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SKIRMANTAS KRIAUCIONIS

NUCLEAR SABOTEUR

Skirmantas Kriaucionis was a postdoctoral researcher in Nathaniel Heintz's laboratory at Rockefeller University when he noticed, in 2008, an inexplicable but recurrent blip in his data from experiments with mouse brain cells. He and Heintz could have ignored it and carried on with the work at hand. But something told them to look a little deeper. This something was right. After much research into the blip, they concluded it harbored that rarest of scientific gems: a fundamental biological discovery. Their findings, reported in *Science* in 2009, added a new DNA base—5-hydroxymethylcytosine (5hmC), previously seen only in bacteria—to the known chemical alphabet of the mammalian genome.

A similar mix of serendipity, insight and persistence paid off for Kriaucionis in 2015. As head of his own lab today at Ludwig Oxford, Kriaucionis focuses on how chemical, or "epigenetic," tags added to DNA—like 5hmC and its classical counterpart, 5-methylcytosine (5mC)—alter gene expression. Such tags help determine which genes are expressed by a given cell, giving each type its specialized function and explaining how a single genome can lead to things as disparate as a taste-bud and a liver.

Epigenetic marks of all sorts have also long been known to be rampantly misplaced across the genomes of cancer cells. Kriaucionis and his team were testing a theory of how this might occur when they made a discovery that had unexpected implications. Their findings, published in *Nature* in 2015, show that a characteristic sloppiness in the way some types of cancer cells handle epigenetically marked bases may be harnessed to devise a new kind of therapy for various cancers.

From pond to lab

Kriaucionis grew up in Kaunas, a city at the confluence of Lithuania's two largest rivers. His mother worked as a bookkeeper and his father as a driver for the local university. His parents often took him to the country, where the family owned a small plot of land and the young Kriaucionis could indulge his interest in bugs and pond life.

His parents, he recalls, actively nurtured his budding interest in science, buying him magnifying glasses and microscopes along with the classics of his favorite science fiction author Jules Verne.

"I was fascinated by how the living world works," says Kriaucionis. "My parents weren't scientists but they were very attentive to their children. That, I think, made the biggest difference."

Naturally, Kriaucionis majored in biology when he enrolled in Vytautas Magnus University in Lithuania's capital Vilnius. There, he was introduced to epigenetics during his thesis research with Saulius Klimasauskas, an authority on the phenomenon in bacteria. He was hooked. For his doctoral research with Adrian Bird at the Wellcome Trust Centre for Cell Biology at the University of Edinburgh, Kriaucionis studied how proteins recognize 5mC, which cells employ to switch genes off.

The researchers found that some types of cancer cells tweak modified nucleosides, permitting their incorporation into new DNA. The practice, however, often kills the cells.

After a stint as a postdoc in Bird's lab, Kriaucionis landed a second fellowship in Heintz's lab at Rockefeller University, where he began exploring why the nuclei of two types of brain cells appeared so different in their organization. That was the research that yielded the discovery of 5hmC which, unlike 5mc, seems highly enriched in brain cells and in stem cells during early development. It too is broadly misplaced across cancer genomes.

Useful error

Since joining Ludwig Oxford in 2010, Kriaucionis has continued to probe the epigenetics of normal and cancer cell biology. In 2012, he and Heintz led a study published in *Cell* showing that 5hmC is associated with genes that are actively expressed and that its presence is detected by the same protein, MeCP2, that recognizes 5mC.

These findings were of relevance to Rett syndrome, a developmental disorder that varies in severity depending on how precisely MeCP2 has been altered. Heintz, Kriaucionis and their colleagues reported that a mutant MeCP2 protein associated with less severe cognitive and speech deficits in Rett patients is capable of binding 5mC, but not 5hmC.

Since then, Kriaucionis has dug deeper into the biology of 5mC and 5hmC. "One of the key questions we're pursuing is how the rearrangement of the epigenetic landscape occurs in cancer," says Kriaucionis. There are two possibilities. One is that the aberrant signaling within the cancer cell induces the effect. The other is that the process is random, and particular epigenetic patterns are ultimately favored because they promote the survival of the cells that harbor them.

As part of their exploration of the latter possibility, Kriaucionis and his colleagues

examined whether modified bases are randomly incorporated into the genomes of cancerous cells. Such bases might come from last night's steak, or from the body's own stew of metabolic byproducts.

The researchers found that the enzymes that help recycle DNA bases—which are borne by molecules known as nucleosides—are highly specific. They reject modified bases, ensuring that the new DNA is epigenetically "clean." When the researchers looked at the recycling process in cancer cell lines, they discovered that some types of cancer cells tend to chemically tweak modified nucleosides picked up from the recycling pool, permitting their incorporation into new DNA. The practice, however, often kills the cells.

They showed, critically, that cancer cells that express unusually high levels of a protein called cytidine deaminase (CDA) are prone to such errors. Previous studies have shown that a number of cancers—from those of the pancreas to the stomach to the testes—overexpress this enzyme. But the phenomenon had been seen as a means by which tumors resist chemotherapies like gemcitabine, which are essentially modified nucleosides designed to kill rapidly dividing cells.

Kriaucionis and his team realized, however, that their modified nucleosides, including 5hmC, were likely to have the opposite effect. Better still, they showed this to be true, at least in an animal model. "The modified nucleosides we used actually kill cells that over-express CDA," says Kriaucionis.

The researchers are now beginning studies to determine whether their nucleosides are amenable to translation into viable candidate drugs for evaluation in human studies. "We are especially keen to determine whether these compounds work against pancreatic cancer," says Kriaucionis. "It is a very aggressive malignancy that overexpresses CDA and is highly resistant to treatment. Current therapy does very poorly for patients. It would be very rewarding if we could improve their outcomes."

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