

MOLECULAR BIOLOGY

Protein Protection from the Sun

New information reported by researchers at the University of Texas Southwestern Medical Center in Dallas could eventually help scientists develop better ways to protect against and treat the adverse effects of too much sunlight. In a paper published in the June 1999 issue of *Molecular Cell*, the researchers demonstrated that the interaction between a protein called Rad23 and a protein complex known as the 26S proteasome is important for the ability of yeast cells to repair DNA damage caused by ultraviolet (UV) light. Human cells contain very similar proteins, so this finding may lead to insights into how human skin responds to UV exposure.

The study built on earlier work by researchers from the Robert Wood Johnson Medical School in Piscataway, New Jersey, published in the 12 February 1998 issue of *Nature*, that first demonstrated a physical interaction between Rad23 and the 26S proteasome. The 26S proteasome is a large, two-part complex involved in the degradation of many different cellular proteins: the 19S regulatory complex is thought to bind to damaged proteins, unfold their twisted lengths, and thread them into the barrel-shaped 20S structure, where they are degraded by protease enzymes.

The site of interaction between the 26S proteasome and Rad23 appears to be Rad23's ubiquitin (Ub)-like domain, a section of the protein that physically resembles true Ub, a small protein that connects to other proteins and targets them to be degraded by the 26S proteasome. (This does not seem to be the case for the Ub-like domain of Rad23, however; its function is still not understood.) Other, earlier research had shown that yeast missing the Rad23 protein or its Ub-like domain were more sensitive to UV radiation. With the *Molecular Cell* study, the Texas scientists were able to show that the physical interaction between Rad23's Ub-like domain and

the 26S proteasome is necessary for optimal DNA repair to take place.

To investigate the relationship between Rad23 and the 26S proteasome, the researchers prepared yeast extracts that had either the Rad23 full-length protein, no Rad23 at all, or a Rad23 from which the Ub-like domain had been deleted. Yeast with the full-length Rad23 were found to repair UV damage very well. Those without the Rad23 protein displayed almost no repair activity. Those with the truncated version of the protein—in other words, those in which a Rad23-proteasome interaction would be impaired—were in the middle, with damage being repaired half as well as with the full-length protein.

Next, the scientists looked at whether the 26S proteasome is important for DNA repair *in vitro*. To explore the role of the 19S regulatory complex, they added to the yeast extract an antibody to inhibit one of the complex's subunits and examined the consequences for DNA repair. Addition of this antibody was found to inhibit 50% of repair activity.

Antibodies against unrelated proteins had no effect on repair activity, indicating that the 26S proteasome does have a role in DNA repair. Eventually, the Texas team's findings may lead to innovations in the prevention and treatment of skin cancer.

Coauthor Steven

J. Russell says the 26S proteasome is already being investigated as a drug target for wasting diseases such as AIDS and cancer in which the complex is overactive, degrading proteins too quickly. Proteasome inhibitors are also being investigated as protectants against inflammation, which may be useful in conditions such as arthritis and sepsis. Russell says, "A couple of recent papers suggest that drugs already in use may work in part by inhibiting the proteasome in addition to their known mechanism."

Russell continues, "Our ultimate goal is to understand exactly how the proteasome is involved in DNA repair. We need to work out the details, but the implication is that we have a novel mechanism of proteasome action and a novel facet of the DNA repair process." —Susan M. Booker



Sun spot. The site of interaction between a protein and a proteasome is yielding clues to the repair of DNA damage from UV light.

Pinpointing Asthma

Researchers at the U.S. Department of Energy's Lawrence Berkeley National Laboratory in Berkeley, California, have uncovered two genes that influence an individual's susceptibility to asthma using a novel way to determine if specific genes are linked to diseases. The two asthma-related interleukin genes, *IL4* and *IL13*, are located in the chromosome 5 region of the human genome. Study scientists believe that finding a way to limit the activity of these genes will reduce the probability of asthma attacks.

In the study, published in the 1 October 1999 issue of *Nature Genetics*, the researchers divided a several-million-base-pair region of chromosome 5 into large chunks and then introduced these pieces separately into the genomes of mice. The scientists then matched the physical characteristics of the mice with the same characteristics exhibited by human asthma sufferers to pinpoint *IL4* and *IL13* as susceptibility genes.

Ending River Blindness

A World Health Organization (WHO) program to eradicate onchocerciasis, or river blindness, has proven hugely successful. River blindness affects millions of people in West Africa.

According to the WHO, the program has so far saved 100,000 people from the immediate risk of contracting the disease and has prevented the potential infection of 12 million children. Also due to these efforts, over one million people infected with river blindness have been successfully treated.

Regulating Medical Recycling

On 1 November 1999 the U.S. Food and Drug Administration (FDA) announced proposals for new rules regarding the reuse of disposable medical devices including surgical clamps, cardiac catheters, and angioplasty balloons.



Critics allege this growing practice, adopted by some hospitals as a cost-cutting measure, poses health risks. The hospitals and companies that resterilize the items counter that the manufacturers of the items label them as disposable only to increase sales.

The FDA has been brought into the debate by Congress to determine which of the devices can be safely reused and how many times, and to classify disposable medical devices using these determinations. Under the proposed regulations, hospitals would have to register with the FDA if they choose to reuse these devices.