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Modified DNA building blocks are cancer's Achilles heel

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In studying how cells recycle the building blocks of DNA, Ludwig Cancer Research scientists have discovered a potential therapeutic strategy for cancer. They found that normal cells have highly selective mechanisms to ensure that nucleosides—the chemical blocks used to make new strands of DNA—don't carry extra, unwanted chemical changes. But the scientists also found that some types of cancer cells aren't so selective. These cells incorporate chemically modified nucleosides into their DNA, which is toxic to them. The findings, published today in the journal *Nature*, indicate that it might be possible to use modified nucleotides for specific killing of cancer cells.

"In the past few years we and others discovered a new set of biological DNA modifications. In the current study, our research group sought to find out what happens to these modified bases when DNA is recycled," says Skirmantas Kriaucionis, lead author and assistant member of the Ludwig Institute for Cancer Research, Oxford. "We were excited that our biochemical analysis uncovered 'loopholes,' which we hope can be exploited for intervention in cancer."

Cells are thrifty when it comes to synthesizing new DNA. In addition to making new nucleotides, they recycle chemical parts from the DNA of dying cells, or DNA that we ingest in our diets. However, one of the four types of nucleotides in DNA—the 'C' in genetic sequences—is often chemically modified. These chemical modifications, which are called 'epigenetic' changes, are important for controlling genes and need to be in the correct places in DNA for cells to function normally. If the

epigenetic modifications are on the wrong C nucleotides, they could make cells cancerous or kill them. The puzzle that Kriaucionis and his colleagues set out to unravel was how cells prevent recycled and chemically modified 'Cs' from ending up in the wrong places in new DNA.

Crucially, they found that the enzymes that recycle nucleotides are highly specific. They don't use the modified nucleosides, so the new DNA is epigenetically 'clean.' However, when they looked at the recycling process in cancer cell lines, the researchers discovered that some of the cancer cells are able to transform these nucleosides, allowing incorporation into new DNA. This process often kills the cells. It was the cancer cell lines that expressed unusually high levels of a protein called cytidine deaminase (CDA) that made this mistake in recycling. CDA is often overexpressed in certain tumor types, including pancreatic cancer.

Exploiting the unexpected killing of cancer cells by epigenetically modified nucleotides, Kriaucionis and his team demonstrated in a model system that modified Cs can be used as a specific anti-cancer agent.

"It has been suggested that CDA inactivates cytidine analogues that are already used in the clinic to treat some blood and pancreatic cancers," says Kriaucionis. "In a strikingly reverse scenario, the nucleosides that we used in our study are relatively harmless until they encounter CDA, which converts them into hostile cytotoxic agents."

The researchers will likely continue to investigate this new avenue for 'epigenetic' drugs as cancer therapies.

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