Mini Review

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Application of Animal Models in MAFLD

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ABSTRACT

Abbreviations: MAFLD: Metabolic Dysfunction-Associated Fatty Liver Disease; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; ALM: Aberrant Lipid Metabolism; IR: Insulin Resistance; AGEs: Advanced Glycation End Product; HFD: High-Fat Diet; HCD: High-Cholesterol Diet; MCD: Methionine and Choline Deficiency; HFHF: High Fat High Fructose; CDAA: Choline-Deficient Amino Acid Diet; LDH: Lactate Dehydrogenase; LDL: Low-Density Lipoprotein

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Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD), formerly called non-alcoholic fatty liver disease (NAFLD), and its usually develop to non-alcoholic steatohepatitis (Nonalcoholic steatohepatitis, NASH). MAFLD is not a single disease entity, it belongs to the complication of metabolic syndrome, which is mainly responsible for liver damage, excluding excessive drinking and other clear interventions (such as viruses, drugs, and genetics) [1]. Different from alcoholic fatty liver disease and other toxic fatty liver disease are mainly in the peripheral lobular zone, MAFLD is a widespread diffuse hepatocytic fat change. Pathological manifestations of the liver is large and soft, under the light microscope, it can be observed that parenchyma cell fatty degeneration, nuclear displacement; mesenchymal proliferations in portal area, immune cell infiltration landscapes; liver lobular area involvement, sometimes visible central vein deviation. MAFLD is mainly divided into four types of pathological changes, Simple steatosis Lobular inflammation, Ballooning and Fibrosis, Ballooning is a important sign of NASH [2]. These pathologies are not necessarily progressive, and two lesions may coexist [3] (Figure 1).

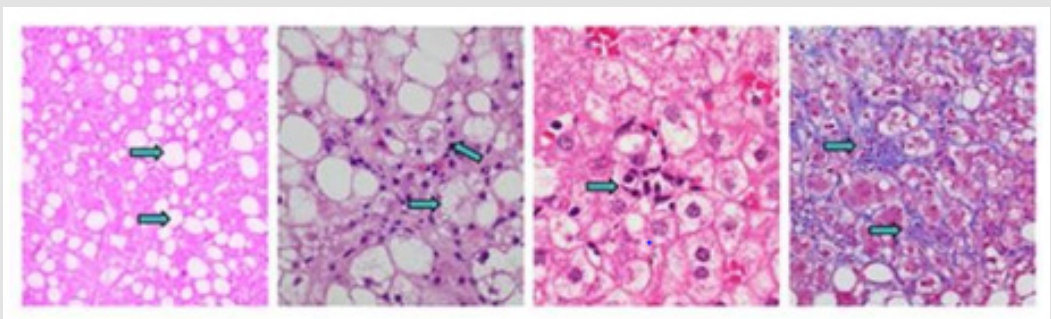

Figure 1: The pathophysiology of MAFLD [3].

Pathogenesis of MAFLD

The pathogenesis of MAFLD is not clear, and it is generally believed to be mainly related to the accumulation of Aberrant lipid metabolism (ALM), insulin resistance (IR), and advanced glycation end product (AGEs) caused by diabetes Some studys suggested that these pathological manifestations are all tissue-specific phenotypes of the same pathophysiological processes [4].

Selection of the Animal Models

In vitro models of MAFLD are HepG2 cells, LX2 cells, macrophages, primary hepatocytes, etc. Animal models mainly include genetic modification type, diet induced type, chemical drug-induced type, and Complex models. The method is mostly used by gavage, intraperitoneal injection and intravenous injection. The models selected took abnormal glucose and lipid metabolism as the main phenotype, roughly including the following several.

Genic Mutation Type

Both ob/ob mice and db/db mice are genetically altered mice associated with leptin epigenetics, and ob/ob mice are a leptin synthesis disorder due to the leptin-encoding gene mutations, and ob/ob mice generally do not have spontaneous inflammation and fibrosis. The db/db mice are leptin receptor knockout mice, homozygous to fertility, and db/db mice are divided into C57BL/6 and BKS types, with survival cycle, blood glucose, liver injury and kidney injury under different genetic backgrounds [5]. Other transgenic mice include foz/foz, ApoE-/-, Srebp-1c transgenic mice, and Nlrp3 transgenic mice [6]. In order to shorten the mold-making cycle and accelerate the progression of the disease [7], the combined diet induction is generally used as a MAFLD model [8,9]. In addition, KKAY mice are a mildly obese type 2 diabetic animal, with a significant increase in blood glucose and blood insulin levels, which can induce non-alcoholic fatty liver disease [10].

Diet-Induced Type

Diet induction includes high-fat diet (high fat diet, HFD), fat energy supply ratio 45% -70% kcal; high-cholesterol diet (HCD) 1.25% cholesterol + 0.5% cholate; high-fat and high-cholesterol diet (cholesterol content 0.5%); methionine and choline deficiency diet (MCD); high-fat and high-fructose diet (high fat high fructose, HFHF) fed for 60 days [11], choline-deficient amino acid diet (CDAA), etc.

Chemical Drug-Induced Type

Chemical drugs induce the common streptozotocin STZ that is intraperitoneally injected into SD rats [12], which often causes kidney damage in addition to causing liver damage.

Complex Model

Composite model refers to the selection of two or more ways induced metabolic correlation fatty liver model, such as diet induced and (or) combined chemical drugs applied to transgenic mice, common means are HFHF (high fat high fructose) diet, MCD (methionine choline deficiency) diet, increased intake of trans fatty acids, injection of bacterial endotoxin (LPS) cause «secondary hit», such as high fat diet combined with STZ induction[13,14]can induce MAFLD on the basis of NASH [15].

Diagnosis of MAFLD

CT and MRI on imaging examination can assess liver size, exclude other space-occupying lesions, and ultrasound transient elastography is combined with an XL probe [16]. Liver tissue biopsy is the most diagnostic significance, but because the biopsy is invasive and prone to bias due to improper collection site [17]. LDH (lactate dehydrogenase), GSH (also prototype glutathione), LDL (low-density lipoprotein), etc. In addition, some commercial kits, such as SteatoTest detection biomarkers, ActiTest, NashTest-2 and FibroTest, have been verified to be used for the diagnosis of liver fat change, fatty inflammation and fibrosis [18].

Discussion

Due to the individual differences between rodent, there are all individual cases of unsuccessful example, how to verify is a inescapable problem. In addition to biochemical indexes such as blood glucose and LDL, liver tissue biopsy is the most standard and effective verification method. In addition, because mice are very prone to hepatitis and the disease spreads quickly, it is easy to interfere with subsequent experiments (especially in inflammatory signaling pathway). Hence, pay more attention to the cleanliness of the feeding environment is necessary.

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