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Perspective

Liver Organoids as a Translational Platform for Hepatitis B Virus Pathogenesis and Therapeutic Evaluation

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ABOUT THE STUDY

Chronic Hepatitis B Virus (HBV) infection remains a pressing global health challenge, affecting over 250 million people worldwide and contributing significantly to liver cirrhosis and Hepatocellular Carcinoma (HCC). Despite existing antiviral therapies that suppress viral replication, a complete cure remains elusive due to the persistence of covalently closed circular DNA (cccDNA) in infected hepatocytes. One major barrier to progress in hepatitis B research is the lack of reliable and physiologically relevant models that faithfully recapitulate human liver function and HBV lifecycle. In this context, liver organoids have emerged as a transformative tool—offering unprecedented opportunities to study HBV pathogenesis, host-pathogen interactions, and drug testing in a controlled yet human-specific environment.

Organoids are self-organizing, Three-Dimensional (3D) cell culture systems derived from stem cells that mimic the architecture and function of actual organs. Unlike conventional Two-Dimensional (2D) hepatocyte cultures or immortalized cell lines, liver organoids more closely resemble the complexity of liver tissue, including the presence of hepatocyte-like cells, cholangiocytes and supporting stromal components. Importantly, liver organoids can be generated from pluripotent stem cells or adult liver tissue, offering both developmental and disease-specific models.

This advancement addresses the limitations of current models. Primary human hepatocytes, though physiologically relevant, rapidly lose their functionality in vitro and are difficult to obtain in sufficient quantities. Animal models, while useful, differ from humans in immune responses, viral tropism, and drug metabolism. Liver organoids bridge this gap by providing a renewable, scalable, and human-specific system that captures essential aspects of liver biology.

Modeling hepatitis B infection in organoids

Recent studies have demonstrated that liver organoids can be successfully infected with HBV, replicating key steps in the viral life cycle. These include virus entry via the NTCP receptor, formation of cccDNA, viral protein expression, and release of viral particles. This is a remarkable achievement, as few in vitro systems can stably support HBV infection. Moreover, organoids derived from HBV-infected patients can be used to study persistent infection and host responses in a personalized manner.

The utility of liver organoids extends to deciphering host-pathogen interactions. For example, they enable researchers to investigate innate immune responses, inflammatory signaling, and epigenetic changes induced by HBV. These insights are critical for developing strategies to eliminate cccDNA reservoirs and achieve functional cure.

Furthermore, liver organoids are amenable to genetic manipulation using CRISPR/Cas9 technology, allowing for targeted knockout or overexpression studies to identify host factors essential for HBV replication or immune evasion. This level of precision is difficult to achieve in animal models or traditional cell lines.

Platform for drug screening and toxicity testing

One of the most promising applications of liver organoids is in the realm of drug discovery. As HBV therapies move beyond viral suppression toward viral clearance and immunomodulation, high-throughput drug screening platforms are in demand. Liver organoids offer a physiologically relevant environment for evaluating antiviral efficacy, cccDNA inhibition, and immunotherapeutic approaches.

Unlike cancer cell lines or over-simplified hepatocyte cultures, liver organoids maintain critical liver functions such as bile acid production, cytochrome P450 enzyme activity, and proper cellular polarization. This makes them suitable not only for efficacy testing but also for predicting hepatotoxicity and drug metabolism two key parameters that often lead to clinical trial failures.

Moreover, patient-derived liver organoids represent an exciting avenue for precision medicine. Organoids from individuals with

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varying genetic backgrounds or comorbidities (e.g., nonalcoholic fatty liver disease or coinfections) can be used to predict patient-specific responses to therapy. This personalized approach may help identify subpopulations more likely to benefit from a particular drug or combination regimen.

Despite their promise, several challenges must be addressed to fully realize the potential of liver organoids in hepatitis B research and drug development. First, ensuring consistent and reproducible organoid generation across laboratories remains a technical hurdle. Variability in differentiation protocols, culture conditions, and source material can affect experimental outcomes.

Second, while organoids are structurally and functionally advanced, they still lack certain features of the in vivo liver, such as vascularization and immune cell integration. Co-culture systems with Kupffer cells or liver sinusoidal endothelial cells are being explored to enhance physiological relevance. Additionally, incorporating organoids into microfluidic platforms (organ-on-chip) may provide more dynamic models that mimic blood flow and intercellular communication.

Finally, the cost and technical complexity of organoid culture currently limit widespread adoption. Standardizing protocols, improving scalability, and developing commercial organoid platforms will be essential for broader utilization in academia and industry.

Conclusion

Liver organoids represent a powerful and innovative model system that has the potential to revolutionize hepatitis B research and drug discovery. By faithfully recapitulating key aspects of liver biology and supporting HBV infection, they provide a much-needed platform for mechanistic studies, therapeutic screening, and personalized medicine. As the field continues to evolve, integration of liver organoids with immunological, vascular, and genomic tools will likely yield even more robust models bringing us closer to a true cure for chronic hepatitis B.