Farnesoid X receptor: a potential key target for maintaining liver organoid growth

Haoran Bai[*,#], *Guanzhong Wu*[#], *Yiqing Shi*[#], *Zhipeng Han*[*]

Department of Oncology, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

***Corresponding authors:**
Haoran Bai,
baihaoran19900808@163.com;
Zhipeng Han,
hanzhipeng0311@126.com.

#Authors equally.

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Liver regeneration is a complex biological process that enables the liver to recover from injury or surgical resection. Understanding the mechanisms behind liver regeneration is pivotal for developing therapeutic strategies for liver diseases, including end-stage liver disease. Liver regeneration involves a series of intricate cellular and molecular events that are initiated following liver injury or partial hepatectomy. Hepatocytes, the primary functional cells of the liver, undergo a process of proliferation to restore liver mass. Key signalling pathways, such as the Wnt/β-catenin, transforming growth factor-β, and extracellular regulated protein kinases pathways, play critical roles in regulating hepatocyte proliferation and survival during regeneration.[1] In addition to hepatocytes, non-parenchymal cells, including Kupffer cells and hepatic stellate cells, contribute to the regenerative process by releasing cytokines and growth factors that modulate inflammation and tissue remodelling.[2] Furthermore, the gut microbiota has been implicated in liver regeneration, influencing both the immune response and metabolic processes that are essential for effective recovery.[3] Understanding these mechanisms not only enhances our knowledge of liver biology but also aids in identifying therapeutic targets for liver diseases.[4]

Recent advances in organoid technology have provided new insights into liver biology and regeneration, offering a promising platform for studying liver development, disease modelling, and regenerative medicine. The advent of organoid technology has revolutionised the study of liver diseases, offering significant advantages over traditional models. Traditional models for studying liver diseases, such as animal models and flat monolayer cultures, often fail to accurately reflect human liver biology. These models can exhibit species-specific differences in drug metabolism and disease progression, leading to challenges in translating findings to patients.

In contrast, liver organoids maintain the genetic and phenotypic characteristics of the donor's liver tissue, providing a more relevant platform for research. Liver organoids are three-dimensional structures derived from liver cells that mimic the architecture and functionality of the liver. This model allows for a more accurate representation of human liver physiology compared to two-dimensional cell cultures or animal models. Moreover, organoids can be cultured for extended periods, allowing for longitudinal studies of disease progression and treatment responses.[5] The ability to manipulate organoid cultures, including genetic modifications and drug treatments, further enhances their applicability in studying liver diseases.[6] Additionally, organoids can be used to explore the effects of the liver microenvironment on disease development, which is often overlooked in traditional models.[7] This capability underscores the importance of organoids in advancing our understanding of liver pathophysiology and improving therapeutic strategies. Recent studies have highlighted the utility of liver organoids in modelling various liver diseases, including hepatitis, fatty liver disease, and liver fibrosis, demonstrating their potential for personalised medicine and therapeutic development.[8, 9] Furthermore, organoids derived from patient-specific induced pluripotent stem cells can provide insights into individual disease pathogenesis, allowing for tailored treatment strategies.[10]

Recent advancements, such as Wnt/β-catenin pathway, transforming growth factor-β pathway and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway and The farnesoid X receptor (FXR) pathway, have highlighted the importance of various signalling pathways that govern liver regeneration, providing insights into how organoids can be utilised to enhance our understanding of liver biology and disease. The modulation of Wnt/β-catenin pathway in organoid cultures has demonstrated the potential for enhancing liver regeneration,

particularly in the context of liver diseases where regenerative capacity is compromised.[1] Manipulating transforming growth factor-β signalling has revealed its dual role in promoting both regenerative and fibrogenic responses, highlighting the need for a balanced approach in therapies targeting liver regeneration in organoid studies.[11] Organoid models have been instrumental in dissecting the role of PI3K/Akt pathway in liver regeneration, providing a platform to study the effects of various growth factors and cytokines on hepatocyte function.[12]

The FXR is a nuclear receptor that plays a crucial role in maintaining bile acid homeostasis, lipid metabolism, and glucose regulation.This pathway is integral to maintaining liver homeostasis and preventing liver injury. FXR's role in liver organoids has been highlighted in various studies, demonstrating that FXR activation can modulate key signalling pathways involved in liver regeneration and repair (**Figure 1**). For instance, the hepatic deletion of X-box binding protein 1 in FXR-null mice has been shown to lead to enhanced liver injury, indicating the protective role of FXR in liver health.[13] Furthermore, FXR agonists, such as GW4064, have been found to protect against intestinal epithelial barrier dysfunction and liver injury, underscoring the therapeutic potential of targeting the FXR pathway in liver diseases.[14] Moreover, organoid models have been utilised to study the effects of FXR on non-alcoholic fatty liver disease, demonstrating that FXR agonists can mitigate steatosis and improve liver function.[7] The development of high-throughput techniques for generating liver organoids has enabled researchers to explore the functional consequences of FXR modulation in a controlled environment, paving the way for personalised medicine approaches in liver disease management.[15] The integration of FXR pathway research with liver organoid technology holds great promise for advancing our understanding of liver biology and disease.

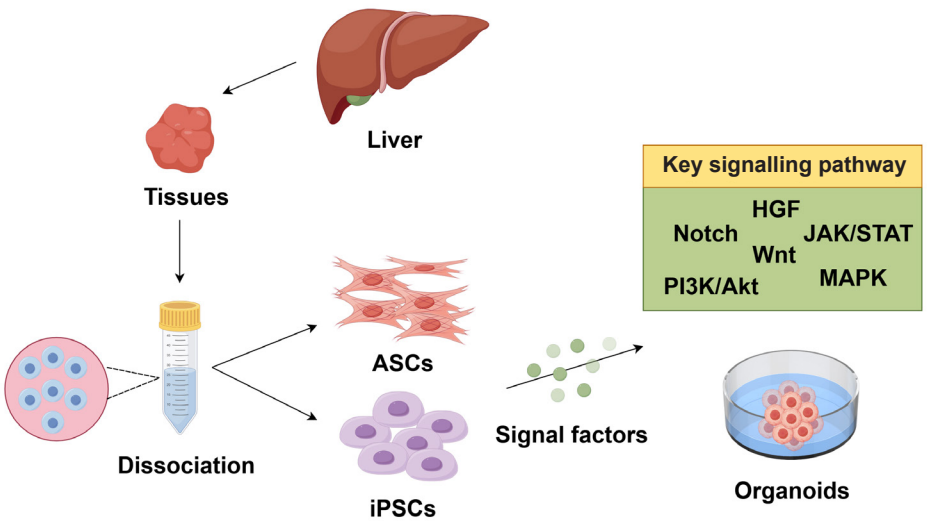

Figure 1. Key signalling pathways in hepatocype growth within organoids. ASCs: adult stem cells; iPSCs: induced pluripotent stem cells; HGF: hepatocyte growth factor; JAK/STAT: Janus kinase/signal transducers and activators of transcription; MAPK: mitogen-activated protein kinase; PI3K/Akt: phosphatidylinositol 3-kinase/protein kinase B.

In summary, the use of organoids in liver disease research presents a promising alternative to traditional models. Their ability to closely mimic human liver biology and disease states positions them as valuable tools in the quest for effective treatments and personalised medicine approaches for liver diseases. As research progresses, it is anticipated that organoids will play an increasingly central role in the study and management of liver-related disorders.

Author contributions

HB, GW and YS performed preparation, creation and specifically writing the initial draft; HB and ZH performed the revision (including prepublication stages). All authors read and approved the final manuscript.

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Conflicts of interest statement

The authors declare that they have no competing interests.

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