How RNA-Altering Drugs Might Improve Anticancer Immunotherapies

In a lab study, brief disruptions of gene machinery make tumor cells more “visible” to immune system.

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In a cross-country collaboration that began a decade ago, cancer researchers have now found that inducing short-lived changes in bits of genetic material known as mRNA can make some tumors more susceptible to immunotherapy drugs.

The team led by scientists at Seattle’s Fred Hutchinson Cancer Research Center and New York’s Memorial Sloan Kettering Cancer Center are reporting their findings in the journal Cell.

Their work shows that drugs that trigger errors in mRNA codes can cause tumor cells to sprout — sort of like adding eyes on a potato — lots of new and varied surface proteins called neoantigens. The body’s immune cells read these odd little protein displays as foreign, and they respond by attacking the tumor cells that carry them.

The paper describes a series of petri dish and mouse experiments confirming that adding these mRNA-disrupting drugs, one of which has been evaluated for safety in unrelated cancer clinical trials, can enhance the impact of cancer treatments that harness the body’s own immune system to stop tumor cells.

“It’s a little counterintuitive,” said Fred Hutch computational biologist Dr. Robert Bradley, co-senior author of the paper and holder of the McIlwain Family Endowed Chair in Data Science. “We normally think of mutations as a bad thing that are a cause for a tumor to start. But once a tumor is there, if it has a lot of mutations it can be a good thing, because it lets us use these new, transformative therapies.”

Tumor Mutation Rates Vary Among Patients

The new mRNA-alteration study focuses on ways to improve the results of checkpoint blockade immunotherapies — drugs like pembrolizumab (marketed as Keytruda) that can cure melanoma and other solid cancers in some patients, but unfortunately do not work for most of them.

Oncologists know checkpoint inhibitors work best in patients whose tumors carry the most

mutations. Tumor mutation rates vary among patients and by cancer type. These immunotherapy drugs will shrink tumors in as many as 40% of patients with melanoma, which features highly mutated tumors, but in as few as 5% of patients with breast cancer, which is far more common but features tumors with fewer mutations.

“About two-thirds of cancers have a lower mutational burden and are not that responsive to the checkpoint blockade drugs. They’ve been a remarkable advance, but they could work better,” said Dr. Omar Abdel-Wahab, the MSK oncologist who co-led the study with Bradley.

Ten years ago, Bradley and Abdel-Wahab first met because they both had been named fellows by the Damon Runyon Cancer Research Foundation and they shared an interest in RNA science. They have collaborated closely ever since on a variety of investigations.

If DNA is the alphabet of our biology’s print-edition cookbook, its cousin, RNA, is analogously a set of short orders placed on disposable Post-it notes. mRNA is short for “messenger” RNA because it ferries essential instructions from the DNA vault to a cell’s protein-making machinery, which manufactures the required structures and enzymes as specified.

These short mRNA notes are just as essential to life as DNA, but they do not linger long in the body. They deliver their coded instructions and are soon gone. Having done their job, these short segments of mRNA code are degraded naturally within human cells in just a few hours.

Should this technology prove itself in the cancer clinic, it would be another feather in the cap for mRNAs, which are the key ingredient of two of the most successful COVID-19 vaccines, those of Pfizer-BioNTech and Moderna. Those injections work by delivering packets of mRNA instructions that cause a vaccinated person’s cells to make replicas of coronavirus’ distinctive spikes. RNA-based COVID-19 vaccines are so safe in part because mRNA degrades so quickly.

Those harmless spike copies provoke our immune system into churning out fleets of antibodies — tiny proteins customized to latch onto spike surfaces — which can recognize and block the real, full-fledged virus should it make an appearance.

A Top Priority in Cancer Research

In cancer research, finding ways to increase the visibility of tumor cells to the immune system — and hence make them more susceptible to checkpoint inhibitors — is a top priority. Neoantigens, which sprout on the surface of cells to signal the presence of larger, mutated proteins below it, make tumor cells more visible.

Therefore, some research strategies are focusing on the use of mutagens — chemicals that damage cellular DNA — as a means of getting tumors to create more mutant proteins, causing the production of more neoantigens on cell surfaces.

“To me, that seems really dangerous, because you are maybe going to create cancerous changes,” Abdel-Wahab said.

He and Bradley knew that RNA offered a potentially safer solution to creating neoantigens. They realized that by using drugs that disrupt the mRNA production process, they can cause tumors cells to make unusual proteins and display neoantigens that the immune system would see and recognize as foreign.

In their Cell paper, the collaborating researchers explored several drugs that disrupt the mRNA production process, using advanced techniques that log massive amounts of data about both the unusual RNAs generated by the drugs and the tiny neoantigen proteins that subsequently dot the tumor-cell surface.

Bradley is an expert in analyzing giant batches of biological data like this, while Abdel-Wahab is a physician-scientist whose research focuses on cell-culture and mouse studies. Over the course of a decade, the collaborating scientists have cross-trained their respective labs in all aspects of this research, and they continue working together toward a common goal of unraveling cancer's mechanisms and vulnerabilities.

Their efforts as reported in the paper are now focused on two drug candidates, one of which has been evaluated by other researchers in early human clinical trials as a potential cancer treatment. Those drugs were identified as having anticancer activities, but the bases for those promising properties were originally unknown. Their ability to make transiently damaged RNA was discovered only recently.

The two experimental compounds, one known as indisulam and the other called MS023, have never been approved by the Food and Drug Administration as cancer drugs, but belong to drug classes that do not appear to be toxic in early trials.

Although both drugs affect cell biology differently, they each coincidentally disrupt a complex molecular machine inside cells called the spliceosome. The mechanism happens to be at the center of Abdel-Wahab and Bradley's research interests for years.

The spliceosome's job is converting raw strips of RNA code — which is littered with short segments of genetic gibberish — into the short, crisply readable instructions of mRNA. The process essentially strips out the gibberish and splices the remaining code together, hence the name "spliceosome."

In different biochemical ways, the two drugs of interest briefly rough up the spliceosome. This latest study shows that this transient disruption causes cells to produce a crop of cell-surface neoantigens that can draw the attention of the immune system. And unlike permanent mutations made by damaging DNA, these altered mRNAs are gone by the time the immunotherapy drugs have gone to work.

An Important 'Proof of Concept'

One example highlighting the promise of the approach was an experiment in mice that had a tumor known as Lewis lung carcinoma. It is well known that checkpoint blockade drugs alone are

ineffective against these tumors. However, when these mice were given mRNA-disrupting indisulam plus a checkpoint drug, their tumor growth slowed substantially.

“This is an important proof of concept that our approach may be effective even for tumors that are non-responsive to immune checkpoint blockade by itself,” Bradley said.

He notes that, like checkpoint inhibitors themselves, these RNA-disrupting drugs affect tumor and healthy cells alike. In principle, neoantigens that might be displayed on healthy cells could cause a dangerous side-effect: triggering the immune cells to attack them as well. Although the Abdel-Wahab and Bradley study did not find any evidence of these unwanted side effects in mice, they said further testing is essential to establish safety in humans. However, the lack of toxicity observed in previous experiment and human trials is encouraging.

The researchers also stress that studies that show promising results for treatments in mice, as theirs do, often do not pan out in clinical trials with human beings.

Because of the work described in the Cell paper, the two researchers believe these drugs should now be tested in human studies specifically to see if they can work synergistically with immunotherapy.

“I think it is ready to take forward, clinically,” Bradley said.

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