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Scientists Discover How UV Radiation Causes Cells to Die to Avoid Cancer Damage

Ultraviolet radiation from the sun can zap DNA, damage cells, and set the stage for the subsequent development of cancer. Scientists have now identified the built-in safety mechanism that forces some cells damaged by UV radiation to commit suicide so they do not perpetuate harmful mutations.

Alberto R. Kornblihtt, a Howard Hughes Medical Institute international research scholar at the University of Buenos Aires and the National Research Council of Argentina, has found that UV radiation causes human cells to create proteins that trigger cell death. It's a built-in safety pathway whose precise mechanism had never been seen before.

"It's better for the cell to die than to spread the mutations," Kornblihtt says. The findings were published in the May 15, 2009 issue of the journal *Cell*.

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All cells in the body rely on the same set of approximately 25,000 genes as the blueprint for the proteins they need to carry out their activities. They expand this limited repertoire through a mechanism called alternative splicing, which allows a cell to produce an assortment of different proteins from the same gene. They achieve this diversity by modifying messenger RNA (mRNA) molecules—the intermediary in the conversion from a gene to a protein.

In their experiments, Kornblihtt and his colleagues—an international team of laboratories from the U.S., France, and Spain—bombarded human cells with a highly energetic form of UV radiation that is typically blocked by the ozone layer, called UV-C. They then looked inside the damaged cells for mRNA, which ferries the genetic message from gene to protein. By examining the sequence of nucleotide letters in the mRNA, Kornblihtt could see which

genes or parts of genes were used to make proteins in the damaged cells—and if they had been alternatively spliced.

They compared mRNA sequences from the damaged cells to the mRNA in healthy cells to see which genes were alternatively spliced. Using special chips that analyzed the mRNA of about 500 genes, Kornblihtt found that 14 percent of the genes switched forms in response to UV-C. “We found that UV radiation causes changes in alternative splicing, but only in a certain subset of genes,” Kornblihtt says.

Manuel Muñoz, a graduate student in Kornblihtt’s lab who is first author of the *Cell* paper, decided to see if any of the genes that switched forms were important in apoptosis, the process that causes cells to commit suicide. Muñoz identified two genes, *Bcl-X* and *caspase 9*, that are known to be involved with apoptosis, or programmed cell death. Apoptosis culls unneeded cells during development and growth and protects organisms by killing defective cells. Defects in apoptosis can be harmful—leading to extended cell survival and the potential for the uncontrolled growth characteristic of cancer.

The *Bcl-X* and *caspase-9* genes can produce two different proteins via alternative splicing. For each gene, one version prevents cell death, while the other version encourages it. Kornblihtt and Muñoz found that, in both cases, UV radiation triggered production of the protein that encourages cell death. “This finding was really striking,” Kornblihtt says.

The researchers then repeated the experiments in cells missing a key protein called *p53*. Normally, *p53* triggers the cascade of events that lead to apoptosis in response to cellular damage. But even in cells lacking *p53*, UV radiation still caused apoptosis, with *Bcl-X* and *caspase 9* helping the process along. “We demonstrated that the cell death mechanisms we found are independent of *p53*,” Kornblihtt says. “That’s an important finding because *p53* is usually needed to cause apoptosis.”

To find out how UV damage induces cell death, Kornblihtt turned to his previous work studying alternative splicing, specifically a key enzyme called polymerase II. Polymerase II is like the Xerox machine of the cell. It reads DNA then makes mRNA copies, which are later processed to make proteins. Kornblihtt had previously shown that the speed that polymerase II moves along a strand of DNA determines whether an alternative splice of mRNA is made. If it moves quickly, the enzyme will skip over some segments of the DNA. But if it moves slowly, it will include those segments, leading to an alternative splice.

Kornblihtt and his colleagues looked to see if there were any obstacles in cells damaged by UV-C that might slow down polymerase II—and thereby induce alternative splicing. They fluorescently tagged the newly formed messenger RNA to measure polymerase II speed, and found that the enzyme slowed in response to UV radiation. This decrease in speed produced the

alternative forms of *Bcl-X* and *caspase 9* that then caused the cells to commit suicide.

Now the group plans to repeat the experiments with UV-A and UV-B, which are less energetic than UV-C but are more common causes of skin cell damage in people. Kornblihtt also wants to find out how UV-C causes polymerase II to slow down. "It's clear that UV radiation indirectly affects the speed of polymerase II," Kornblihtt says. "Although we don't know exactly how this happens yet."