Mice models of NAFLD-related HCC

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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

<table>
<thead>
<tr>
<th>Model</th>
<th>Feature and Advantages</th>
<th>Disadvantages</th>
<th>Reference</th>
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<tr>
<td>WD/ CCL4</td>
<td>A western diet combined with low weekly dose of CCL4 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.</td>
<td>Severe NASH and fibrosis are not fully induced even after long-term feeding. CCL4 is poisonous to animals, and can induce DNA damage. Cholesterol absorption in mice is much less efficient than in humans.</td>
<td>[1] [2]</td>
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<td>STAM</td>
<td>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.</td>
<td>Develop type 1 diabetes due to a lack of insulin rather than through insulin resistance (IR).</td>
<td>[1] [3] [4] [5]</td>
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<td>DIAMOND</td>
<td>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.</td>
<td>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.</td>
<td>[1] [3] [4] [6] [7]</td>
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<td>CDA/HFD</td>
<td>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.</td>
<td>The low penetrance of HCC induction. Lack of information related factors that distinguish the mice that evolve to HCC from the tumor-free mice.</td>
<td>[4] [8]</td>
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<th>Genetic manipulations</th>
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<td><strong>FFC</strong></td>
<td>The high fat, fructose and cholesterol diet, include features of the metabolic syndrome and efficiently causes hepatic steatosis, steatohepatitis and fibrosis.</td>
<td>The mice does not continue to evolve advanced fibrosis or HCC.</td>
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<td><strong>ALIOS</strong></td>
<td>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.</td>
<td>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.</td>
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<td><strong>HFC/DEN</strong></td>
<td>a high-fat, choline-deficient (HFCD) diet with injection of diethylnitrosamine (DEN), the time to HCC development is 20 weeks.</td>
<td>The HCC initiation is mainly dependent on DEN (a kind of chemical carcinogens).</td>
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</table>

### References

1. Castro RE, Diehl AM (2018) Towards a definite mouse model of NAFLD. *J Hepatol* 69: 272-274. [Crossref]