SOUTHWESTERN NEWS

Media contact: Susan A. Steeves
(214) 648-3404
susan.steeves@email.swmed.edu

EMBARGOED FOR MONDAY, OCT. 11, 1999

UT SOUTHWESTERN RESEARCHERS DISCOVER STRUCTURE OF MOLECULE THAT REPAIRS SUN AND CIGARETTE DAMAGE

DALLAS – October 12, 1999 – The crystal structure of an enzyme that hunts down DNA damage caused by sunlight and cigarettes then snaps it up like a Venus' flytrap is described in today's *Proceedings of the National Academy of Sciences.*

UT Southwestern Medical Center at Dallas researchers provide the first structural information on any component of the deoxyribonucleic acid (DNA) nucleotide excision repair (NER) system, living organisms' most fundamental and important repair mechanism. Knowledge of how the NER system recognizes and disposes of DNA damage eventually may lead to preventions for various forms of cancer.

"When this system breaks down a variety of diseases can develop, most notably xeroderma pigmentosum, a disease associated with neurological abnormalities and a very high incidence of skin cancer," said Dr. Mischa Machius, who collaborated on the study with Dr. Johann Deisenhofer, Nobel laureate, professor of biochemistry and Howard Hughes Medical Institute (HHMI) investigator. "The enzyme also will recognize and remove DNA damage done by cancer therapies designed to kill tumor cells. In that way, the NER mechanism is counterproductive to radiation and chemotherapy."

Until the UT Southwestern scientists solved the crystal structure of the central component of the NER system – the Ultimate Damage Recognition component UvrB – little was known about the structural basis of how the system differentiates between healthy and damaged DNA and how it recognizes a variety of lesions.

Although the researchers looked at UvrB as part of the bacterial NER system, which operates with only three enzymes, UvrB functions in the same way in the corresponding human DNA repair system. The human mechanism contains 16 components.

(MORE)

"UvrB is a remarkably versatile enzyme," said Machius, lead author of the study and a HHMI postdoctoral fellow. "It binds to any DNA, then, along with another enzyme, travels along patrolling for a damaged spot. Once it finds a lesion, it tightens its grip on that DNA segment."

After UvrB attaches to the DNA, it unwinds the two strands of DNA and separates them. Then the NER system incises the lesion on each side and disposes of it.

The UT Southwestern scientists said their observations of the crystal structure shed light on the workings of UvrB in restoring DNA and preventing disease development.

"We believe that UvrB actually traps the damage site in one of its domains," Machius said, "a mechanism that was entirely unexpected and that is unprecedented in nature."

Previous studies have suggested that NER recognizes damage because of how a lesion affects DNA flexibility rather than because of its chemical makeup.

This model, if proven, would help to explain the whole NER system and could aid in development of more effective cancer drugs.

The other researchers involved in the study were HHMI research technicians Lisa Henry and Maya Palnitkar.

###