Heterogeneity of liver cancer cells helps explain tumor progression in patients

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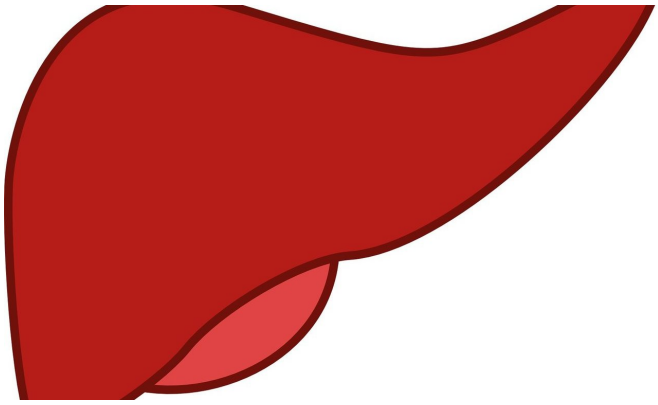

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Many liver cancer tumors contain a highly diverse set of cells, a phenomenon known as intra-tumor heterogeneity that can significantly affect the rate at which the cancer grows, Mount Sinai researchers report. The immune system's contribution to this heterogeneity can have major clinical implications.

In a study published in January in *Nature Communications*, the team reported that this heterogeneity—either within the same tumor or between different tumor regions in the same tumor nodule—appears in about 30 percent of patients with hepatocellular cancer (HCC), the most common form of liver cancer, and that some of these tumors grow rapidly by hijacking different gene networks.

"Tumors are a complex ecosystem, and we're developing for the first time a blueprint of the different ways they can evolve in patients with liver cancer by interacting with the immune system," says Augusto Villanueva, MD, Ph.D., Assistant Professor in the Liver Cancer Program at The Tisch Cancer Institute at Mount Sinai, and corresponding author of the study. "By better understanding how tumors progress, we're learning more about how they adapt to pharmacological pressures, and how they can develop mechanisms of resistance to cancer therapies. This greater awareness will hopefully lead to the identification of biomarkers that can predict which patients will be responsive to treatment."

Among the clinical implications associated with intra-tumor heterogeneity identified by the research team was the discovery that a single liver cancer biopsy could potentially mischaracterize a liver tumor.

"Some tumors are very homogeneous in terms of their genetic makeup and immune cell infiltration, while others are very heterogeneous," says Dr. Villanueva. "This means that a biopsy from the same tumor could yield different information depending on where it was taken, and could thus affect clinical decision-making for the patient. That's why our work aimed at learning how tumors evolve and the different trajectories they can take is so important to future cancer research, as well as to effectively treating the disease."

As immunotherapy continues to transform cancer research and treatment, one of the most promising areas is liver cancer, which has become the fastest-rising malignancy in the United States in terms of incidence and mortality, responsible for 33,000 new cases annually. Two phase 2 clinical trials using PD-1 immune checkpoint inhibitors, which help the body's immune system recognize and attack cancerous cells, have achieved unprecedented responses in humans, prompting the Food and Drug Administration to grant them accelerated approval status for second-line treatment of advanced hepatocellular cancer.

More recently, a phase 3 clinical trial combining a PD-1 immune checkpoint inhibitor with an antiangiogenic improved survival compared to the current first-line standard of care, sorafenib. Still,

only about 30 percent of patients with HCC are believed to respond favorably to immune checkpoint inhibition—an outcome not uncommon with immunotherapies.

"The immune system imposes significant constraints on liver cancer evolution, and by investigating the interaction of immune cells and cancer cells at the molecular level we're trying to predict or anticipate mechanisms of tumor resistance," explains Bojan Losic, Ph.D., Associate Professor of Genetics and Genomic Sciences, Cancer Immunology Program, at Icahn School of Medicine at Mount Sinai, and lead author of the study. "Our work is particularly relevant considering the remarkable success of immune checkpoint inhibitors in some heterogeneous solid tumors."

To understand the mechanisms that drive tumor progression on a patient-by-patient basis, the research team from Mount Sinai and other medical centers around the world performed an integrated molecular analysis of gene expression, immune activities, and DNA mutations from multiple regions of the same tumor nodule in 14 liver cancer patients. The study was the first to use single-cell RNA sequencing in multiple regions of the same tumor nodule, and was among the first to assess the contribution of the immune system to liver cancer evolution.

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