and Diabetes-Resistant (ON-DR) strains[12]. Blood glucose levels in OGTT at 5 weeks of age before (A) and 10 weeks of age after high-fat diet (HFD) feeding (B). Insulinogenic index (Δ[insulin]$_{0–15\ min}$/Δ[glucose]$_{0–15\ min}$) in OGTT before HFD feeding (C). Glucose- and K^+-induced insulin secretion of pancreatic islets isolated from ON mice before HFD (D). Immunohistochemical images for α- (red) and β-cells (brown) of pancreatic islets in ON mice before and after HFD (E). Relative gene expression levels of pancreatic islets isolated from ON mice before HFD (F). Gene expression levels were normalized to *Gapdh*, and the normalized expression levels of ON-DP mice were expressed as relative values to those of ON-DR mice. Data are expressed as mean ± standard error of the mean. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$ *vs*. age-matched ON-DR mice (Student's *t*-test).

ON mice after HFD. In contrast, β-cell mass was significantly increased by HFD in ON-DP mice compared to ON-DR mice (**Fig. 2E**). Even with such morphological adaptation of β-cells, ON-DP mice with low insulin secretory capacity were unable to fully compensate for the insulin resistance acquired by HFD, and as a result, the abnormal glucose metabolism was exacerbated. Therefore, low insulin secretory capacity due to spontaneous β-cell

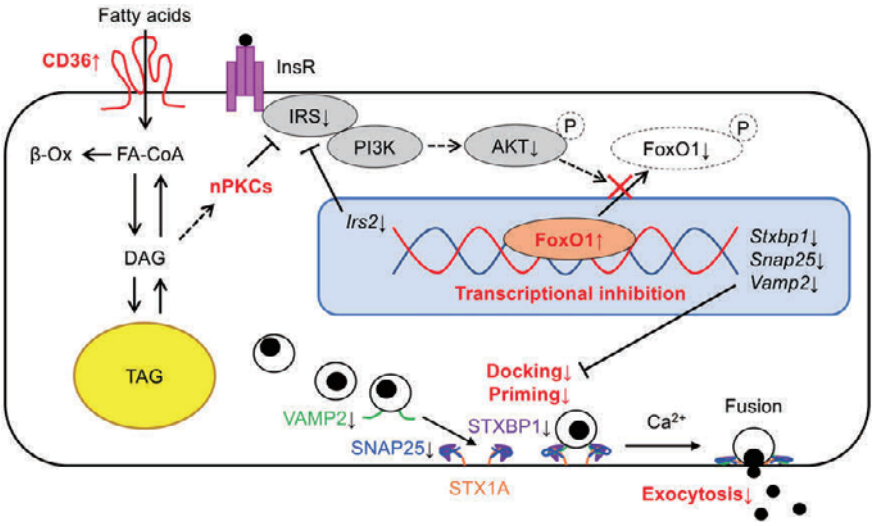

Fig. 3 Model describing the CD36-driven pathway of pancreatic β-cell lipotoxicity[14]. CD36-mediated facilitation of lipid influx (including fatty acids) increases intracellular diacylglycerol, leading to the translocation of PKCε to the plasma membrane (activation). Activated PKCε induces abnormal phosphorylation of IRS1 and consequently attenuates PI3K/AKT signaling. The subsequent retention of FoxO1 in the nucleus leads to transcriptional inhibition of Irs2 and exocytotic genes, which in turn inhibits insulin granule docking with exocytosis dysfunction and consequently impairs insulin secretion in β-cells.
β-Ox, β-oxidation; FA, fatty acid; InsR, insulin receptor; TAG, triacylglycerol.

dysfunction is considered a critical factor predisposing to HFD-induced diabetes.

Islets from ON-DP mice showed not only lower GSIS, but also lower potassium-stimulated insulin secretion (KSIS) compared to those from ON-DR mice (**Fig. 2D**), suggesting certain impairment of the insulin secretion cascade below the ATP-dependent potassium (K_{ATP}) channels. In fact, gene expression analysis of the islets revealed reduced expression of SNARE proteins involved in insulin granule exocytosis and membrane fusion, such as syntaxin 1A (STX1A) and synaptosomal-associated protein, 25 kDa (SNAP25), in ON-DP mice independent of HFD (**Fig. 2F**). Accordingly, abnormalities in the exocytosis machinery, the last step of the insulin secretion cascade, are likely to be a cause of spontaneous β-cell dysfunction in ON-DP mice[13].

Possible Involvement of CD36 in β-Cell Function

Islets from ON-DP mice also showed higher gene expression of CD36, a fatty acid translocase, compared to ON-DR mice (**Fig. 2F**). Based on the finding, we formulated a new research hypothesis: "High expression of CD36 in pancreatic β-cells may induce defective exocytosis, leading to impaired insulin secretion". To investigate this, we used a clonal β-cell line (INS-1 cells) with the TET-On system to study the influence of CD36 on β-cell function[14]. Overexpression of CD36 resulted in defective exocytosis due to a ~50% reduction in the number of docked granules, leading to decreased GSIS and KSIS in INS-1 cells. These effects were associated with reduced expression of key exocytotic proteins, including SNAP25, vesicle associated membrane protein 2 (VAMP2), and syntaxin binding protein 1 (STXBP1). The reduction in these exocytotic proteins was likely caused by the inhibition of intracellular insulin signaling and a subsequent increase in the nuclear localization of the inhibitory transcription factor, forkhead box protein O1 (FoxO1). These findings strongly suggest the existence of the CD36-driven pathway of pancreatic β-cell lipotoxicity (**Fig. 3**)[15]. Accordingly, further *in vivo* studies are crucial to verify the relationship between elevated CD36 expression in β-cells, impaired insulin secretion, and the development of diabetes.

Feeding Behavior under High-Fat Diet

During the selective breeding of the ON mouse strains,

HFD intake and post-HFD body weight were monitored along with blood glucose parameters[16]. As the generation progressed, clear differences between the two strains emerged not only in glycemic parameters but also in HFD intake and post-HFD body weight. Specifically, ON-DP mice consumed more HFD, gained more body weight, and developed more severe insulin resistance with higher levels of inflammatory cytokine expression in visceral adipose tissue compared to ON-DR mice[6]. When the HFD intake of ON-DP mice was restricted to the same level as that of ON-DR mice (pair feeding), the excessive weight gain, worsening of insulin resistance, and subsequent development of diabetes were completely reversed even after HFD[17]. This suggests that feeding behavior is also a critical factor predisposing to HFD-induced diabetes, which led us to analyze the pathogenesis of hyperphagia in ON-DP mice.

Hypoleptinemia Preceding Obesity

Leptin is an anorexigenic hormone secreted by adipocytes that acts on the hypothalamic arcuate nucleus (ARC), a center for appetite regulation. In obesity, such as after HFD, "hyperleptinemia" is generally observed due to increased leptin secretion from enlarged adipocytes and decreased leptin sensitivity in the ARC, so called "leptin resistance"[18]. Conversely, ON-DP mice showed "hypoleptinemia" due to spontaneously low leptin secretion capacity from adipocytes with an intact leptin sensitivity, resulting in hyperphagia and subsequent excessive weight gain by HFD[17].

Before HFD, there were no differences in adipose tissue mass or adipocyte morphology in body weight-matched ON mice. However, plasma leptin levels were significantly lower in ON-DP mice compared to ON-DR mice. In the ARC, the number of phosphorylated STAT3-positive cells, an indicator of leptin signaling activation, significantly decreased in ON-DP mice. However, the enhancement of STAT3 phosphorylation in the ARC immediately after intraperitoneal administration of leptin was at the same level in ON-DR mice. When leptin was administered intraperitoneally twice daily for three days, the HFD intake of ON-DP mice was suppressed to the same level as that of ON-DR mice. These results suggest that leptin sensitivity is still intact in ON-DP mice before HFD. Overall, it was concluded that the hyperphagia of HFD observed in ON-DP mice is due to a deficiency in circulating leptin levels, so-called "hypoleptinemia", rather than leptin resistance.

To elucidate the cause of hypoleptinemia in ON-DP mice, we isolated epididymal adipose tissue from ON mice before HFD and examined *ex vivo* leptin secretion and gene expression levels in response to a secretagogue, insulin. The adipose tissue from ON-DP mice showed lower leptin secretion and leptin (*Lep*) gene expression in response to insulin stimulation compared to that from ON-DR mice. Therefore, a defect in the regulation of *Lep* gene expression in adipocytes was suggested in ON-DP mice. An analysis of methylation of CpG sites in the promoter region of *Lep* gene in adipocytes revealed that the methylation rate in this region was significantly higher in ON-DP mice compared to ON-DR mice. This higher methylation rate was negatively correlated with *Lep* gene expression levels, suggesting that the hypoleptinemia observed in ON-DP mice is due to abnormal epigenomic regulation.

Hyperglycemia and Atherosclerosis: Issues with Existing Animal Models

The increased risk of atherosclerotic disease is already observed in individuals with IGT[19,20]. These epidemiologic studies have suggested that postprandial hyperglycemia is a better predictor of cardiovascular disease than fasting hyperglycemia. Repeated blood glucose fluctuations, known as glycemic spikes, have been implicated in the initiation and progression of atherosclerotic lesions in IGT[21]. The existing animal models used to study the relationship between hyperglycemia and atherosclerosis are primarily apoE or LDL receptor (LDL-R) knockout mice with diabetes induced by streptozotocin administration or crossed with leptin-deficient mice (such as *ob/ob* or *db/db* mice)[22,23]. However, ApoE and LDL-R knockout mice have extremely high levels of non-HDL cholesterol in the blood and rapidly develop advanced atherosclerotic lesions, making it difficult to evaluate the independent effect of hyperglycemia from that of hyperlipidemia on atherosclerosis. In addition, diabetes induced by streptozotocin administration or crossed with leptin-deficient strains results in markedly high fasting blood glucose levels. Therefore, these models are not suitable for analyzing the effects of blood glucose fluctuations associated with IGT on atherosclerotic lesion formation.

As a Model for Replicating Hyperglycemia and Atherosclerosis

Based on the glucose metabolism phenotype of ON mice, it was hypothesized that the female ON-DP mice could be used as a model to reproduce atherosclerotic lesion formation due to blood glucose fluctuations *in vivo*. To

test this, female ON mice were fed an atherogenic diet (AD; containing 1.25% cholesterol and 0.5% cholic acid) for 20 weeks[24]. Before and after 10 weeks and 19 weeks of AD feeding, post-challenge blood glucose levels in OGTT, but not FBG, were consistently higher in ON-DP mice compared to ON-DR mice, confirming that female ON-DP mice exhibit an IGT-like glycemic phenotype under AD. There were no significant differences between the strains in plasma lipid levels, which were close to those of healthy humans. When the size of the atherosclerotic lesion around the aortic sinus was quantitatively analyzed using serial sections stained with Oil Red O, the size in ON-DP mice was approximately four times larger than that in ON-DR mice. In fact, the size was positively correlated with glycemic parameters, *i.e.*, FBG, insulin, and the area under the curve (AUC) of blood glucose levels in OGTT, but not with any plasma lipid levels.

To provide more direct evidence that glucose fluctuations contribute to atherosclerotic lesion formation, we established a glycemic spike model in wild-type C57BL/6 mice[25]. These mice were subjected to artificial blood glucose fluctuations induced by twice-daily oral glucose injections for 20 weeks during AD. The treatments increased the size of atherosclerotic lesions fourfold, which, coincidentally, was comparable to the difference in lesion size between ON-DP and ON-DR mice. Therefore, AD-fed ON-DP mice are considered a useful animal model to reproduce atherosclerotic lesions caused by blood glucose fluctuations and may contribute to the understanding of the pathophysiology of macrovascular complications in IGT and the early stage of diabetes.

Implications for Type 2 Diabetes and Obesity in Humans

Our previous study in human islets showed that higher gene and protein expression of CD36 was observed in islets from obese donors with T2D compared to those from obese donors with NGT[14]. Indeed, exocytosis dysfunction was observed in pancreatic β-cells from obese donors with diabetes. Furthermore, functional inhibition with a CD36 antibody on a human β-cell line, EndoC-βH1 cells, increased the number of docked granules fivefold, accompanied by increased expression of exocytotic proteins, resulting in improved early-phase GSIS[14]. Therefore, we believe that CD36 could be a therapeutic target to improve impaired insulin secretion in T2D associated with obesity.

Regarding hypoleptinemia preceding obesity, a prospective cohort study of Pima Indians showed that lower plasma leptin levels at baseline were associated with greater weight gain over three years[26]. Another prospective cohort study of 150 Canadian university students also found that lower plasma leptin levels at baseline predicted weight gain over two years[27]. In addition, individuals with heterozygous mutations (ΔG133) in the leptin gene have lower plasma leptin levels compared to those without the mutation, resulting in a high frequency (76%) of obesity (BMI >30 kg/m^2)[28]. In contrast to these epidemiologic studies, little basic research has been conducted on the basis of hypoleptinemia due to the lack of animal models that replicate this phenomenon. Hence, ON mice are expected to be a useful animal model not only for understanding the clinical relevance of hypoleptinemia in the development of obesity, but also for establishing a new prevention strategy for obesity.

Metformin, a drug for the treatment of T2D, has been shown to significantly reduce the risk of cardiovascular complications in patients with T2D. We recently reported that metformin treatment reduced atherosclerotic lesion size in the aortic sinus to 59% of that observed in AD-fed ON-DP mice[29]. This confirms the inhibitory effect of metformin on atherosclerotic lesion formation. These results suggest that ON mice are also useful for testing the anti-atherosclerotic effects of diabetes drugs.

Conclusion

The ON mouse strains are invaluable tools for diabetes and obesity research because of their distinct and well-characterized metabolic phenotypes, their relevance to T2D and obesity in humans, and their potential to reveal the "gene-environment interactions" underlying these diseases. Researchers can use them to investigate disease mechanisms, study complications, and develop and test new therapeutic interventions for T2D and obesity. Thus, ON mice will not only serve to elucidate pathophysiology that has not been elucidated in existing animal models, but will also contribute significantly to the development of comprehensive prevention and treatment strategies, including those for the complications, of T2D and obesity.

Acknowledgements: All animal experiments were performed in accordance with ethical permits issued by the Nippon Medical School Animal Policy and Welfare Committee (Tokyo, Japan). We would like to thank Hitoshi Sugihara and Masato Iwabu (Nippon Medical School) for invaluable supervision, Akira Asai (Nippon Medical School) for significant contribu-

tions, and Momoyo Kawahara (Nippon Medical School) for technical assistance for ON mouse studies, and Lena Eliasson (Lund University) for invaluable supervision and significant contributions for CD36 and human islet studies. The work is financially supported by JSPS KAKENHI (22KK0281, 22K 07008, 21K05453, 19K23872, 17KK0184, 17K08780, 15K08434, 26460497, and 25860300), European Foundation for the Study of Diabetes, Japan Diabetes Society, Japan Diabetes Foundation, Japan Association for Diabetes Education and Care, Diabetes Wellness Sverige (720-2964 JDWG), Uehara Memorial Foundation, Scandinavia-Japan Sasakawa Foundation, Sumitomo Life Welfare Foundation, Ono Medical Research Foundation, Asahi Life Foundation, MSD Life Science Foundation.

Conflict of Interest: The authors declare that there is no duality of interest associated with this manuscript.

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(Received, June 2, 2024)
(Accepted, July 12, 2024)