New DNA repair pathway

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(PhysOrg.com) -- UC Davis researchers have found a new pathway for repairing DNA damaged by oxygen radicals. The results are published this week in the journal *Proceedings of the National Academy of Sciences*.

"This new inducible pathway gives cells greater capacity to repair oxidative damage," said Peter Beal, professor of chemistry at UC Davis and senior author of the paper.

As part of its inflammatory response, the body's immune system produces oxygen radicals, or reactive oxygen species, to kill bacteria, parasites or tumors. But chronic inflammation, for example in the gut, has been linked to cancer, said co-author Professor Sheila David, also of the Department of Chemistry.

Oxygen radicals are strongly linked to cancer and aging and are also formed during metabolism and upon exposure to environmental toxins and radiation. Understanding more about how this damage can be repaired could lead to a better understanding of the causes of some cancers.

Oxygen radicals can react with the four bases that make up the "letters" of DNA -- A, C, G and T -- so that the "spelling" of genes gets changed. The accumulation of spelling errors (called mutations) can lead to cancer.

David's laboratory studies an enzyme called NEIL1 that detects and

repairs these aberrant or damaged bases before changes in the genome become permanent.

Beal's group works on RNA editing. The first step in turning a gene into a protein is to make a copy of the DNA in RNA. This messenger RNA is then translated into the chain of amino acids that makes up a protein. In some cases, this RNA is "edited" between the transcription from DNA and the translation into protein.

At a conference last year, Beal -- who happens to be David's husband -- spotted NEIL1 among a list of genes that had just been discovered to be subject to RNA editing, and passed the news on to David.

On investigation, they found that NEIL1's messenger RNA is edited by an enzyme called ADAR1. In that editing, one of the chains of amino acids that make up NEIL1 changes from lysine to arginine, causing a slight, but noticeable, change in the structure of the protein.

Using a cell line derived from nerve cells, the team found no editing of NEIL1 RNA in resting cells. But when the cells were treated with interferon, which is produced during inflammation and to fight off viruses, the cells started making ADAR1 and editing NEIL1.

"The interferon-treated cells had two forms of the NEIL1 protein, one with lysine and one with arginine," Beal said.

NEIL1 can fix a number of different damaged DNA bases that form when normal DNA bases are attacked by oxygen radicals. Beal and David found that the two different forms of NEIL1 had different abilities to act upon the damaged DNA bases: the basic, lysine version had a broader range but lower activity, while the edited, arginine form had higher activity but was effective against a more limited range of targets. That might give the cell more flexibility in responding to DNA

damage.

Beal and David believe that the whole system works something like this: Inflammation creates oxygen radicals, which damage DNA, which is repaired by NEIL1. Inflammation also generates interferon, which induces ADAR1, which then edits NEIL1 to produce the more active, specific form to cope with more severe types of DNA base damage.

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