MEMORIAL SLOAN-KETTERING CANCER CENTER • DECEMBER 2001

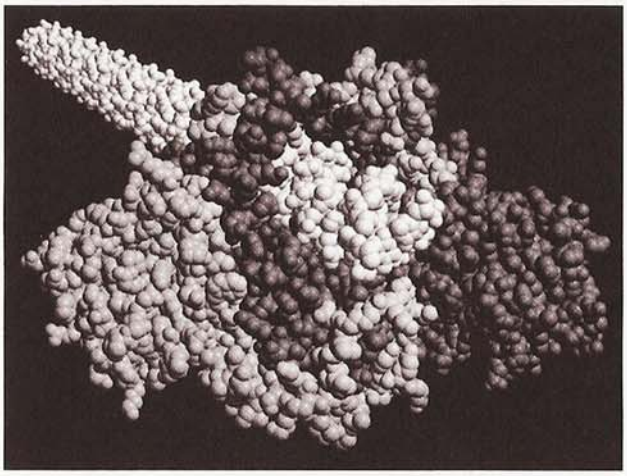
Center News

Keeping the Genome Intact: Suppression of Instability Protects Against Cancer

Like a book of life, DNA contains the instructions that organisms need to grow, reproduce, and perform all the other functions crucial to life. But in the same way that pages of a book can be torn out and lost or put back in the wrong order, DNA also can be damaged by losses, gains, or rearrangements, leading to mistakes in vital information.

Protecting the integrity of the genome — the total genetic content contained in the cells — is crucial because when that integrity is lost, genetic mutations result. The accumulation of these mutations can lead to many diseases, most notably cancer. DNA damage can occur spontaneously or can be induced by a variety of agents, including ionizing radiation, such as x-rays, and many chemotherapy drugs. There are many human syndromes that result from defects in DNA-repair processes (see sidebar on page 5).

MSK structural biologist and Howard Hughes Medical Institute Investigator Jonathan Goldberg recently made a major advance toward understanding one of the "caretakers" of genomic integrity



A molecular model illustrates the interaction between the Ku protein and DNA. The Ku70 subunit (black) and the Ku80 subunit (gray) come together to make Ku's ring-shaped structure. The ring surrounds DNA (white) and protects the broken strands until they are repaired.

when he published a paper in *Nature* elucidating the structure of a protein called Ku. The Ku protein was previously known, but until this study, no one knew how it performs its critical role — recognizing and repairing broken DNA strands.

Ku repairs double-strand breaks in DNA via a

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Protecting the Integrity of Genomic Information

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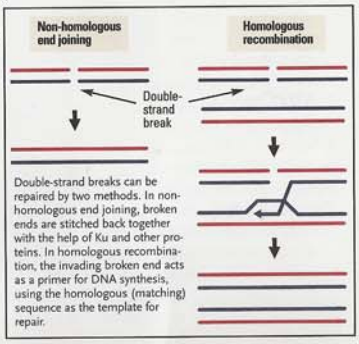
mechanism called non-homologous end joining (NHEJ), whereby broken strands are quickly stitched back together with a minimal loss of information. "Double-strand breaks are the most severe kind of DNA damage," said Dr. Goldberg. "Unlike single-strand breaks, in which genetic information is maintained on the strand that remains unbroken, if you break both strands you have the danger of permanently losing information."

Dr. Goldberg's laboratory crystallized the Ku protein and determined its structure using x-ray crystallography, which allows researchers to determine a molecule's shape by looking at how its atoms scatter x-rays. His results showed that Ku is shaped like a ring and that it recognizes broken strands of DNA by threading onto them like beads on a string. Ku then cradles the broken strands and prevents them from being degraded while at the same time assisting in the repair process. The precise mechanism of repair is not yet understood, however, and it's something Dr. Goldberg will continue to investigate.



Double-strand breaks can be repaired by two methods. In non-homologous end joining, broken ends are stitched back together with the help of Ku and other proteins. In homologous recombination, the invading broken end acts as a primer for DNA synthesis, using the homologous (matching) sequence as the template for repair.

In addition to breaks caused by agents such as radiation, double-strand breaks in DNA also occur naturally in the immune system. This process, called VDJ recombination, is part of gene-shuffling events that create diversity in the body's arsenal of antibodies. Ku also is involved in this process, because it's required to stitch together the broken ends after the genes have been spliced. "This process in immune cell is an important one for cancer biologists to study," Dr. Goldberg said, "because these breaks are thought to be the initiating steps in a number of cancers, including leukemias and lymphomas."

MSKCC investigators Jonathan Goldberg and Maria Jasin expand their understanding of genomic integrity by discussing their research results.

Gloria C. Li, of MSK's Department of Radiation Oncology, studies the role of Ku in repairing double-strand breaks resulting from ionizing radiation and VDJ recombination by looking at mice that have the Ku protein "knocked out." Ku is made of two subunits, called Ku70 and Ku80. Dr. Li has examined the function of each of them and found that both parts of Ku are essential for the normal development of the immune system. Mice lacking Ku80 have no B cells or T cells — two cell types critical to immunity. Mice lacking Ku70 have no B cells but some T cells; however, those mice had an ex-tremely high incidence of lymphoma. "This suggests that Ku80 performs the caretaker function," Dr. Li said, "whereas Ku70 may have a role in tumor suppression. In addition, mice with these mutations are extremely sensitive to radiation."

NHEJ is not the only way to repair DNA double-strand breaks. Another more complex but more accurate method is called homologous recombination, according to investigator Maria Jasin, William E. Snee Chair in the Cell Biology Program. Homologous recombination occurs when cells find genetic sequences on the chromosome that match the ones that are damaged and copy them back into the break site. This process has been long studied in lower organisms such as yeast, and Dr. Jasin's work has been key to showing its importance in mammals.

Much of Dr. Jasin's research centers on understanding how homologous recombination protects the genome, including the role that *BRCA1* and *BRCA2* (genes linked to hereditary breast and ovarian cancer) have in this process. The proteins made by these genes play their caretaker role by interacting with a protein called Rad51, which is required to repair breaks using homologous recombination. When these caretaker genes are mutated or missing, repair is faulty, creating a predisposition to cancer.

"When the proteins that preserve genomic integrity are corrupted," said Kenneth J. Marians, head of the Molecular Biology Program, "it can lead both directly and indirectly to cancer. Thus, understanding how these proteins work and cooperate with one another — which is a large part of what we do at MSK — is essential to understanding oncogenesis."

Genomic integrity research is a growing area for MSKCC. The Center recently recruited a new investigator, John H. Petrini, whose research at the University of Wisconsin Medical School has focused on a protein complex involved in DNA repair in both mammals and yeast. There also are several collaborations among different labs, both formal ones that result in publishing joint studies and more informal ones in which investigators toss around ideas and discuss results with each other.

"What's so important about genomic integrity research at MSK is the interplay of the different laboratories and the involvement of clinicians. For example our work with *BRCA1* and *2* has been in collaboration with Mary Ellen Moynahan of the Department of Medicine," said Dr. Jasin. "This is not research you can do in a vacuum, because the issues are very intertwined. Because we have a large number of investigators looking at different areas, we are able to gather a large picture of this field."

Defects Can Lead to Loss of Integrity

An inability to repair DNA double-strand breaks isn't the only way a cell's genomic integrity can be lost. MSK geneticist Nathan Ellis studies a variety of genetic and molecular mechanisms that cells use to maintain complete and correct genetic information. An error in any of these mechanisms has the potential to lead to the accumulation of genetic damage.

Much of Dr. Ellis's work focuses on Bloom's syndrome, a disease characterized by chromosome instability and a high frequency of genetic recombination, which result in susceptibility to many types of cancer. He also studies an inherited form of colon cancer that results from a defect in a DNA repair mechanism called the mismatch repair pathway. "Sometimes when DNA is copied during cell division, the wrong chemical compound is put in," Dr. Ellis said. "This pathway is supposed to correct that kind of error."

Other DNA repair defects can result in the loss of genomic integrity as well, Dr. Ellis said. For example, the syndrome xeroderma pigmentosum is caused by a defect in cells' ability to repair damage caused by the sun's ultraviolet rays — resulting in a major susceptibility to skin cancer. Other examples of syndromes resulting from defective repair and response to DNA damage include ataxia telangiectasia, Li-Fraumeni syndrome, Fanconi anemia, and Werner syndrome, all of which are characterized by increased cancer susceptibility.

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