Study finds potential biomarkers for lung cancer immunotherapy resistance

July 12 2024, by Eva Cornman

Workflow. (A) Four independent YTMA471 blocks, were analyzed; each block containing one non-adjacent tumor core per patient. (B) For the CK compartment 34 cores had evaluable CK+tissue in all four YTMA blocks (marked with magenta); 22 cores had evaluable CK+ tissue in at least one block and consisted the validation set. Credit: *Journal for ImmunoTherapy of Cancer* (2024). DOI: 10.1136/jitc-2024-009039
Immunotherapy can be a highly effective treatment for non-small cell lung cancer (NSCLC), but some patients are resistant to the therapy or develop intolerable side effects.

Now, researchers from Yale School of Medicine (YSM) have identified two ribosomal RNA genes that could serve as potential biomarkers to assess whether patients will respond to immunotherapy for NSCLC, though further research is needed. NSCLC is the most common form of lung cancer, often triggered by smoking.

The study was published on June 10 in the Journal for ImmunoTherapy of Cancer. Researchers screened over 18,000 genes from tissue samples of NSCLC patients who had undergone a cancer treatment called immune checkpoint inhibitor therapy (ICI).

ICI works by preventing a cellular interaction that prevents the immune system from destroying tumor cells. Out of the thousands of genetic candidates, researchers identified two that were significantly associated with poor outcomes after ICI.

While ICI has been a transformative treatment for lung cancer, some patients can become resistant to the therapy, and researchers aren't exactly sure how or why. Finding a gene that correlates with resistance to the treatment could help physicians guide patients in deciding whether to use ICI, potentially preventing an unnecessary risk of side effects, especially in the early cancer setting.

According to David Rimm, MD, Ph.D., Anthony N. Brady Professor of Pathology, professor of medicine (medical oncology), member of Yale Cancer Center, and principal investigator of the study, one in five patients undergoing ICI treatment loses thyroid function and must take thyroid replacement pills, and as many as one in 100 patients will die from other complications of ICI therapy.
And when there's a possibility that the tumor will be resistant to immunotherapy, Rimm says, the risk of these daunting side effects isn't worth it. "[ICI] is not a drug that you want to give lightly," says Rimm. "In early cancer, we want to make sure that the patient is going to benefit before they get the drug."

Rimm's current research may help identify patients who are best suited for immunotherapy. "You can imagine someday a patient might be tested for these biomarkers, and then if they're negative they could have immune checkpoint inhibitors in the adjuvant setting," says Rimm, meaning treatment given after initial cancer treatments like chemotherapy and surgery.

"If they're positive, we might want to opt for other adjuvant options and not expose them to the risk of an immune checkpoint inhibitor."

**ICI is transforming lung cancer treatment**

ICI therapy was first used in 2011 to treat melanoma. Since then, ICI drugs have been used to treat a variety of cancers, such as breast cancer, colon cancer, and lung cancer.

"Immune checkpoint inhibitors are probably the most important new drug in oncology in the last 15 years," says Rimm.

Immune checkpoints are naturally-occurring proteins that help prevent the immune system from destroying healthy tissue. Immune cells called T cells contain checkpoint proteins, and healthy cells contain checkpoint inhibitors. When a T cell encounters a healthy cell, its checkpoint protein interacts with the checkpoint inhibitor. This essentially "turns off" the T cell, leaving the healthy cell alone.

But sometimes cancer cells will also display checkpoint inhibitors and
turn off the T cell when it should be active. ICI drugs may work by blocking the binding of the checkpoint protein and the checkpoint inhibitor, leaving the T cell active and free to attack the cancer, or they may control immune regulatory cells.

Rimm's team used tissue samples from NSCLC patients to search for biomarkers that could identify whether a patient's cancer would become resistant to ICI therapy. The two biomarkers that the team found were ribosomal RNA genes. The researchers were surprised by this finding and were able to only speculate about how these RNA genes might contribute to immunotherapy resistance. More research will be necessary, Rimm says.

"This discovery was the result of what they sometimes have called in our field a 'fishing expedition,'" because we have no underlying hypothesis. Thus, at this point, we do not know how these genes work to regulate the immune system," he adds. "This is the very first piece of evidence. I would need a whole pile of evidence before we take this to patients."

A 'spatially informed' approach

While future studies are needed to understand the mechanisms of these biomarkers and to determine if the same biomarkers show up in other cohorts of NSCLC patients, Rimm maintains that the most important takeaway from the study was the "spatially informed" approach that the researchers took to find these genes.

Typically, scientists looking for cancer biomarkers will take tumor tissue and mix it up, combining tumor cells, immune cells, and inflammatory cells. They will then look for biomarkers in this cellular soup, making it difficult to identify the specific cell type from which a certain biomarker was found.
But in this study, the researchers took a more delicate approach. Using a new technology called digital spatial profiling, they sampled biomarkers specifically from tumor cells, and not from surrounding inflammatory or immune cells.

"If you use a technology that takes biomarkers from specific regions of the tumor … you get more information than if you just mix up the whole thing," Rimm says. "Ultimately, we believe that we need to measure those biomarkers from tissue in ways that are specific to specific cells."

The field is already moving toward this type of approach, Rimm says, which may allow researchers to discover new biomarkers that have not been identified.

**More information:** Myrto K Moutafi et al, High-throughput transcriptome profiling indicates ribosomal RNAs to be associated with resistance to immunotherapy in non-small cell lung cancer (NSCLC), *Journal for ImmunoTherapy of Cancer* (2024). **DOI:** 10.1136/jitc-2024-009039

Provided by Yale University


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