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Protein averts cell suicide but might contribute to cancer

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Scientists have discovered how an unusual protein helps a cell bypass damage when making new DNA, thereby averting the cell's self-destruction.

But they also discovered that this protein, an enzyme called Dpo4, often makes errors when copying the genomic DNA sequence that later might cause the cell to become cancerous.

The findings by researchers with Ohio State University 's Comprehensive Cancer Center are described in two back-to-back papers in *The Journal of Biological Chemistry*.

"Unrepaired DNA damage presents a big roadblock for the DNA replication machinery, which cannot go around it," says Zucai Suo, assistant professor of biochemistry. "This damage will trigger cell death because the DNA is not replicated.

"This protein bypasses the damage and saves cells from self-destructing, but it is very error prone, which suggests that it may also play a role in cancer."

Dpo4 is one of a family of enzymes called Y-family DNA polymerases that were first discovered about 10 years ago and are only now becoming understood.

"These enzymes provide a survival mechanism for cells," says first

author Kevin Fiala, a graduate student in Suo's laboratory. "They allow DNA replication to continue, so the cell doesn't die. But they don't repair the DNA damage that exists."

DNA damage is a routine problem for cells, Suo says. For example, every cell loses more than 10,000 DNA bases daily. Dedicated repair enzymes fix 80 percent or more of this damage, but the rest remains.

Cells use Y-family enzymes to bypass that remaining damage when making new DNA prior to cell division, thus forcing these enzymes to copy damaged DNA.

How these bypass enzymes work, however, isn't known. The Dpo4 protein used in this research comes from a microorganism. It is relatively easy to produce in large quantities and to study, and it is similar to one of the four such enzymes found in humans.

For this research, Fiala developed a new way to sequence very short lengths of DNA. "This allowed us to pin down exactly what mistakes Dpo4 makes," he says.

The findings reveal why the enzyme makes mistakes.

DNA resembles a spiral staircase that is made from separate halves, with half-steps protruding from each. The half-steps fit together down the center to form the complete staircase.

In DNA, the half-steps are known as the bases – the ‘A's, ‘C's, ‘G's and ‘T's – that run the length of a DNA helix. A complete step is formed by pairs of bases according to a rule: ‘A' always pairs with ‘T,' and ‘C' always pairs with ‘G.'

When cells make new DNA, the two strands separate, and each old half

becomes a template for a new partner. The DNA-making machinery travels along the old half, building the new half according to the bases it finds on the old half. When it meets an ‘A' on the old half, it pairs it with a ‘T' on the new half (and vice versa); when it meets a ‘G' on the old half, it pairs it with a ‘C' on the new strand. In the end, there are two complete DNA molecules instead of one, each made up of an old half and a new half.

But trouble arises during the building if one of the bases – one of the half steps – is missing. When the DNA replication machine encounters the gap, it stalls. If the standstill continues, the cell will self-destruct.

It's at this point when Dpo4 jumps in. It adds a base opposite the gap and then leaves, allowing the DNA-making machinery to bypass the damage and continue construction.

The action averts cell suicide, but the gap – and the stop-gap base – might become a mutation that, in conjunction with later genetic damage, causes the cell to eventually become cancerous.

"The objective of this enzyme is to allow replication to continue, not to repair the damage," says Fiala. The damage will persist, and cells might try to repair it later. But as long as DNA replication can continue, the cell survives."

Currently, Suo's laboratory is investigating human Y-family DNA polymerases.

Source: Ohio State University