SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS FIND LEVER INVOLVED IN ULTRAVIOLET-RAY SENSITIVITY

DALLAS – June 18, 1999 – Investigation of two important cell systems has revealed that a large protein complex, previously thought to mainly regulate protein degradation, also plays a significant role in sensitivity to cancer-causing ultraviolet light.

UT Southwestern Medical Center at Dallas researchers reported the findings in today's issue of *Molecular Cell*. The scientists reached their conclusion when they joined their studies of a biological machine called the proteasome and the protein Rad23, which is involved in repair of DNA damaged by ultraviolet light. If the repair machine fails to work, as in the disease xeroderma pigmentosum, mutations occur that lead to skin cancer, said Steven Russell and Dr. Simon Reed, two of the paper's authors.

"Clearly these two systems have important roles in human health and disease," said Russell of the work, done in vitro and in live yeast, which involved genes also found in humans. "This is a seminal finding about the relationship between the proteasome and the repair complex. The knowledge will lead to new insights into both systems."

The team of investigators discovered that by deleting a part of Rad23, a component of the nucleotide excision repair (NER) machinery, they could increase sensitivity to UV radiation. This means for DNA repair to work properly, that particular domain of Rad23, which binds to the proteasome, must be present. They also showed that inhibiting an ATPase, one of the proteasome's energy sources, diminishes NER activity, thus increasing UV sensitivity.

"If you hit the yeast with high enough levels of light, they get so much DNA damage that they die. Lower amounts of UV rays also will cause damage but they can repair it and survive, much the way people do if their systems are functioning normally," Reed said. "This work shows that mutations in the proteasome can cause yeast to be less resistant to ultraviolet light, which supports the idea that the proteasome is involved in repair."

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Next the researchers will study each step in the repair process to uncover when the defect that allows UV sensitivity occurs. If they can determine exactly how the mechanism works, it may be possible to manipulate it for people who are genetically predisposed to skin cancer.

The researchers said they believe part of the secret lies in how the proteasome affects proteins. "It's useful to think of these proteins as machines cranking through the steps: The DNA is pulled apart into separate strands, cuts are made, and the damaged part is taken out. This process probably requires a change in the shape of the repair proteins, just like a lever moving on a piece of industrial equipment," said Russell. "We believe the proteasome may cause those shape changes by using energy from the ATPases. We want to know what proteins are changing shape and what the changes are."

Russell is working on his medical degree and doctorate in UT Southwestern's Medical Scientist Training Program. Reed is a postdoctoral fellow in pathology. Other researchers involved in the study were: Dr. Stephen Johnston, professor of biochemistry and internal medicine and co-director of the Center for Biomedical Inventions; Dr. Errol Friedberg, chairman of pathology; and Dr. Wenya Huang, pathology postdoctoral fellow.

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