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Mice models of NAFLD-related HCC

Anna Chen, Anqian Lu and Jin Yang*

Translational Medicine Center, The Affiliated Hospital of Hangzhou Normal University, China

Abstract

Nonalcoholic fatty liver disease (NAFLD)-related hepatocellular carcinoma (HCC) shows growing tendency across the world, thus requiring the convenient mice models mimic the pathology and pathogenesis of human disease to accelerate the findings of this disease. Herein, we summarized the mice model of NAFLD-HCC recently developed.

An ideal mice model must meet the following factors. 1) The natural history of NAFLD progress, from NAFLD,nonalcoholic steatohepatitis (NASH), to the end-stage of the disease. 2) The pathology concordance with human NAFLD, including steatosis, ballooning, lobular inflammation, fibrosis stage and nodule formation. 3) Other factors such as modelling period, and possible pathogenesis should be taken into consideration. Here, we summarized the models in Table 1.

In total, mouse genotype, diet and chemical inducer constitute the main strategies for developing NAFLD-HCC model, therefore the combination of these factors is also a widely-used method, such as db/db mice supplemented with iron [3], and melanocortin 4 receptor-deficient mice (MC4R-KO) fed a high-fat diet [14], which aims at the specific pathogenesis of the disease. Indeed, different model combination is an option for the preclinical study due to the heterogenesis of the disease.

Table 1: Mice models of NAFLD-HCC

Model	Feature and Advantages	Disadvantages	Reference
Diet-and chemical-induced			
WD/ CCL_4	A western diet combined with low weekly dose of CCl_4 injections. Western Diet (WD): high-fat, high-fructose and high-Cholesterol. The key metabolic and histologic features of human NASH appeared within 12 weeks, and result in HCC development at 24 weeks. The model closely replicates transcriptomic hallmarks of human NASH.	Severe NASH and fibrosis are not fully induced even after long-term feeding. CCL_4 is poisonous to animals, and can induce DNA damage. Cholesterol absorption in mice is much less efficient than in humans.	[1] [2]
STAM	Mice treat with Streptozotocin (STZ) shortly after birth, then fed a high fat diet (HFD). Develop NASH, fibrosis and HCC after 8, 16 and 20 weeks of HFD, respectively.	Develop type 1 diabetes due to a lack of insulin rather than through insulin resistance (IR).	[1] [3] [4] [5]
DIAMOND	Based on an isogenic strain of C57BL/6J (B6) and 129S1/SvImJ (S129), fed a HFD with glucose-fructose in drinking water. Mice develop steatosis, IR within 16 weeks, and nodule formation by 52 weeks. A strong concordance with the human NAFLD transcriptome.	Suppression of cholesterol synthesis. A longer time to achieve the NASH standard. Genetic background of DIAMOND mice is unique, making it difficult to cross them with other gene targeted mice.	[1] [3] [4] [6] [7]
CDA /HFD	A choline-deficient, L-amino acid-defined, high-fat diet, without individual difference and loss of weight, is another amelioration of MCD (Methionine-/Choline-Deficient). NASH pathology develops at 3 weeks, and continue to develop HCC from 36 weeks until 60 weeks without carcinogenesis in any other organ. Histological changes were similar to human NASH, also this progression would not affect adiposity or insulin sensitivity.	The low penetrance of HCC induction. Lack of information related factors that distinguish the mice that evolve to HCC from the tumor-free mice.	[4] [8]

Correspondence to: Jin Yang, Translational Medicine Center, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang, 310015, China, E-mail: hz_zhiy@163.com

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FFC	The high fat, fructose and cholesterol diet, include features of the metabolic syndrome and efficiently causes hepatic steatosis, steatohepatitis and fibrosis.	The mice does not continue to evolve advanced fibrosis or HCC.	[1] [3]
ALIOS	Mice fed a high-fat/fructose diet with sedentary lifestyle, produces features of early human NASH at 6 months. The genes were increased in hepatic expression of lipid metabolism and insulin signaling.	Differences between mice and human histopathology were observed in the pattern and distribution of steatosis, fibrosis and cell proliferation. HCC develop only after 12 months of feeding.	[9]
HFCD /DEN	a high-fat, choline-deficient (HFCD) diet with injection of diethylnitrosamine (DEN), the time to HCC development is 20 weeks.	The HCC initiation is mainly dependent on DEN (a kind of chemcial carcinogens).	[5]
Genetic manipulations			
MUP-uPA	Based on feeding HFD to MUP-uPA transgenic mice. The mice develop NASH with up to 85% of them progressing to HCC. Making a distinction between the mice that develop tumors and those that do not through monitoring and following the mice at the start of NASH, which enables biomarker discovery and discrimination of molecular drivers of HCC development.	The development of HCC is slow. The mutational landscape varies from mice to mice, this heterogeneity make the drug progression more complicate.	[4]
PTEN knock-out	PTEN is a tumor suppressor gene, which spontaneously progress to steatohepatitis, with histologic features of human NASH.	Insulin hypersensitivity and lessened fat are contrary to the human NASH. Compared to males, the liver lesion in mice were weaken in females, were similar to human disease, thus sex difference should be considered.	[5] [10] [11] [12]
ob/ob db/db	The Leptin-deficien mice. ob/ob mice are diabetic owing to the deficiency of leptin gene and genetically obese. db/db mice have a defective leptin receptor gene. That exhibits human matabolic syndrome.	No matter in the obese humans or NASH patients, it is not prevalent to congenital leptin deficiency or leptin resistance caused by gene mutations. Both ob/ob and db/db mice need extra stimulator to make NASH develop HCC, but even though treating with the carcinogen diethylnitrosamine , which is still more possible to induce HCC directly, not go through NASH.	[3] [5] [11] [13]
foz/ foz	The obese mice, which carry a mutated Alms1 gene and may play a vital role in appetite regulation. Develop hepatic steatosis, obesity, diabetes, and IR, show significant upregulation of cholesterol levels.	The severity of NASH is dependent on mice strain.	[3] [12] [13]

References

1. Castro RE, Diehl AM (2018) Towards a definite mouse model of NAFLD. *J Hepatol* 69: 272-274. [Crossref]
2. Tsuchida T, Lee YA, Fujiwara N, Ybanez M, Allen B, et al. (2018) A simple diet- and chemical-induced murine NASH model with rapid progression of steatohepatitis, fibrosis and liver cancer. *J Hepatol* 69: 385-395. [Crossref]
3. Santhekadur PK, Kumar DP, Sanyal AJ (2018) Preclinical models of non-alcoholic fatty liver disease. *J Hepatol* 68: 230-237. [Crossref]
4. Febbraio MA, Reibe S, Shalapour S, Ooi GJ, Watt MJ, et al. (2019) Preclinical Models for Studying NASH-Driven HCC: How Useful Are They? *Cell Metab* 29: 18-26. [Crossref]
5. Kishida N, Matsuda S, Itano O, Shinoda M, Kitago M, et al. (2016) Development of a novel mouse model of hepatocellular carcinoma with nonalcoholic steatohepatitis using a high-fat, choline-deficient diet and intraperitoneal injection of diethylnitrosamine. *BMC Gastroenterol* 16: 61. [Crossref]
6. Oseini AM, Cole BK, Issa D, Feaver RE, Sanyal AJ (2018) Translating scientific discovery: the need for preclinical models of nonalcoholic steatohepatitis. *Hepatol Int* 12: 6-16. [Crossref]
7. Asgharpour A, Cazanave SC, Pacana T, Seneshaw M, Vincent R, et al. (2016) A diet-induced animal model of non-alcoholic fatty liver disease and hepatocellular cancer. *J Hepatol* 65: 579-588. [Crossref]
8. Ikawa-Yoshida A, Matsuo S, Kato A, Ohmori Y, Higashida A, et al. (2017) Hepatocellular carcinoma in a mouse model fed a choline-deficient, L-amino acid-defined, high-fat diet. *Int J Exp Pathol* 98: 221-233. [Crossref]
9. Dowman JK, Hopkins LJ, Reynolds GM, Nikolaou N, Armstrong MJ, et al. (2014) Development of hepatocellular carcinoma in a murine model of nonalcoholic steatohepatitis induced by use of a high-fat/fructose diet and sedentary lifestyle. *Am J Pathol* 184: 1550-1561 [Crossref]
10. Anezaki Y, Ohshima S, Ishii H, Kinoshita N, Dohmen T, et al. (2009) Sex difference in the liver of hepatocyte-specific Pten-deficient mice: A model of nonalcoholic steatohepatitis. *Hepatol Res* 39: 609-618. [Crossref]
11. Ibrahim SH, Hirsova P, Malhi H, Gores GJ (2016) Animal Models of Nonalcoholic Steatohepatitis: Eat, Delete, and Inflame. *Dig Dis Sci* 61: 1325-1336. [Crossref]
12. Lau JK, Zhang X, Yu J (2017) Animal models of non-alcoholic fatty liver disease: current perspectives and recent advances. *J Pathol* 241: 36-44. [Crossref]
13. Jiang M, Wu N, Chen X, Wang W, Chu Y, et al. (2019) Pathogenesis of and major animal models used for nonalcoholic fatty liver disease. *J Int Med Res* 47: 1453-1466. [Crossref]
14. Itoh M, Suganami T, Nakagawa N, Tanaka M, Yamamoto Y, et al. (2011) Melanocortin 4 receptor-deficient mice as a novel mouse model of nonalcoholic steatohepatitis. *Am J Pathol* 179: 2454-2463. [Crossref]