NEWS BIOLOGY

Surprising strategy would fight mutant cancer cells by making more mutations

Chemotherapies that induce new DNA errors may help unleash the immune system on tumors

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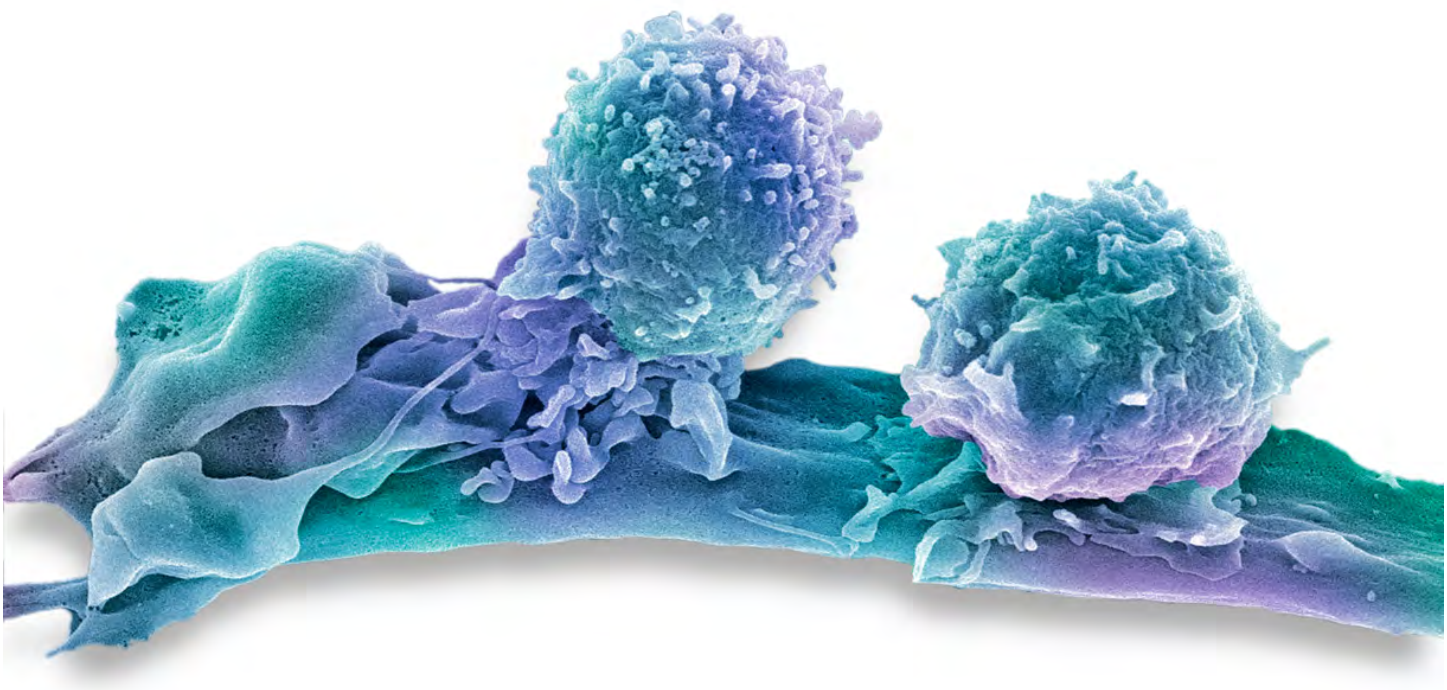

T cells (spheres) may attack a tumor better if the cancer has deliberately added mutations. STEVE GSCHMEISSNER/SCIENCE SOURCE

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Lab studies and several small clinical trials already hint the strategy may help. “There might be an opportunity to begin to remodel the genetics of the tumor in such a way” that immunotherapy works better, a leader of one trial, cancer geneticist Luis Diaz of Memorial Sloan Kettering Cancer Center, said at a plenary session here at the annual meeting of the American Association for Cancer Research (AACR).

Still, some cancer researchers are leery of purposely inducing mutations and say animal experiments suggest doing so could cause more harm than good. “I question the rationale,” says melanoma immunotherapy researcher Antoni Ribas of the University of California, Los Angeles.

Drugs called checkpoint inhibitors remove a molecular brake that keeps immune sentries called T cells from attacking tumors. They work best on cancers such as lung tumors triggered by smoking-induced DNA damage and melanomas, which accumulate mutations from ultraviolet (UV) light. Many of these genetic changes cause cells to make “neoantigens,” novel protein fragments on tumor cells that flag them to T cells.

The notion that forcing cancer cells to make more neoantigens might bolster immunotherapy traces back to studies of tumors with defects in certain mechanisms that repair DNA. These cancer cells accumulate many mutations, and in 2015 a team led by Diaz, then at Johns Hopkins University, reported that checkpoint drugs work well on multiple tumor types with these “mismatch” DNA repair defects.

Cancer geneticist Alberto Bardelli of the University of Turino and colleagues went further by deliberately inactivating a mismatch repair gene in tumor-bearing mice. They reported in *Nature* in 2017 that the change resulted in a buildup of DNA errors in the cancer cells and boosted the effectiveness of checkpoint drugs.

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Since then, two Italian trials have documented similar effects in people. One study gave the standard chemotherapy drug temozolomide, which disables mismatch repair genes, to 33 people with advanced colon cancer, which normally does not respond to checkpoint inhibitors because it has too few mutations. The chemotherapy alone shrank tumors in eight people but another seven people similarly responded after all later received two checkpoint inhibitors. Tumor growth halted in the overall group for an average of 7 months, the team reported last month in the *Journal of Clinical Oncology*.

In four patients who had tumor biopsies analyzed, as well as in 14 of 16 patients in a trial described in a poster at the AACR meeting, the team showed that temozolomide had induced mutations. Bardelli says the preliminary data offer a “proof of concept.”

Diaz wondered whether inducing a specific kind of mutation would work even better. His team was particularly interested in a type that shifts how a cell’s proteinmaking machinery reads a gene’s messenger RNA. Such a “frameshift” mutation can change many of the amino acids of a gene’s protein, making it more foreign to the immune system.

Postdoc Benoit Rousseau and others in the Diaz lab tested temozolomide and another chemotherapy drug, cisplatin, on cancer cells and found the combination produced 1000 times more frameshift mutations than either drug alone. When cancer cells treated with the drug combination were injected into mice, the resulting tumors vanished in response to a checkpoint drug.

Diaz’s team is now giving the combination to people with metastatic colon tumors before they receive a checkpoint drug. In two of the first 10 patients, tumor cell DNA shed into their blood showed they had developed relatively high levels of frameshift mutations—and their tumors stopped growing. “It’s early days,” Diaz cautions, but the results give “a flavor of what we’re expecting.”

Still, there’s an obvious safety concern: The chemotherapy drugs might also create mutations in a patient’s healthy cells. Diaz says his group has not seen new tumors in mice treated with the drugs.

Some researchers worry the approach will be counterproductive. They say tumors made up of one or just a few genetically identical cell lineages, or clones, respond better to checkpoint inhibitor drugs than highly heterogenous masses do. Ribas fears that inducing more mutations creates new clones in a tumor and dilutes the impact of any T cells unleashed. He points to a 2019 study in which an Israeli group used UV light to create mutations in melanoma tumors in mice and found the increased diversity of cancer cells actually hampered the checkpoint inhibitor response.

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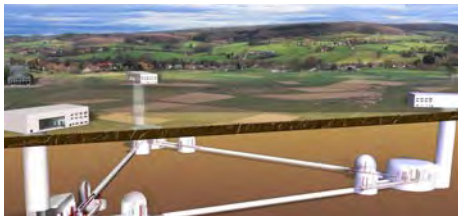

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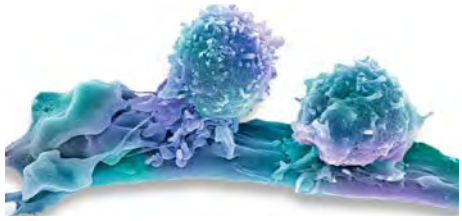

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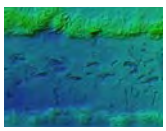

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