New study identifies link between presence of oncofetal ecosystem and liver cancer recurrence

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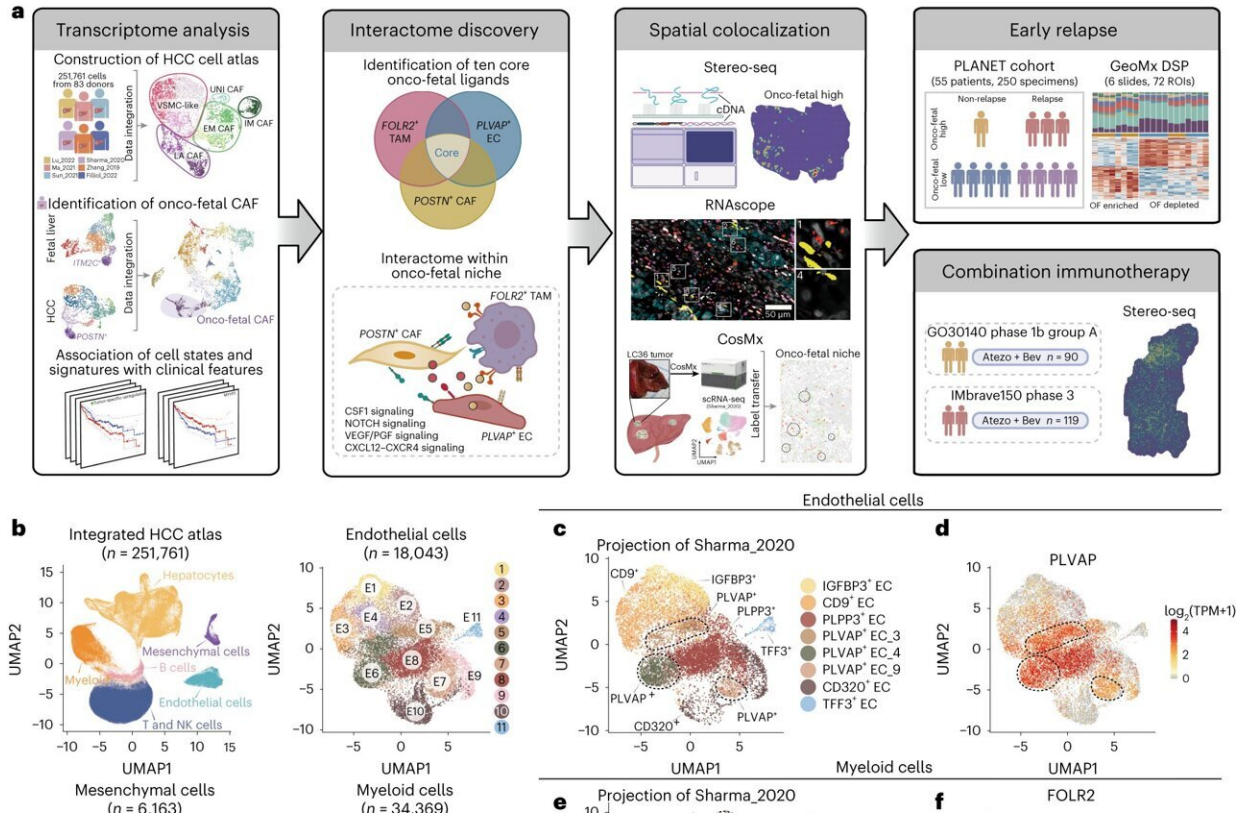

Construct a single-cell atlas of HCC. Credit: *Nature Cancer* (2024). DOI: 10.1038/s43018-023-00672-2

A team of researchers has found a causal link between the presence of

oncofetal ecosystems (re-emergence of fetal program/features driven by the tumor) in the primary liver cancer hepatocellular carcinoma (HCC) and cancer recurrence and response to immunotherapy. These findings, which pave the way for the use of oncofetal ecosystems as biomarkers to treat HCC, were published in Nature Cancer.

Liver cancer is the sixth most common cancer in the world and fourth most common cause of cancer deaths globally. In Singapore, it is the third most common cause of cancer deaths in males and fifth most common cause in females. HCC is usually diagnosed at a late stage, when prognosis is poor, highlighting a great clinical need to improve the understanding of HCC to better manage the disease.

An earlier breakthrough study, by the same team of researchers, from the National Cancer Center Singapore (NCCS), Agency for Science, Technology and Research (A*STAR), the Harry Perkins Institute of Medical Research and global research partners, found that HCC cells adopt a fetal-like environment to escape immune surveillance and grow more aggressively. This provided novel insights into the processes that drive HCC development.

In their latest work published in *Nature Cancer*, the team built on their previous discovery and focused on understanding how the changes in the oncofetal ecosystem, known as oncofetal reprogramming, impacts HCC. Oncofetal reprogramming causes the cancer cell environment in the liver to mimic certain aspects of cells in fetal development, leading to the suppression of the body's immune system.

The team compiled a single-cell atlas of 251,761 cells from over 80 donors with liver cancer and used advanced techniques, such as single-cell RNA sequencing and single-cell spatial transcriptomics, to analyze them. The team identified a cell called POSTN+ cancer-associated fibroblast to be central in this process.

Further analysis revealed that oncofetal reprogramming is implicated in EMT (epithelial to mesenchymal transition—which typically makes cancer more aggressive) and tumor cell proliferation, ultimately playing a role in early recurrence and response to immunotherapy.

"Oncofetal cells are very adaptable and behave like embryonic cells. They originate within the tissue surrounding tumors and provide a 'fertile soil' for 'malignant seeds.' This is the reason that even after a tumor has been surgically removed, these cells remain and can lead to cancer recurrence," said study co-senior author Professor Ankur Sharma, Lab Head of the Onco-Fetal Ecosystem Laboratory at the Harry Perkins Institute of Medical Research in Perth, Western Australia.

"By analyzing the microenvironment, which surrounds and nourishes the tumor, we found some patients have high levels of fetal-like cells. Their presence predicts the likelihood of recurrence."

"This translational discovery based on basic research mapping the tumor microenvironment, not only provides us with a novel biomarker but, more importantly, offers a tangible solution to better treat HCC—a ray of hope for patients and a new direction for oncology," said study co-senior Associate Professor Florent Ginhoux, Senior Principal Investigator, A*STAR's Singapore Immunology Network (SIgN).

"We can now link the discovery of fetal-like reprogramming of the tumor ecosystem with a clinical outcome in HCC patients. This is very significant, as it opens promising opportunities to group early-stage HCC patients that have higher likelihood of early recurrence and improve their care management," said study co-senior author Professor Pierce Chow, Senior Consultant Surgeon, Singapore General Hospital and NCCS and Professor, Duke-NUS Medical School.

"It also presents the possibility of therapeutically targeting the cell-based

signature in the tumor microenvironment with combined immunotherapy."

Additionally, the team plans to investigate whether fetal POSTN+ cancer-associated fibroblasts are also presented in other cancers. Further clinical application of this study would be to develop a biomarker that shows response to combined immunotherapy.

More information: Ziyi Li et al, Presence of onco-fetal neighborhoods in hepatocellular carcinoma is associated with relapse and response to immunotherapy, *Nature Cancer* (2024). DOI: 10.1038/s43018-023-00672-2

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