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Misreading of damaged DNA may spur tumor formation

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The DNA in our cells is constantly under assault from oxygen, the sun's radiation and environmental stresses. Most of the time, our cells can repair the damage before it gets copied into a permanent mutation that could lead to cancer.

Adding a wrinkle to our understanding of how cancers begin, scientists have found that cells can turn on tumor-promoting growth circuits as a result of misreading damaged DNA without copying it: a process called "transcriptional mutagenesis."

The results are published online this week in *Proceedings of the National Academy of Sciences.*

"This reveals a new aspect of tumor development that could be especially important for cells that make up most of the body's tissues: differentiated cells that are not replicating their DNA," says Paul Doetsch, PhD, professor of biochemistry at Emory University School of Medicine and deputy director of basic research at Emory Winship Cancer Institute.

All cells, including non-dividing cells that are not replicating their DNA, continue to transcribe, or make RNA, from some of their genes in order to produce proteins and carry out their normal functions.

Doetsch and postdoctoral researcher Tina Saxowsky, PhD, examined what happens when mouse cells are presented with DNA pre-loaded with

a damaged building block in a critical place.

The DNA encoded the gene Ras, one of the genes most often mutated in human cancers. The damage came in the form of 8-oxoguanine, which is generated when guanine, one of the four bases making up DNA, reacts with oxygen. (The four bases are: Adenine, Guanine, Cytosine and Thymine.) Cells unable to repair the damage tend to replace the modified guanine (G) with thymine (T).

"It's one of the most common forms of genetic damage," Doetsch says. "Constantly dealing with oxidation is the price we pay for breathing air."

If the cells misread the G as T during the process of transcription, some of the Ras protein they make comes in the hyperactivated form found in cancers. By looking at other proteins controlled by Ras, the authors could detect some of the cell's growth circuits starting to turn on.

By reading the RNA the cells make from the Ras DNA, Saxowsky found that even normal mouse cells misread the damaged DNA about three percent of the time. Sometimes the cell's machinery sees the damaged G as T, and sometimes it skips a letter. However, the mouse cells were more likely to misread the 8-oxoguanine (14 percent of the time) if they came from mice engineered to lack an enzyme that normally repairs the damage, called 8-oxoguanine glycosylase.

Doetsch says his group's findings suggest that DNA damage, if it hits certain critical genes in a cell, could lead to transcriptional mutagenesis that in turn spurs the cell to divide.

"Let's say that DNA damage lands in a gene that normally prevents a cell from dividing when it's not supposed to," Doetsch says. "If enough mutant proteins get made from the gene, the cell divides and the DNA is copied. Now, in one of the daughter cells the damage becomes a

permanent mutation driving further growth. It's another way for tumor promotion to happen, except the growth signal needed to push the process along isn't coming from a chemical or a hormone."

He and Saxowsky are performing additional experiments to test the hypothesis that transcriptional mutagenesis can lead to cell division directly.

Transcriptional mutagenesis could explain a phenomenon seen in bacteria called adaptive mutagenesis, Doetsch says. When faced with starvation conditions, bacteria can relax their standards of accuracy when copying their DNA, apparently in an effort to mutate their way out of a dead end.

It appears that bacterial enzymes that make RNA from DNA are more susceptible to transcriptional mutagenesis than those from mammals, Doetsch notes, but further studies are required.

Cancer is essentially the "selfish" growth of a small group of cells at the expense of the person they came from, an issue that does not arise in one-celled organisms such as bacteria, he says.

Citation: 8-oxoguanine-mediated transcriptional mutagenesis causes Ras activation in mammalian cells, Saxowsky, T.T. et al. Proceedings of the National Academy of Sciences, Early online publication November 17, 2008

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