DATE: Day 28 Month April Year 2026

SUMMARY of

FY2025 RESEARCH RESULTS REPORT

For International Collaborative Research with IPR, The University of Osaka

Research Title		Using single-cell genomics to investigate the progression of hepatocellular carcinoma
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Summary

Hepatocellular carcinoma (HCC) is a highly heterogeneous and progressive malignancy that evolves from healthy liver tissue through intermediate disease states such as cirrhosis, ultimately leading to tumor formation, vascular invasion, and metastasis. This study leverages single-cell RNA sequencing to investigate liver cancer progression at high resolution, with the central hypothesis that HCC development occurs as a continuous transcriptional drift rather than a discrete transition between normal and malignant states. To capture the full spectrum of disease progression, publicly available scRNA-seq datasets (GSE136103 and GSE149614) were integrated, resulting in a unified dataset comprising 129,410 cells and 22,531 genes across six stages: healthy liver, cirrhotic liver, HCC-adjacent normal tissue, primary tumor, vascular invasion, and lymph node metastasis. The integrated analysis revealed distinct clustering of major liver, stromal, and immune cell populations, confirming the robustness of the preprocessing and integration pipeline. Stage-wise UMAP projections demonstrated a clear and gradual restructuring of the cellular landscape. Healthy samples exhibited tightly organized and well-defined clusters, while cirrhotic and tumor-adjacent tissues showed subtle deviations, suggesting early transcriptional changes. Primary tumor samples displayed expansion into new regions corresponding to malignant transformation, and advanced stages such as vascular invasion and metastasis exhibited increasingly dispersed and fragmented distributions, reflecting heightened transcriptional heterogeneity and loss of cellular identity. In parallel, analysis of cell type composition revealed dynamic changes across disease stages. Early stages were enriched in immune cell populations, indicating active immune surveillance. As progression occurred, there was a marked increase in hepatocyte-derived malignant cells and fibroblasts, alongside a reduction and redistribution of immune populations. This shift reflects a transition from an immune-regulated environment to a tumor- and stroma-dominated microenvironment. Notably, cirrhotic and HCC-adjacent tissues were found to be transcriptionally similar, suggesting that tumor-adjacent regions are not truly normal but exist in a pre-malignant state. Overall, the findings support a model in which HCC progression is driven by continuous transcriptional reprogramming and increasing cellular plasticity. The study provides a comprehensive single-cell atlas of liver cancer progression, offering insights into how cellular composition, organization, and identity evolve across stages. Looking forward, this framework can be extended by integrating additional omics layers such as epigenomics and proteomics to uncover regulatory mechanisms underlying disease progression. Incorporating trajectory inference methods and clinical data may further enable identification of key biomarkers and therapeutic targets.

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