Research leads to better understanding of the immune system in kidney cancer

March 11 2021

In two new studies published in *Cancer Cell*, researchers used the emerging technology of single-cell RNA sequencing to draw a clearer picture of how kidney tumors' microenvironments change in response to immunotherapy. The researchers believe that this work points to potential targets for new drug therapies. Credit: Dana-Farber Cancer Institute

In the last two decades, immunotherapy has emerged as a leading treatment for advanced renal carcinoma cancer (more commonly known as kidney cancer). This therapy is now part of the standard of care, but it doesn't work for all patients, and almost all patients, no matter how they respond initially, become more resistant to treatment over time. The immune system plays a critical role in kidney cancer disease progression and in response to therapies, and so a fundamental challenge in the field is to understand the underlying "immune circuitry" of this disease.

In two new studies published today in *Cancer Cell*, researchers from Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard used the emerging technology of single-cell RNA sequencing to draw a clearer picture of how kidney tumors' microenvironments change in response to immunotherapy. The researchers believe that this work points to potential targets for new drug therapies.

"We have a standard of care for treating kidney cancer patients, but many patients do not respond to existing therapies, and we need to discover new targets," said Eliezer Van Allen, MD, an oncologist at Dana-Farber, associate professor of medicine at Harvard Medical School, associate member at the Broad Institute, and co-senior author on one of the papers.

"These companion studies shed important new light on the biology of advanced kidney tumors and their surrounding environments. With this increased understanding, researchers will be able to identify new potential drug treatment targets and, overall, expand the number of patients who can receive effective treatment," remarked Catherine J. Wu, MD, chief of the Division of Stem Cell Transplantation and Cellular Therapies at Dana-Farber, professor of medicine at Harvard Medical School, an institute member at the Broad, and co-senior author on one of the papers.

"A patient's immune system plays a critical role in controlling both the progression of cancer and the response to immune therapies," adds Toni K. Choueiri, MD director of the Lank Center for Genitourinary Oncology at Dana-Farber, an associate member at the Broad, and the Jerome and Nancy Kohlberg Professor of Medicine at Harvard Medical School. Choueiri is co-senior author on both papers. "We don't quite know why some tumors respond and some don't. We also don't know why kidney cancers become resistant to immunotherapy. These two studies are a large team effort to give us a sharper image of what happens on not just the cellular level but down to the RNA of each of those cells."

With immunotherapy, patients are typically given an immune checkpoint blockade (ICB) (often in combination with VEGF tyrosine kinase inhibitors; TKIs). The drugs are designed to stop the immune system from stopping itself, thus allowing it to attack the tumor like any other unwanted pathogen. However, immunotherapy is only successful in about half of ccRCC patients, and almost all patients build resistance to the treatment over time.

About 76,000 Americans are diagnosed with kidney cancer in the U.S. each year, which is also responsible for more than 13,000 deaths annually, according to the American Cancer Society.

Finding new targets to disrupt an immune dysfunction circuit

In one study, researchers performed single-cell RNA and T cell receptor sequencing on 164,722 individual cells from tumor and adjacent non-tumor tissue. These samples came from 13 patients with clear cell renal cell carcinoma (ccRCC), which make up 80 percent of kidney cancer cases, at different stages of disease: early, locally advanced and

advanced/metastatic.

In most solid tumors, the presence of a specific type of immune cell, the CD8+ T cell is a good thing. Their presence shows the immune system is working. However, researchers found that in advanced stage disease these CD8+ T cells were "exhausted," and not able to carry out their usual function.

They also discovered more anti-inflammatory or "M2-like" macrophages, a type of white blood cell that suppresses the immune system, in advanced stage disease. CD8+ T cells and macrophages were playing off each other and caught in an "immune dysfunction circuit," said co-lead author David A. Braun, MD, Ph.D., an oncologist at Dana-Farber and instructor of medicine at Harvard Medical School. In advanced disease samples, macrophages produce molecules that support CD8+ T cell exhaustion, at the same time those CD8+ T cells make molecules that supported the life of pro-tumor macrophages.

These findings are important because they "open up a whole new landscape of potential treatment targets," said Braun. "We already target some of the immune system pathways in kidney cancer, but our work uncovered many other immune inhibitory pathways supporting cell dysfunction. As we move forward, we can look at all of these interactions and identify new opportunities to disrupt the circuit, with the goal of restoring the immune system's anti-tumor effect and ultimately improving outcomes for patients with kidney cancer."

Choueiri and Wu are co-senior authors on the study, "Progressive immune dysfunction with advancing disease stage in renal cell carcinomas."

Identifying treatments beyond the PD-1/PD-L1 axis

The other study published today looks at tumor and immune reprogramming during immunotherapy in ccRCC.

Most current immunotherapy treatments for ccRCC target the PD-1/PD-L1 axis, a pathway that makes proteins that halt the immune system from attacking cancer cells. Stop the stoppers, and the immune system can go after cancer cells.

But these drugs are only effective in half of ccRCC patients, and almost all patients eventually develop resistance to the drug.

"There may be immune evasion mechanisms outside of PD-1/PD-L1 that play an important role in response or resistance," said Kevin Bi, computational biologist at Dana-Farber and co-lead author on the paper.

Researchers used single-cell RNA sequencing to look 34,326 total cells drawn from samples from eight patients, seven of whom had metastatic renal cancer and one with localized disease. Five samples were from patients who had already received treatment, either through ICB, or a combination of ICB and TKI. Those treated with ICB were all given drugs that specifically targeted the PD-1/PD-L1 axis.

Researchers found that ICB remodels the cancer microenvironment and changes how cancer and immune cells interact, in a few ways:

- In patients whose cancer responded to treatment, subsets of cytotoxic T-cells, which are cancer-fighting lymphocytes, express higher levels of co-inhibitory receptors and effector molecules.
- Macrophages from treated biopsies shift towards pro-inflammatory states in response to an interferon-rich microenvironment but also upregulate immunosuppressive markers.
- In cancer cells treated with ICB, researchers found two

subpopulations, differing in angiogenic signaling and upregulation of immunosuppressive programs.
- In advance stage cancers treated with ICB, expression signatures for cancer cell subpopulations and immune evasion were associated with the PBRM1 mutation, the second most commonly mutated gene in ccRCC.

These findings show the importance of exploring immune pathways away from the PD-1/PD-L1 axis, said Meng Xiao He, a graduate student in the Harvard Biophysics program, member of the Van Allen lab at Dana-Farber, and a co-lead author on the paper.

"We need to look at things that are not just CD8+ T cells. We should look at macrophages, some of the other immune checkpoints, and assess what may be targetable," he said. "We're still in the early days of trying to understand the mechanisms of immunotherapy resistance in different diseases. There's a lot of room to keep trying so that more people respond, and those responses hold."

Choueiri and Van Allen are co-senior authors on the study, "Tumor and immune reprogramming during immunotherapy in advance renal cell carcinoma."

More information: "Progressive immune dysfunction with advancing disease stage in renal cell carcinomas" *Cancer Cell* (2021). DOI: 10.1016/j.ccell.2021.02.013

Provided by Dana-Farber Cancer Institute

cancer.html