SCRIPPS RESEARCHERS DETERMINE STRUCTURE OF DNA REPAIR ENZYME
Implications for Cancer and Aging

LA JOLLA, CALIFORNIA Oct. 16, 1992 -- Researchers at The Scripps Research Institute (TSRI) in La Jolla have determined the three-dimensional structure of an enzyme that plays an important role in the recognition and repair of damaged DNA.

Since DNA damage has been implicated in many degenerative processes, the new findings may help researchers better understand cancer and aging.

A team led by John A. Tainer, Ph.D., at TSRI has published its results in this week’s issue of *Science*, the journal of the American Association for the Advancement of Science.

"Understanding the structure of this enzyme will help us better understand how it recognizes and repairs damaged DNA," Tainer says. "Ultimately, this should also help us deal with cancer and aging, since unrepaired DNA generates mutations responsible for cancer and degenerative diseases."

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In addition, scientists at TSRI plan to use the structures of DNA-repair enzymes to design new types of anti-cancer drugs. For example, inhibitors of DNA-repair enzymes could be used to decrease repair in cancer cells and improve the destruction of tumors by radiation and chemotherapies.

DNA, which is the source of genetic information within a cell, utilizes more than 50 different types of DNA repair enzymes to help maintain the genetic record. Among these are several DNA glycosylases, each of which recognize a single type of altered base in DNA and catalyze its removal. Additional enzymes involved in repair are DNA polymerase and DNA ligase.

The DNA-repair enzyme studied by the researchers was endonuclease III, which recognizes, cleaves and repairs the damaged DNA of the bacteria Escherichia coli.

The researchers noted in Science that since bacterial, yeast, bovine and human DNA-repair enzymes are similar, the study of E. coli endonuclease III is applicable to more complex and less defined systems, including human cells, and has "broad implications in understanding DNA repair."

They said that endonuclease III "acts both as a DNA N-glycosylase, removing oxidized pyrimidines from DNA, and an AP lyase," which nicks the damaged DNA segment in preparation for rebuilding by DNA polymerase.
In determining the enzyme's structure, the researchers were surprised to find an iron-sulfur cluster "unlike any of the other well characterized DNA repair enzymes." Its primary function appears to be in binding interactions between the enzyme and the phosphate backbone of DNA.

The method used to determine the enzyme structure was x-ray diffraction in which x-rays are bounced off a tiny crystal of pure protein to create a distinctive pattern that can be analyzed to measure the exact position of each atom.

Additional authors of the Science article were TSRI researchers Che-Fu Kuo, Ph.D., Duncan E. McRee, Ph.D., and Cindy L. Fisher, Ph.D.; and Suzanne O’Handley, Ph.D. and Richard P. Cunningham, Ph.D. of the Department of Biological Science, Center for Biochemistry and Biophysics, State University of New York at Albany.

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