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MICE MODELS IN METABOLIC SYNDROME RESEARCH - A REVIEW

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Abstract

Metabolic syndrome (MetS) consists in a cluster of metabolic complications, characterized by the simultaneous prevalence of at least three of the following medical conditions: central obesity, hyperglycemia, dyslipidemia and hypertension. MetS is a disorder with a complex etiology and an alarming prevalence rate, so the establishment of appropriate animal models mimicking MetS in humans is essential for understanding the pathophysiological mechanisms involved and for developing new therapeutic strategies. Although numerous animal models of MetS have been currently developed, the choice of a particular model requires a careful analysis in relation to the usefulness and suitability, in order to improve the applicability of the preclinical research to the clinical on.
The aim of this review is to summarize the main mice models, this species being the most frequently used in the study of MetS and obesity. Several approaches have been used in order to induce MetS in animal models including specific diet administration, genetic techniques, and chemically-induction. Apart from pathophysiological similarities with the human MetS, a suitable animal model should also have an increased accessibility and reliability, as well as being easy to reproduce in future research.

Key words*: metabolic syndrome, obesity, diet, animal models.*

INTRODUCTION

Obesity and metabolic syndrome are among the leading causes of worldwide morbidity and mortality, as their prevalence is rapidly increasing, reaching epidemic proportions especially in developing countries. In 2022, almost 2.5 billion adults were overweight, and over 890 million of these were obese (WHO, 2022). MetS includes a number of metabolic obesity-associated disorders such as hypertension, dyslipidemia, insulin resistance, nonalcoholic fatty liver and kidney dysfunction (Panchal & Brown, 2011). Human patients with MetS usually show a specific profile that includes systemic inflammation, oxidative stress and a pro-thrombotic state, linked to an increased risk of cardiovascular pathologies, type 2 diabetes, osteoporosis, cancer development and premature mortality (Della Vedova et al., 2016; Kulkarni et al., 2014; Mostafa et al., 2023).
MetS has a complex etiology due to the interaction of both environmental and genetic factors, being the consequence of a metabolic imbalance between the caloric intake, the basal metabolism, and the total energy expenditure, which leads to excessive or abnormal deposits of adipose tissue (Lang et al., 2019; Kaur, 2014).
The choice of appropriate animal models mimicking MetS in humans is highly important for the biomedical research, in order to understand not only the pathophysiological mechanisms of obesity but also the metabolic associated disorders (Wong et al., 2016). Animal models allow researchers to create a controlled environment and provide the opportunity to examine correlations among different metabolic pathways, in particular the cellular and molecular mechanisms involved in the early stages of their development, in order to refine diagnostic criteria and be able to establish therapeutic alternatives (Chalvon-Demersay et al., 2017; Wayhart & Lawson, 2017). The major challenge for researchers is to develop an animal model showing more than two of the key features of human MetS and to understand why metabolic comorbidities sometimes occur and

sometimes don`t (Della Vedova et al., 2016; Wayhart & Lawson, 2017).

Preclinical models of MetS comprise various species of animals such as: primates (Li et al., 2015; Bremer et al., 2011; Nugent et al., 2021), pigs (Zhang & Lerman, 2016; Cluzel et al., 2022), rabbits (Lozano et al., 2019; Arias-Mutis et al., 2018), dogs (Gregory et al., 2023) and even zebra fish (Benchoula et al., 2019).

However, murine models are widely used in MetS research, being relatively easy to breed maintain, and manipulate, while having standardized phenotyping protocols, essential in mouse strains characterization. Furthermore, the available genome database provides information about genome sequences in most commonly studied inbred murine lines (Wayhart & Lawson, 2017).

The extensive use of mice in human studies, is also due to the genetic homology between the two species and to the availability of manipulating the mouse genome and developing numerous methods of obtaining transgenic, knock-out, and knock-in lines (Perlman, 2016).

This paper will focus on the primary mouse models used in MetS research, though no murine model can exactly reproduce all aspects of human MetS. Therefore, the main criteria represents whether a certain model comes closest to fulfilling the key features of human MetS, especially obesity, type 2 diabetes, hypertension, and liver dysfunction, and to establish their suitability to evaluate potential treatments (Panchal & Brown, 2011). Herein we present the most important genetic models, dietary manipulated and chemically-induced murine models, often used in the study of MetS. This review has some limitations, as it does not refer to the surgical-induced models of metabolic syndrome in mice.

Genetic models of obesity and insulin resistance

Leptin-deficient mice (Lep$^{ob/ob}$ mice)

The ob/ob mouse is a monogenic model, most used in the study of the metabolic syndrome, mainly type 2 diabetes. The Lep$^{ob/ob}$ mouse has the origin in a spontaneous mutation at the Jackson Laboratory and has been known since the 1950s, but it wasn't used until 1994, when the mutated gene was well characterized. This mutation of the leptin gene results in the total lack of leptin production (Fuchs et al., 2018; Lutz & Woods, 2012).

Leptin is blood circulating hormone derived from the adipose tissue and encoded by the obese (*ob*) mouse gene. Its primary role is to regulate long-term energy balance, being involved in food intake, appetite control, and body mass. Leptin also has reproductive and neuroendocrine functions and mediates fetal growth, proinflammatory immune responses, angiogenesis and lipolysis (Obradovic et al., 2021; Dornbush & Aeddula, 2023).

In Lep$^{ob/ob}$ mice, hyperphagia and obesity occur due to the increased activity of neuropeptide Y neurons, which normally bind to leptin and regulate metabolic homeostasis and satiety (Wayhart & Lawson, 2017).

Currently, Lep$^{ob/ob}$ mice develop hyperphagia, hyperinsulinemia, hyperglycemia, reduced energy consumption and increased body mass, associated to elevated plasma cholesterol levels, mainly affecting high-density lipoprotein cholesterol, which doesn`t promote atherosclerosis (Panchal & Brown, 2011; Kennedy et al., 2010; Bracke et al., 2019; Plummer & Hasty, 2008).

In Lep$^{ob/ob}$ mice, obesity develops by 4 weeks of age, but the weight growth curve is still ascending at the age of 12 months. Lep$^{ob/ob}$ mice can exceed 100 grams when fed with a standard chow diet, which is four times greater than a wild-type mouse (Kennedy et al., 2010; Bracke et al., 2019). The blood glucose level usually reaches a peak after 12 weeks of age and eventually decreases and normalizes (Platt et al., 2016).

This mouse model shows hepatic steatosis and liver inflammation from an early age (Fang et al., 2022), and later the cardiac function is altered, developing left ventricular hypertrophy associated with fibrosis (Ren & Ma, 2008; Dobrzyn et al., 2010). However, unlike humans with metabolic syndrome, Lep$^{ob/ob}$ mice, did not show increased heart rate or abnormal blood pressure (Osório, 2014).

Due to leptin-deficiency, the hypothalamic-pituitary-adrenal (HPA) axis activity is increased in Lep$^{ob/ob}$ mice, leading to adrenal hyperplasia with elevated cortisol levels (Malendowicz et al., 2007; Sainsbury et al., 2002).

Physical appearance of a $Lep^{ob/ob}$ mouse compared to a wild-type mouse (Bracke et al., 2019).

Leptin receptor-deficient mice ($LepR^{db/db}$ mice)

The $LepR^{db/db}$ mouse model is frequently used to study type 2 diabetes and insulin resistance. $LepR^{db/db}$ mice have a mutation in the leptin receptor gene present on chromosome 4, leading to hyperglycemia, hyperinsulinemia and dyslipidemia (Chen et al., 1996, Kennedy et al., 2010).

Compared to $Lep^{ob/ob}$ mice, which develop extreme obesity, $LepR^{db/db}$ mice are more diabetic, showing an impaired glucose tolerance following oral glucose intake. (Suriano et al.,2021, Giesbertz et al., 2015).

In $LepR^{db/db}$ mice, the adipose tissue distribution is mainly subcutaneous, while $Lep^{ob/ob}$ mice develop epididymal fat and hepatic steatosis (Suriano et al., 2021). $LepR^{db/db}$ mice showed vascular endothelial dysfunction at an early age, although blood pressure was normal (Panchal & Brown, 2011). The main difference between the two monogenic models is that $LepR^{db/db}$ mice have increased circulating leptin levels, proportional to the adiposity degree, while $Lep^{ob/ob}$ lack in circulating leptin (Kennedy et al., 2010).

Melanocortin receptor deficient mice (MC4R/MC3R-KO mice)

The mechanisms by which changes in central nervous system signaling affects weight balance and homeostatic networks is related to the central melanocortin system, melanocortin receptors 3 and 4 being the most studied (Nogueiras et al., 2007; Song et al., 2008; Cone, 2005).

Melanocortin 4 receptor (MC4R) is a G protein coupled receptor, highly expressed in the hypothalamic nuclei, that plays an important role in food intake and energy expenditure. As a result, MC4R mutation leads to severe obesity, associated with hyperphagia, hyperglycemia, dyslipidemia, hyperinsulinemia and, cardiovascular disfunction (Nogueiras et al., 2007; Martinelli et al., 2011; Kennedy et al., 2010).

MC4R-KO mice fed with a high-fat diet exhibit accelerated body weight gain, dyslipidemia and hepatic steatosis, similar to human non-alcoholic steatohepatitis (Adan et al., 2006; Itoh et al., 2011; Collet et al., 2017). Despite the excessive lipid accumulation, MC4R deficient mice are rather hypotensive than hypertensive (Greenfield et al., 2009; Tallam et al., 2005).

Unlike MC4R-KO animals, Melanocortin 3 receptor deficient mice (MC3R-KO) develop visceral adiposity, but remain resistant to many of the negative features of obesity, such as insulin resistance, hyperglycemia and hepatic steatosis, even when fed a high-fat diet (Kennedy et al., 2010; Ellacott et al., 2008). The explication seems to be that expression of MC3R is mostly restricted to certain hypothalamic nuclei, where this receptor is mainly involved in central energy homeostasis, and less in food intake, compared to MC4R (Begriche et al., 2013).

Genetic models of hyperlipidemia

Low-density lipoprotein receptor- deficient mice ($LDLR^{-/-}$ mice)

$LDLR^{-/-}$ mice serve as models for studying familial hypercholesterolemia. These mice have a mutation in the low-density lipoprotein receptor gene, therefore they exhibit a moderate-increased blood cholesterol level, ~250 mg/dl on a normal chow diet (Kennedy et al., 2010).

When fed with a high-fat diet, the risk of developing atherosclerotic lesions is increased and mice show hepatic inflammation and steatosis, due to increased sensitivity for Ox-LDL uptake (Bentzon et al., 2010; Sanan et al., 1998; Bieghs et al., 2012).

Apolipoprotein E- deficient mice ($ApoE^{-/-}$ mice)

$ApoE^{-/-}$ mice are widely used as metabolic syndrome models, particularly for cardiovascular pathologies, because of the severe hypercholesterolemia and spontaneous atherosclerotic lesions.

Apolipoprotein E (ApoE) is a glycoprotein synthesized mainly in the liver, intestine, and artery wall and plays a central role in lipoprotein metabolism, being the principal ligand for low-density lipoprotein (LDL) receptor. It is involved in regulating the clearance of lipoproteins and maintaining normal plasma lipid levels (Getz & Reardo, 2009; Khalil et al., 2021).

ApoE deficiency results in severe hyperlipidemia, with an increased VLDL level, low HDL level and atherosclerotic lesions on an

early age (Meir, 2004; Kennedy et al., 2010; Nakashima et al., 1994). In ApoE$^{-/-}$ mice, atherosclerosis develops due to an impaired triglyceride uptake in the liver and the adipose tissue with the accumulation of VLDL and chylomicron residue in the plasma and foam cell accumulation in the artery wall (Pendse et al., 2008).

Compared to Lep$^{ob/ob}$ and LepR$^{db/db}$ mice, ApoE $^{-/-}$ mice are not obese and do not develop insulin resistance and hyperglycemia, even on a high-fat diet (Lo Sasso et al., 2016; Hofmann et al., 2008; Zhang et al., 2023). It seems that ApoE deficiency prevents the obesity and weight gain in mice by restraining adipose tissue expansion and improves glucose tolerance and insulin sensitivity (Zhang et al., 2023).

ApoE$^{-/-}$ mice exhibit hypertension, tachycardia and endothelial dysfunction mainly due to the atherosclerotic lesions (Vasquez et al., 2012).

Genetic models of obesity with hyperlipidemia

In order to develop a mouse model that more accurately reflects the features of human MetS, researchers crossed the Lep$^{ob/ob}$ and LepR$^{db/db}$ mice, with LDLR$^{-/-}$ and ApoE$^{-/-}$ backgrounds, resulting double knockout animals.

Lep$^{ob/ob}$/LDLR$^{-/-}$ and LepR$^{db/db}$ /LDLR$^{-/-}$ mice develop extreme obesity, with hypercholesterolemia characterized by increased VLDL and LDL. Atherosclerotic lesions develop spontaneously therefore this model is extremely useful for the study of cardiovascular pathologies (Kennedy et al., 2010, Lloyd et al., 2008). Double knockout mice showed important atherosclerotic lesions throughout the aorta by the age of 6 months (Hasty et al., 2001).

Meanwhile, Lep$^{ob/ob}$/ApoE$^{-/-}$ and LepR$^{db/db/}$ApoE$^{-/-}$ mice show features more specific to type 2 diabetes associated to a hyperlipidemic profile (Wu et al., 2005).

Triple knockout mice

These model from results from crossing and Lep$^{ob/ob}$/ApoE$^{-/-}$ and Lep$^{ob/ob}$/LDLR$^{-/-}$ mice with Apolipoprotein B100 background. Apolipoprotein B (ApoB) is the main component of LDL and plays a major role in regulating lipid metabolism by carrying lipoprotein molecules into the circulation: chylomicrons, LDL, VLDL, intermediate-density lipoprotein (IDL), and lipoprotein (a) (Devaraj et al., 2023). Triple knockout mice are severely obese with insulin resistance, hyperlipidemia, and hypertension, allowing researchers to study multiple pathologies that occur together in MetS (Kennedy et al., 2010; Lloyd et al., 2008).

Genetic models of metabolic syndrome without obesity

Adiponectin-deficient mice (Adipo$^{-/-}$ mice)

Adiponectin is an adipokine hormone secreted by the adipose tissue, with a key role in regulating glucose and lipid metabolism. Adiponectin is known to have anti-inflammatory, insulin-sensitizing, anti-obesity, anti-atherogenic, and antioxidant effects (Zhao & Liu, 2014; Khoramipour et al., 2021). Adiponectin also protects the liver through its anti-fibrosis and anti-inflammatory role (Gamberi et al., 2018).

As a result of the adiponectin deficiency, Adipo$^{-/-}$ mice develop obesity, hyperlipidemia, insulin-resistance, glucose tolerance and increased serum levels of hepatic markers (Asano et al., 2009; Nawrocki et al., 2006). When fed with a high fat diet, Adipo$^{-/-}$ mice show an increased systolic blood pressure with endothelial dysfunction (Ouchi et al., 2003).

Transgenic aP2 SREBP- 1c mice

This transgenic mouse model overexpresses nSREBP-1c gene (sterol regulatory element-binding protein-1c), which leads to features of congenital generalized lipodystrophy, a human autosomal recessive disorder (Shimomura et al., 1998). Although obesity and lipodystrophy differ in the way of the adipose tissue distribution, glucose and lipid metabolism resemble in both pathologies (Nakayama et al., 2007). These mice exhibit severe insulin resistance with hyperinsulinemia and hyperglycemia, and important liver steatosis. Animals have a reduced body weight, elevated plasma triglyceride and total cholesterol, and minimal serum levels of leptin and adiponectin (Shimomura et al., 1998). An important feature of transgenic aP2 SREBP- 1c mouse model is that no special diet is required for studying MetS mechanisms.

Diet-Induced Metabolic Syndrome

Diet plays an important role in the development of MetS in humans, therefore diet-induced animal models of obesity and MetS show a great interest. Researchers often use purified diets to study metabolic disorders, being more similar to the mechanisms found in human MetS, compared to genetic animal models (De Moura et al., 2023). Purified diets consist in purified ingredients, which essentially contains one main nutrient and minimal non-nutrient substances. In addition, purified diets have very little variability from batch to batch, compared to chow diets, and so help to minimize data variability and allow researcher to select and use individual nutrients to their purpose (Pellizzon & Ricci, 2020).

High-fat Diet

The most used diets for inducing mouse MetS models are high-fat diet (HFD), high-carbohydrate diet (HCD) and the respective combinations of the last two, collectively termed "Western diets" (Preguiça et al., 2020).

The high-fat diet-induced obesity in mice is essential for understanding the connections between the hyperlipidemic diet in humans and the development of MetS (Wang & Liao, 2012). A normal rodent diet contains about 10% fat, while in a HFD lipids range from 41 to 60%, due to the addition of purified lard, butter or pure cholesterol as ingredients. Due to the high caloric intake, the satietogenic potential of the diet is increased which will reduce food intake but still induce obesity (De Moura et al., 2021).

Although there are several mouse strains susceptible to develop diet-induced obesity, the C57BL/6J inbred mouse strain mouse is the most commonly used due to the similarities with human MetS (Martins et al., 2022; Kennedy et al., 2010).

Long-term high-fat diet intake in mice causes peripheral insulin resistance with moderate hyperglycemia followed by insufficient β-cell compensation, resulting in hyperinsulinemia, together with increased expression of oxidative stress and inflammation markers (Mosser et al., 2015). Blood tests show moderate-increased levels of total cholesterol, LDL and triglycerides, and reduced serum levels of HDL. Animals are susceptible to non-alcoholic fatty liver disease and endothelium damage, while hypertension is usually reported (Yang et al., 2014; Wang & Liao, 2012; Preguiça et al., 2020).

High-Carbohydrate Diet

Even though a high-fat/high-carbohydrate diet is the main cause for the development of obesity and metabolic syndrome in both humans and animals, evidence show that a high-carbohydrate/low-fat diet also represents an important risk factor in MetS (Zhang et al., 2023). An increased intake of intense refined carbohydrates, such as starch, disaccharide sucrose (consisting in α-glucose and β-fructose) and high fructose corn syrup) is associated to weight gain, insulin resistance, hyperglycemia, and hyperlipidemia (Chung & Lim, 2019). Increased plasma levels of triglycerides and cholesterol are the consequence of the fructose accumulation in the liver that supports lipogenesis. However, compared to the high-fat diet intake, in this case the weight gain is a slower process and might be better counterbalanced by corresponding energy expenditure (Basciano et al., 2005).

Costa et al. (2023) showed that an eight weeks high-carbohydrate diet in BALB/c mice led to mild obesity characterized by important visceral adiposity in the mesenteric, epididymal, and retroperitoneal, tissues, with increased serum levels of triglycerides, total cholesterol, leptin, and glucose. Zhang et al. (2023) concluded that high-carbohydrate diet led to a more severe cholesterol accumulation in the liver compared to a high-fat diet in C57BL/6 male mice. Also, results showed elevated fasting glucose levels (>300 mg/dl), increased lipid blood profile and mildly increased liver transaminase levels in mice fed with a hypercaloric diet, enriched with fructose, for a 60 days period (Ioniță et al., 2022).

High-fat/ High-Carbohydrate Diet

Diets containing high saturated fats and high carbohydrates most resemble the western diet that affects humans nowadays, leading to a high risk of obesity and MetS. Several studies have shown that the interaction between high-fat and high-sugar diets in rodent represents an important triggering factor in obesity (Morales et al., 2022; Rasool et al., 2018; Liu et al., 2018; Lang et al., 2019). Mice fed with a high-fat/high-

fructose diet for a 12 weeks period showed important weight gain, with visceral fat deposition, dyslipidemia, hyperinsulinemia, impaired glucose tolerance, hypertension, and hyperuricemia (Zhuhua et al., 2015).

A high-fat/high-carbohydrate diet given for 8 to 16 weeks in C57BL/6J mice led to an important weight gain with visceral adipose tissue, increased plasma levels of triglyceride and free fatty acids, associated with liver steatosis, fibrosis, and insulin resistance (Liu et al., 2018). Jarukamjorn et al. (2016) reported that a HF/HC diet induced the progression of nonalcoholic fatty liver disease in mice. A similar diet in mice (45% kcal fat, 15% kcal fructose) led to an inflammatory response, antioxidant imbalance, and oxidative stress with liver (Bayliak et al., 2022).

This model is extremely useful in MetS research due to the similarities with the human diet (referred as "cafeteria diet"), strongly responsible for inducing several obesity comorbidities.

Chemically Induced Models of diabetes and obesity

Streptozotocin (STZ) is an alkylating agent, initially known for its antineoplastic properties, which is selectively toxic to the beta cells of the pancreatic islets in mammals. Experimentally, STZ is widely used in research to induce type 1 and 2 diabetes mellitus (Furman, 2021). STZ damages pancreatic β cells, resulting in hypoinsulinemia and hyperglycemia. STZ can induce hyperglycemia and hypoinsulinemia by two mechanisms, depending on the dosage. In a single high dose, STZ damages pancreatic β cells because of the alkylating cytotoxic nitrosourea compounds.

When given in multiple, low doses, STZ induces the release of GAD (Glutamic acid decarboxylase), an autoantigen involved in in the development of autoimmune diabetes, in both human and mice. The result is a decrease in the β-cells number and Langerhans islets, pancreatic inflammation with lymphocytic infiltration, and insulitis, leading to impaired insulin production and hyperglycemia (Graham et al., 2011; Lenzen, 2008; Dufrane et al., 2006; Paik et al., 1980).

Graham et al., 2008, showed that a single STZ high dose injected intraperitoneally in mice induced diabetes in 96.5% of the cases by experimental day 5. Furman (2021) used a diabetes-inducing protocol by administering multiple, low STZ doses in CD1 and C57BL/6 mice on 5 consecutive days.

STZ side effects should also be carefully evaluated, because hepatotoxicity and kidney damage were reported, especially in high-dosage protocols (Kohl et al., 2013; Noshahr et al., 2020). However, multiple, low STZ dose animal models resemble more accurate human type 2 diabetes, being widely used for testing the effectiveness of potential antidiabetic agents.

Alloxan is an organic, pyrimidine derivative compound, widely used as a diabetogenic agent tool by causing pancreatic beta-cell destruction. Alloxan is a toxic glucose analogue which is transported into the beta pancreatic cells by GLUT2 glucose transporter (Lenzen, 2008).

Alloxan induces pancreatic islets damage by two different mechanisms: the inhibition of glucokinase with reduced insulin secretion and the induction of reactive oxygen species (ROS) formation which leads to beta cells necrosis, both pathways resulting in hyperglycemia and hypo-insulinemia (Queiroz et al., 2021).

The frequency, dosage and routes of Alloxan administration for type 2 diabetes induction in mice may vary, intraperitoneally single injection being the most accepted, with ranges between 100 to 200 mg/kg body weight (Njogu et al., 2018; Ighodaro et al., 2017; Queiroz et al., 2021).

Lower doses of Alloxan were associated with a reversibility and the auto-reversion of the blood glucose level, fact that should be carefully monitored and taken in consideration when inducing type 2 diabetes (Lenzen, 2008; Ighodaro et al., 2017). Another limitation in Alloxan use consists in a large variability regarding the mortality rate in mice, that can result from a hypoglycemic initial shock or severe kidney damage (Jain & Arya, 2011; Szkudelski, 2001).

STZ seems to be a more convenient diabetogenic agent due to a more constant level and longer duration of hyperglycemia together with a higher stability in solution before and after injection. In the same time, STZ is more selective to beta-pancreatic cells, feature that lowers the cellular toxicity and animal mortality (Manik et al., 2017; Lenzen, 2008; Ighodaro et al., 2017).

Monosodium glutamate (MSG) is a neurotoxin derived from L-glutamic acid, widely used as a flavor enhancer in a variety of food products. MSG is widely used for the experimental development of obesity and metabolic abnormalities in rodents (Zanfirescu et al., 2019).

In mice, MSG can be administered for several times, subcutaneously or intraperitoneal (2-4 mg/g of body weight) usually during the neonatal period in order to induce obesity (Martins et al., 2022). MSG toxic activity is selective for the arcuate nucleus of the hypothalamus, resulting in obesity, insulin resistance, and infertility. MSG administered in mice led to severe obesity, hyperlipidemia, hyperglycemia, and increased transaminase enzyme levels, associated to liver steatosis and fibrosis. In addition, serum cytokines levels (TNF-α and IL-6) in MSG treated animals were increased (Sasaki et al., 2011; Hernández Bautista et al., 2019). MSG administration in neonate mice allow researchers to study the connection between hypothalamus and MetS complications (Cameron et al., 1978).

CONCLUSIONS

The mouse models used to study obesity and metabolic syndrome are an extremely important tool in research, allowing the understanding of the molecular and cellular mechanisms underlying the development of MetS and metabolic obesity-associated abnormalities, but also the evaluation of new therapeutic strategies. Translating the preclinical research into humans can be a challenge, therefore, the choice of a proper animal model for the study of MetS, is compulsory. Mice models allow researchers to better monitor functional, biochemical, and histopathological changes and to have a more accurate view over this metabolic disorder.

Although numerous animal models of MetS are currently available, further research is still needed in order to better evaluate their advantages and limitations for testing potential therapies in human MetS.

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