Hepatic organoids: ideal models for non-alcoholic fatty liver disease drug finding and molecular mechanism research

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With the improvement of living standards and changes in dietary habits, the non-alcoholic fatty liver disease (NAFLD) has become one of the most common metabolic diseases clinically, with a global prevalence exceeding 25%. NAFLD often presents as a multisystem disease characterized by excessive deposition of triglycerides within hepatocytes, with over 5% of hepatocytes exhibiting steatosis. The clinical progression of NAFLD can mainly be divided into two stages: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL represents the early stage, primarily characterized by hepatocellular steatosis (which can be reversed with early intervention) and further progression leading to NASH. Besides hepatocellular steatosis, NASH also exhibits hepatocyte inflammation, injury, and fibrosis. Research indicates that 25% of NAFL patients may progress to NASH, and 35% to 50% of NASH patients further develop into liver cirrhosis or even liver cancer. Additionally, NAFLD is closely associated with various chronic diseases and tumors, such as obesity, hyperlipidemia, diabetes, breast cancer, and colorectal cancer. Despite the high and rising incidence of NAFLD, there are currently no clinically proven safe and effective drugs specifically targeting each stage of NAFLD.

The liver is one of the most critical metabolic organs in the human body, playing a crucial role in substance metabolism, detoxification, and other functions. Currently, standard in vitro models for drug screening and mechanistic studies of liver diseases (such as the human liver cell line LO2) mainly adopt 2D monolayer culture methods, which make it challenging to maintain the three-dimensional morphology and intercellular connections of liver cells and express fewer liver-specific metabolic enzymes, resulting in significant discrepancies from the actual situation in the liver in vivo. Standard animal models may also lead to biased experimental results due to interspecies differences; moreover, animal experiments may easily mask toxic side effects that may occur in humans. Studies have shown that only 43% of clinical drug therapeutic effects and toxicities can be accurately detected in rodent models. Therefore, it is crucial to establish a human-derived in vitro evaluation model that is more similar to the liver regarding cell composition, tissue structure, and specific functions for the discovery and mechanistic studies of NAFLD treatment drugs.

Organoids refer to aggregates of cells cultured in vitro, derived from adult stem cells or pluripotent stem cells, which undergo directed differentiation and self-assembly to form tissue-like structures resembling organs, thus maximally simulating the structure and function of tissues in vivo and allowing long-term stable passaging. Compared to traditional cell models, organoids have advantages such as high fidelity, short culture periods, and stable passaging and have been widely used in drug screening and mechanistic studies in recent years. The cell sources for liver organoids used in disease modeling mainly include stem cells, cell lines, and primary cells, especially organoids derived from induced pluripotent stem cells, which have been successfully used to study various liver and biliary diseases. Recently, Hans Clevers’ team at the Hubrecht Institute in the Netherlands reported successfully establishing a hepatic organoid model with steatosis using free fatty acids, which was used to simulate the early NAFL stage. Through this hepatic organoid model, the critical target gene PADS2 for NAFLD treatment was successfully screened, demonstrating the feasibility of liver organoids in studying lipid deposition and drug targets in the early stages of NAFLD. The human-derived hepatic organoid model with steatosis perfectly complements the shortcomings of existing in vivo and in vitro research models for NAFLD, providing new research strategies and ideal models for studying the efficacy and mechanisms of action of NAFLD drugs.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis.

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