New method reveals insights into interplay between immune system and tumors

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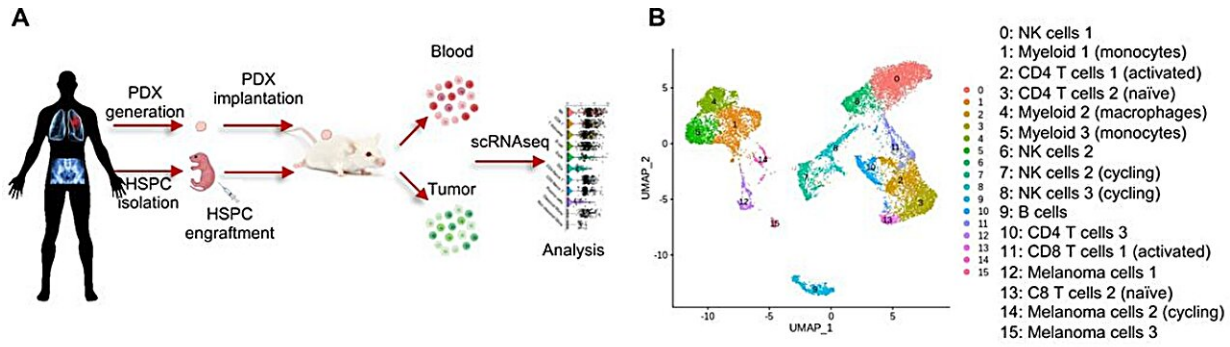

Single cell genomics reveals multiple human immune cell types in tumors and blood of autologous MISTRG6 PDX mice, including innate immune cell types present in the TME. (A) Schematic representation of scRNAseq experiments. (B) UMAP embedding displaying unsupervised clustering of 14,603 human cells from blood and melanoma PDX of autologous MISTRG6 mice. Cell types were identified by marker genes and identities are listed. Credit: *Journal for ImmunoTherapy of Cancer* (2023). DOI: 10.1136/jitc-2023-006921

How a person's immune system interacts with tumor cells influences how cancer progresses and can explain why treatment causes tumors to shrink for some patients but not others. Yale researchers have developed a new method to better understand these complex interactions, recreating patients' specific tumor microenvironments in mice for more in-depth and individualized study.

They describe the technique in the *Journal for ImmunoTherapy of Cancer*.

One of the inherent challenges of cancer research is the difficulty of untangling the complex, interactive tumor environment. A vast array of immune cells, both adaptive and innate, are at play within and around a tumor. And because immune systems vary greatly among individuals, the tumor microenvironment in each person is also different.

"Most of our preclinical studies rely on mouse models, but there are interspecies differences between human and mouse," said Dr. Michael Chiorazzi, assistant professor of internal medicine at Yale School of Medicine and lead author of the study. "So researchers have been using mice that allow transfer of human cells to study how the cells act and behave in a more physiologic environment rather than a plastic dish."

Until now, however, this approach has required a large number of human cells—which often come not from patients with cancer, but from donated stem cells—and reconstitutes a limited number of cell types.

The new method developed by Chiorazzi and his colleagues allows researchers to use a modest number of immune precursor cells, collected from patients with cancer through bone marrow samples, and more fully reconstitute that person's immune system in a mouse. They can then grow tumor tissue from that same person in the mouse as well.

"This allows us to do this in a personalized way, where we can model an individual patient's tumor and their immune system in the same mouse," said Chiorazzi, who is also a member of the Yale Cancer Center. "And it's a widely applicable technique that's almost tumor agnostic. We've been able to do this with melanoma, lung cancer, head and neck cancer, pancreatic cancer, and colon cancer."

For the study, researchers took a mouse line developed for cancer research and made one additional genetic tweak, swapping the gene that encodes for the immune molecule interleukin-6 for the human version.

"That genetic change increased the engraftability of human immune cells by a significant amount," said Chiorazzi. "And that opened the door to the rest of the work."

The method, say the researchers, serves as an improved platform for the study of how the tumor microenvironment influences cancer growth and how individual differences affect that process. Further, the approach may allow researchers to test how a patient might respond to treatment by first giving that treatment to mice with the patient's immune and tumor cells.

"How one patient's immune system responds to cancer and anti-cancer drugs is different from another based on their genes," said Chiorazzi. "This system captures that diversity, while other systems only focus on the cancer cells."

It may also be useful for drug testing.

"We're starting to use the system as a screening method for new drug combinations that could increase the effectiveness of existing treatments," Chiorazzi said.

Ultimately, the technique will allow researchers to pursue questions that have been challenging to ask with previous approaches.

"The ability to study cancer in a more immunologically, genetically, and biologically relevant way is where the power of this approach lies," said Richard Flavell, Sterling Professor of Immunobiology at Yale and senior author of the study. "It will help advance our understanding of

interpersonal differences in cancer progression and treatment response."

More information: Michael Chiorazzi et al, Autologous humanized PDX modeling for immuno-oncology recapitulates features of the human tumor microenvironment, *Journal for ImmunoTherapy of Cancer* (2023). DOI: 10.1136/jitc-2023-006921

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