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EDITORIAL

When Liver Slices Meet Single-cell Technology

Precision-cut tissue slices represent a versatile ex vivo model that closely mimics the physiological and cellular complexity of the in vivo environment. Among these, precision-cut liver slice (PCLS) techniques were initially developed as tools for hepatotoxicity testing but have since become widely used to investigate diverse liver pathologies, including fibrosis, cirrhosis, and alcoholic liver disease.[1–4] By preserving the complex multicellular architecture and microenvironment of the liver, PCLS enables the study of cell-to-cell and cell-to-matrix interactions, which are difficult to capture in traditional cell culture systems. This model offers several advantages over in vivo approaches, offering shorter experimental durations, the capacity for high-throughput and parallel analyses using serial sections, and a substantial reduction in animal usage. More importantly, PCLS can also be prepared from human liver specimens, thereby enhancing the translational relevance of basic research.[5] Collectively, PCLS provides a robust and ethically favorable ex vivo system for mechanistic and therapeutic studies of chronic liver diseases.

In this study,[6] the authors integrated their expertise in single-cell technology[7] with the PCLS platform to achieve high-resolution characterization of various cell populations. They demonstrated that PCLS preserves, yet exhibits dynamic changes in, the identity of intrahepatic parenchymal and nonparenchymal cells, as revealed by single-nucleus RNA sequencing (snRNA-seq). Through snRNA-seq, they delineated immune and fibrotic pathways within immune cells and fibroblasts while maintaining the liver microenvironment. Complementary assessments, including ATP production assays, immunohistochemical staining, and transcriptomic profiling, collectively confirmed that all major liver cell types retained viability, transcriptional identity, and cellular interactions for up to 5 days in culture.

As a proof-of-concept, the authors treated PCLS with interleukin-4 (IL-4), a cytokine known to promote hepatic repair and regeneration, to test the capacity of the PCLS platform to model dynamic cellular crosstalk. At the molecular level, exogenous IL-4 treatment stimulated the proliferation and differentiation of hepatocytes and cholangiocytes while suppressing the activation of mesenchymal cells. Moreover, in PCLS derived from a thioacetamide-induced liver injury model, IL-4 treatment reduced collagen deposition around portal tracts, suggesting a potential antifibrotic effect. Together, these findings establish PCLS combined with snRNA-seq as a powerful ex vivo platform for investigating hepatic cell identity, function, and intercellular communication.

Despite these advantages, PCLS has several limitations. The process of tissue slicing can induce mechanical damage and local hypoxia, resulting in hepatocellular injury at the cut surface. This damage triggers an inflammatory and fibrotic response, which complicates the interpretation of tests for antifibrotic interventions. In addition, PCLS lacks physiological perfusion and therefore cannot reproduce the unidirectional sinusoidal blood flow, bile secretion dynamics, or shear stress that shape liver function. The absence of blood circulation and lymphatic systems also restricts the recruitment of immune cells in response to tissue injury, limiting the ability of PCLS to model immune cell trafficking and systemic inflammatory responses. Moreover, the relatively short culture lifespan restricts the long-term use of PCLS for studying the progression of chronic diseases or therapeutic effects.

To address these challenges, ongoing efforts have focused on refining PCLS culture systems. Recent advances include optimizing media formulations with valproic acid supplementation,[8] developing mechanical chambers,[9] and testing elevated oxygen levels.[5] In addition, integrating immune cell co-cultures into PCLS may enable the study of immune cell recruitment, inflammation, and macrophage polarization, as demonstrated in models of lung fibrosis.[10] Combined with cutting-edge techniques such as snRNA-seq, continued optimization and standardization of PCLS methodologies, particularly those that enhance viability, immune competence, and mechanical reproducibility, will be crucial to fully establish this platform as a valuable preclinical and translational tool for mechanism studies and therapeutic development.

In summary, this study highlights the use of snRNA-seq with the PCLS technique as a promising ex vivo platform that closely recapitulates the in vivo liver environment, enabling studies on cellular changes and their interactions during specific interventions, such as IL-4 supplementation. These results suggest that PCLS can serve as a robust and translationally relevant model for investigating hepatic regeneration, immune modulation, and fibrotic responses, thereby providing valuable insights for the study of liver pathogenesis and the development of targeted therapies.

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