



The image displays the crystal structure of a short DNA helix methylated on both strands at the center cytosines. The structure was taken from the Protein Data Bank (accession number 329D), with rendering using POV-Ray and postprocessing in Adobe Photoshop.

The Silencing of the Genes

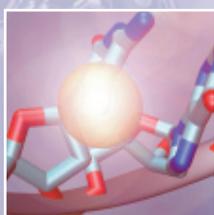
When we think of cancer, we usually think of gene mutations that ultimately cause cells to start dividing out of control. But increasingly, researchers are finding that mutations may not always be the crucial events in cancer—and that some cancers may even develop with minimal genetic mutations. In short, the starring role of genetics in cancer is under challenge from an up-and-coming field of study known as epigenetics.

Epigenetics involves the study of changes in gene expression that don't result from changes in the DNA sequence and that can be passed from one cell generation to the next. These gene-expression changes fundamentally

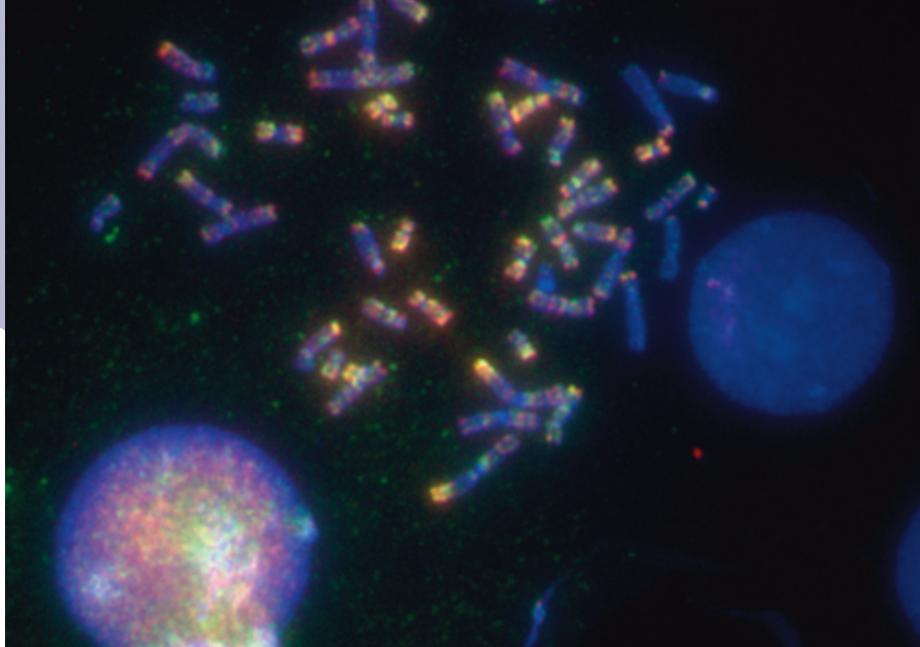
involve silencing genes so they can no longer produce the proteins that they code for.

Rather than altering DNA sequences, epigenetic changes “gum genes up”—studding genes with molecules that keep them from being expressed. The main epigenetic modification—adding methyl groups to the cytosine bases of DNA—acts like a switch to turn genes off.

You might assume that epigenetic gene silencing is always bad. But it's actually essential for life—and is happening in every cell type in our bodies right now to suppress the majority of genes whose expression isn't needed or wanted. Consider that your brain cells and liver cells are genetically identical but differ starkly in appearance



Epigenetic disturbances in chromosomes of acute lymphocytic leukemia cells. Regions featuring genes with lower-than-normal cytosine methylation (hypomethylation) are green, and regions with higher-than-normal cytosine methylation (hypermethylation) are red. Normal cells have a balance of these distributions, producing a yellow color throughout. But here, large areas of abnormal methylation appear as distinctly red and green regions, reflecting massive disturbances of epigenetic regulatory patterns seen in many types of cancer.



and function. The reason: different genes have undergone epigenetic gene silencing in brain cells than have been silenced in liver cells.

Unfortunately, it's just a small leap from "appropriate" gene silencing to faulty silencing that leads to cancer.

"Epigenetic gene silencing has been found in every type of cancer that researchers have looked at," says Dr. John Greally, Assistant Professor of Medicine and Molecular Genetics, who is spearheading epigenetics research at Einstein and is co-director of the Albert Einstein Cancer Center's Cell Growth and Differentiation Program.

So far, says Dr. Greally, studies have turned up nearly 70 genes that are epigenetically altered in cancer, with new ones being discovered almost weekly. Most of these inappropriately silenced genes are tumor suppressor genes, sometimes referred to as "guardians of the genome."

When DNA is mutated or damaged, tumor suppressor genes act to prevent cells from dividing until the DNA has been repaired. If repair isn't possible and cells are vulnerable to becoming cancerous, tumor suppressor genes either permanently prevent them from dividing or make them undergo programmed cell death (the process known as apoptosis). So the epigenetic silencing of tumor suppressor genes greatly increases the risk for cancer.

What causes this silencing of genes so vital to preventing cancer? "That's the \$64,000 question," says Dr. Ari Melnick, who is also an Einstein epigenetics researcher, the Diane and Arthur B. Belfer Faculty Scholar, and co-director of the Albert Einstein Cancer Center's Immuno-Oncology Program. According to Dr. Melnick, one major contributor to faulty gene silencing may well be the aging process. "We know that cancer tends to affect older people," Dr. Melnick notes, "and as people age, there appears to be a greater chance that random methylation of genes will occur that will be unfavorable to the cell and result in cancer."

The methyl groups responsible for

epigenetic gene silencing tend to cluster on a key part of genes: the promoter region, which initiates the transcription of DNA into RNA. Dr. Greally has developed a technique, called the HELP assay, that is able to detect the cytosine methylation "marks" throughout the genome, including every promoter region.

The HELP technique is showing that tumors can be differentiated according to their epigenetic "signature"—a finding that could have major practical implications. In a collaborative research effort, Drs. Greally and Melnick have determined that chemotherapy-sensitive and chemotherapy-resistant prostate tumors have very different epigenetic signatures.

"If we can classify patients according to their particular epigenetic subtype, we may be able to predict how they'll respond to therapy," says Dr. Melnick. "The ultimate goal is to tailor cancer therapy so that each patient will receive the optimal treatment based on their tumor's specific epigenetic signature."

Unlike gene mutations, epigenetic "marks" are not permanent and in fact are reversible—a finding that has excited cancer researchers. A number of drugs have shown promise for targeting and reversing aberrant epigenetic changes such as those that cause tumor suppressor genes to be silenced. In just the past two years, the U.S. Food and Drug Administration has approved two such drugs, and several other potential "epigenetic cancer therapies" are now being tested in clinical trials.

Drs. Greally and Melnick are involved in one of these trials, in which patients with a pre-leukemia condition called myelodysplastic syndrome are being treated with two different epigenetic therapies.

"We're hopeful that drugs targeting aberrant epigenetic changes will ultimately make a real difference in cancer treatment," says Dr. Greally. ■

Two major gifts are helping to enhance Einstein's leadership role as one of the nation's most prominent sites for the study of epigenetics.

Janet Hershaff, President of the National Women's Division New York Chapter and her husband, Arthur, a member of the College's Board of Overseers, have made a gift of \$500,000 to fund a new Cancer Center program studying epigenetic changes that lead to leukemia and lymphomas. Researchers will assess epigenetic changes using advanced technologies that have been developed at Einstein. One such technology, known as the HELP assay, can detect epigenetic changes at key regions in every gene. Mr. and Mrs. Hershaff's gift will support the work of Dr. John Greally, Assistant Professor of Medicine (hematology) and of Molecular Genetics, and Dr. Ari Melnick, Assistant Professor of Medicine (oncology) and of Developmental & Molecular Biology.

Another gift that will significantly aid research in epigenetics has been received from Mary and Jay Goldberg. Mr. Goldberg is also a member of Einstein's Board of Overseers. Their gift of \$100,000 will help to fund the purchase of powerful computers and other equipment that are critical to enhancing the epigenetic research program at Einstein.