Correspondence

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Optimizing post-transplantation outcomes: the role of multi-omics, artificial intelligence, and animal models in addressing immunosuppression-associated hepatotoxicity

Yongguang Liu, PhD[a,*], Runtao Feng, MD[a], Jianrong Chen, MD[a], Hongyan Yan, MD[a,*], Xiaoyou Liu, PhD[b,*]

Dear Editor,

We have a profound interest in the article entitled 'Portal vein thrombosis and liver transplantation: management, matching, and outcomes: a retrospective multicenter cohort study' published by Benedetto *et al*. in the *International Journal of Surgery*. This study discovered that the evaluation of patients with portal vein thrombosis and donor selection before liver transplantation (LT) is of paramount importance in improving post-transplantation prognosis[1]. We wish to seize this opportunity to further examine the hepatotoxicity caused by anti-rejection drugs post-transplantation and its correlation with the prognosis of transplant recipients. Additionally, we aim to explore the utilization of multi-omics, artificial intelligence (AI), and animal models to optimize transplant patient management strategies.

The primary objective of the study by Benedetto *et al*. was to investigate the influence of pre-transplantation factors on short-term postoperative outcomes. However, in the current landscape of solid organ transplantation, a crucial factor impacting the long-term survival benefit of patients is the complications associated with postoperative immunosuppressive therapy. It is well-established that although immunosuppressive drugs such as tacrolimus and cyclosporin A (CsA) can effectively suppress the body's immune rejection response, they can also trigger numerous adverse reactions, including hepatotoxicity. Immunosuppression-associated hepatotoxicity (IAH) occurs following all types of solid organ transplants, but it remains relatively uncommon[2]. Consequently, IAH has emerged as one of the primary obstacles to the long-term survival of transplant recipients. Immunosuppressants currently widely used in clinical practice, such as tacrolimus and CsA, possess a degree of hepatotoxicity, which can cause liver function impairment post-transplantation and even lead to graft failure[3,4]. Therefore, an in-depth investigation of the mechanism and harm of hepatotoxicity induced by immunosuppressants is of immense importance to guide the rational clinical use of drugs and improve patient prognosis.

Currently, the mechanism of IAH has not been fully elucidated, but it is generally believed to be associated with factors such as direct hepatotoxicity, mitochondrial dysfunction, inflammatory response, and oxidative stress damage caused by immunosuppressive drugs[3]. Furthermore, the liver, as the largest metabolic organ in the human body, plays a pivotal role in the biotransformation process of immunosuppressive drugs. Immunosuppressive drugs can influence the activity of liver cytochrome P450 enzymes, leading to drug interactions, a decrease in the liver's ability to clear drugs, and an exacerbation of drug exposure and toxic reactions in the liver[3]. Simultaneously, immunosuppressive treatment can also impact lipid and glucose metabolism in liver cells, resulting in fatty liver disease, liver fibrosis, and aggravating liver damage.

With the rapid advancement of omics technology, it has become possible to systematically analyze the molecular mechanisms of IAH using multi-omics methods such as genomics, transcriptomics, proteomics, and metabolomics. Technologies such as gene chips and high-throughput sequencing can provide a comprehensive picture of gene expression profiles, thereby screening out key genes and signaling pathways closely related to IAH. Protein chips and proteomics can identify proteomic changes associated with IAH and offer new insights for elucidating the mechanism of IAH. Metabolomics can detect changes in metabolites within the body, reflect the body's metabolic response to drugs, and help discover potential IAH biomarkers. Integrating different omics data can characterize the molecular mechanism of IAH from multiple dimensions. Van den Hof *et al*.[5] used a combined strategy of transcriptomics, proteomics, and metabolomics to identify the key pathways and biomarkers of CsA in the process of hepatocytotoxicity, laying a technical foundation for the study of IAH. Madill-Thomsen *et al*. utilized RNA sequencing to identify expression profiles related to graft fibrosis, loss, and steatohepatitis in liver tissue specimens of liver transplant recipients and constructed a diagnostic model to predict graft function[6]. High-throughput screening technologies such as Liver-on-a-chip (LiOC) reconstruct the status of liver tissue at a

[a]Department of Organ Transplantation, Zhujiang Hospital, Southern Medical University and [b]Department of Organ Transplantation, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, People's Republic of China

Yongguang Liu and Runtao Feng contributed equally to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Organ Transplantation, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, People's Republic of China. Tel.: +86 133 1883 6080. E-mail: liuyg168@smu.edu.cn (Y. Liu), and Tel.: +86 133 5288 9098. E-mail: 2421177122@qq.com (H. Yan); Department of Organ Transplantation, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 51012, People's Republic of China. Tel.: +86 189 2221 7771. E-mail: 9054400@qq.com (X. Liu).

International Journal of Surgery (2024) 110:5207–5209

Received 2 April 2024; Accepted 14 April 2024

Published online 3 May 2024

http://dx.doi.org/10.1097/JS9.0000000000001521

microscopic scale. Combining this technology with patient-derived induced pluripotent stem cell-differentiated hepatocytes has the potential to enable individualized risk prediction of IAH. Moreover, the emergence of technologies such as high-content imaging and organoids provides new opportunities to explore the IAH in a microenvironment more closely resembling the human body. These studies demonstrate the immense potential of multi-omics technologies in elucidating the mechanisms of adverse reactions to immunosuppressants and discovering new diagnostic and prognostic markers.

In recent years, AI has been widely applied in the medical field, providing new avenues for precision medicine. Machine learning (ML) algorithms can automatically extract valuable features from massive omics data and build prediction models to achieve early warning of drug toxicity. Deep learning (DL) algorithms can also mine the intrinsic connections between different omics data and discover new toxicity markers and drug targets. Research demonstrates that AI plays a crucial role in the field of kidney transplantation, including predicting the survival rate of patients after transplantation and precise medication of immunosuppressants[7,8]. Algorithms based on DL can accurately predict the risk of acute rejection in liver transplant recipients by integrating clinical and omics data before and after transplantation, and can individually adjust the immunosuppressant regimen, which is expected to prevent rejection more accurately while minimizing adverse reactions[9]. We believe that combining AI with multi-omics data to build an integrated diagnosis and prognosis prediction model and further guide the precise use of immunosuppressants is an essential approach to improving the long-term quality of life of liver transplant recipients.

Animal models play a crucial role in drug toxicity assessment. Constructing an animal model can explore the dynamic changes of important genes and proteins in the process of IAH *in vivo*, verify the key molecules obtained by multi-omics and AI analysis, and deepen the understanding of the mechanism of IAH. Simultaneously, animal experiments can also evaluate the impact of different dosages and durations on hepatotoxicity, providing a basis for guiding rational clinical use of drugs. Translational medicine research combines multi-omics data from organ transplant patients and animal models, which is expected to promote the establishment of accurate prediction models for IAH and early screening of high-risk patients.

In summary, multi-omics, AI, and animal models each have their strengths in studying hepatotoxicity caused by immunosuppressants after transplantation. The three complement each other and provide new ideas and methods for comprehensively analyzing the hepatotoxicity issues related to immunosuppressive drugs after transplantation. In the future, we should strengthen the integrated analysis of multi-omics data, focus on the innovative application of AI algorithms in predicting immunosuppressive drug-related hepatotoxicity after transplantation, and attach importance to the combination of animal experiments and clinical research, striving to make greater breakthroughs in improving the safety of immunosuppressive drugs and the long-term survival of transplant recipients. This is of far-reaching significance for further enhancing the efficacy of organ transplantation and benefiting the majority of patients.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

This work was supported by Basic and Applied Basic Research Foundation of Guangdong Province (Grant No. 2022A 1515012304), and the National Natural Science Foundation of China (Grant No. 82170764).

Author contribution

Y.L., H.Y., and X.L.: conceptualization and design; Y.L., R.F., and X.L.: writing and discussion of the main content of this manuscript; Y.L., R.F., and J.C.: figures of this manuscript; Y.L., R.F., J.C., H.Y., and X.L.: revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Yongguang Liu, Hongyan Yan, and Xiaoyou Liu

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgement

Not applicable.

References

[1] Di Benedetto F, Magistri P, Di Sandro S, *et al*. Portal vein thrombosis and liver transplantation: management, matching, and outcomes: a retrospective multicenter cohort study. Int J Surg 2024;Mar 4. [Epub ahead of print]. doi:10.1097/JS9.0000000000001149. Epub ahead of print. PMID: 38445440.

[2] Pourrezagholi F, Amini H, Moradi O, *et al*. Tacrolimus-induced cholestatic hepatotoxicity after renal transplantation: a case report. J Med Case Rep 2024;18:116.

[3] Lee SK, Choi JY, Jung ES, *et al*. An immunological perspective on the mechanism of drug induced liver injury: focused on drugs for treatment of hepatocellular carcinoma and liver transplantation. Int J Mol Sci 2023;24: 5002.

[4] Faheem SA, El-Sayed NM, Moustafa YM, *et al*. Pyrvinium pamoate ameliorates cyclosporin A-induced hepatotoxicity via the modulation of Wnt/β-catenin signaling and upregulation of PPAR-γ. Int Immunopharmacol 2022;104:108538.
[5] Van den Hof WF, Van Summeren A, Lommen A, *et al*. Integrative cross-omics analysis in primary mouse hepatocytes unravels mechanisms of cyclosporin A-induced hepatotoxicity. Toxicology 2014;324: 18–26.
[6] Madill-Thomsen KS, Abouljoud M, Bhati C, *et al*. The molecular phenotypes of injury, steatohepatitis, and fibrosis in liver transplant biopsies in the INTERLIVER study. Am J Transplant 2022; 22:909–26.
[7] Basuli D, Roy S. Beyond human limits: harnessing artificial intelligence to optimize immunosuppression in kidney transplantation. J Clin Med Res 2023;15:391–8.
[8] Díez-Sanmartín C, Sarasa Cabezuelo A. Application of artificial intelligence techniques to predict survival in kidney transplantation: a review. J Clin Med 2020;9:572.
[9] Bhat M, Rabindranath M, Chara BS, *et al*. Artificial intelligence, machine learning, and deep learning in liver transplantation. J Hepatol 2023;78:1216–33.