Medical & healthcare, Drug discovery

Platform using human iPS cell-derived hepatic organoids for pharmaceutical research

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Abstract

The liver plays a central role in the metabolism, uptake, and excretion of drugs. The use of functional human hepatocytes is crucial for accurately predicting drug metabolism and toxicity in vivo. In recent years, attempts have been made to utilize human hepatocytes derived from human induced pluripotent stem cells (iPSCs) for these purposes; however, there were challenges in conducting stable and efficient drug discovery research due to low hepatic function, including drug-metabolizing capacity, and the fact that the process required approximately one month to produce the cells. In this study, we have established hepatic organoids (iHOs) from human iPSCs, enabling their proliferation and maintenance in culture. We have also developed a technology to differentiate these iHOs into iHO-Heps (two-dimensionally cultured iHOs) under simple two-dimensional culture conditions and investigated their applicability to drug metabolism and hepatotoxicity assays (Fig. 1). We demonstrated that iHO-Heps possess functions equivalent to or better than those of commonly available primary human hepatocytes (PHHs) and conventional human iPSCs-derived hepatocytes and are suitable for pharmacokinetic and hepatotoxicity assays.

Background & Results

The iHO-Heps model developed in this study has been shown to be more useful than conventional hepatocytes models used in drug discovery research and is expected to contribute to more efficient drug development, as well as accelerate research in various fields, including regenerative medicine.

Significance of the research and Future perspective

Assessing drug metabolism and toxicity using human hepatocytes is crucial for accurately predicting in vivo outcomes. However, currently available PHHs have limitations such as batch-to-batch variability and a decline in hepatic function during culture. To address these issues, hepatocytes derived from human iPSCs were developed, but they still had limitations for stable and efficient drug discovery research due to low hepatic function, including drug-metabolizing capacity, and requiring approximately one month for preparation.

Recently, organoid culture technology has enabled the long-term in vitro proliferation of differentiated cells. Several groups have reported human iPSC-derived hepatic organoids, but achieving both cell proliferation and functional maturation remained challenging.

In this study, we have established human iPSC-derived hepatic organoids (iHOs) that could be maintained for more than 10 passages and have developed a novel two-dimensional culture protocol to mature them into hepatocytes (iHO-Heps) with high hepatic function. The iHOs (Fig. 2A) proliferated approximately 100,000-fold in 3 passages (Fig. 2B), could be maintained for more than 10 passages, and expressed hepatocyte-specific marker genes at higher levels than the original human iPSC-derived hepatocytes (Fig. 2C). The iHO-Heps, matured using the two-dimensional culture protocol, exhibited a cobblestone-like morphology characteristic of hepatocytes (Fig. 2D) and possessed most major hepatic functions, including albumin and urea secretion, bile canalicular formation, and glycogen storage. They also showed drug-metabolizing enzyme activity comparable to or higher than that of PHHs (Fig. 2E), and their sensitivity to hepatotoxic drugs (troglitazone) was similar to that of PHHs (Fig. 2F).

These results demonstrate that the iHO-Heps model possesses hepatic function comparable to or even better than that of PHHs, and its versatility allows the use of established model systems in drug discovery research. Furthermore, since it can be derived from iHOs with high cell proliferation capacity, it is also suitable for large-scale drug discovery assays.

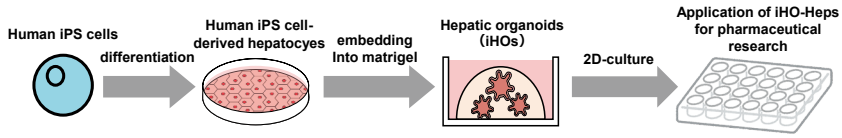

Figure 1. Overview of this research

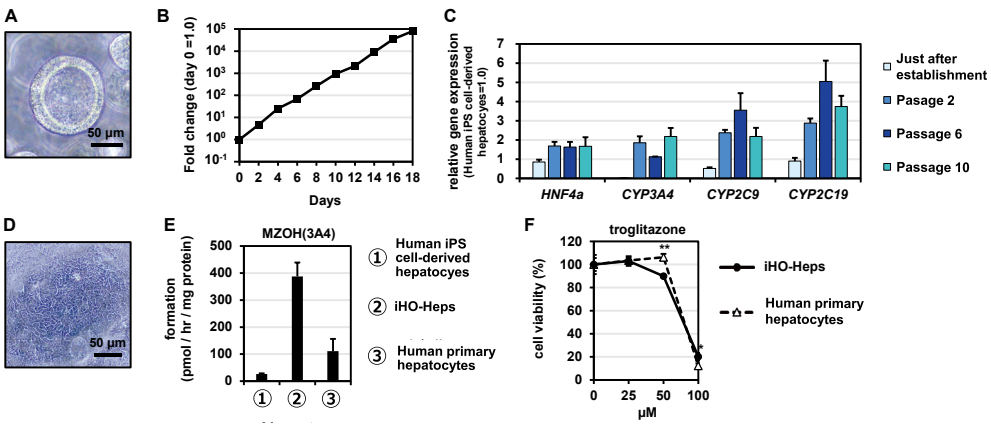

Figure 2. Results obtained in this study

Patent PCT/JP2023/006121, Japanese Patent Application No.2024-503155

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Keyword liver, iPS cells, pharmacokinetics, organoid