When we think about the causes of cancer, gene mutations usually come to mind. But mutations are not the only culprits in cancer. Scientists now know that gene expression—whether a gene turns on or stays silent—is directed by chemicals that latch onto genes. These chemical alterations are referred to as “epigenetic” changes because—unlike mutations—they don’t alter the gene’s DNA structure. Instead, the epigenetic “marks” on genes control whether a gene is turned on or not.

One common epigenetic change occurs when bulky chemical units called methyl groups (chemical formula CH\(_3\)) latch onto genes. This is called methylation, and it generally prevents a gene from being turned on.

“Methylation is a normal way of regulating genes in the cell,” says Amit Verma, M.B.B.S., above left, associate professor of medicine and of developmental and molecular biology. “But it sometimes occurs inappropriately, turning off genes that suppress cell growth and division. When that happens, cancer can result.”

To study methylation, Dr. Verma needed a technique for scanning genes, looking for methyl groups—which is why he turned to John Greally, M.B., B.Ch., Ph.D., associate professor of genetics, for HELP.

HELP (which stands for Hpa II tiny fragment Enrichment by Ligation-mediated PCR) is a technique developed by Dr. Greally that allows investigators to evaluate
The Silence of the Genes (continued from page 1)

the methylation status of all 25,000 human genes. “Even though a gene may appear perfectly normal, with no mutations, its abnormal methylation pattern may tip us off to its role in causing cancer,” says Dr. Greally, who is also Einstein’s Faculty Scholar for Epigenomics, an endowed academic position established by Dr. Ruth L. Gottesman, chairperson of the Einstein Board of Overseers, and her husband, David S. Gottesman.

The good news: While correcting a DNA mutation is extremely difficult, methyl groups and other epigenetic marks are readily reversible. Fixing the aberrant chemical marks associated with cancer could lead to effective treatments or even cures.

Einstein researchers are using HELP to pinpoint epigenetic changes involved in several types of cancer.

Myelodysplastic syndrome

This group of blood conditions is sometimes referred to as “pre-leukemia” because about one-third of patients develop acute myeloid leukemia after a myelodysplastic syndrome (MDS) diagnosis.

The Food and Drug Administration has approved two methylation-blocking drugs for treating MDS. “Unfortunately, only about one in three MDS patients responds to the drugs,” says Dr. Verma. “Now, using Dr. Greally’s HELP assay, we’re identifying the epigenetic patterns in MDS patients who respond or don’t respond. Then treatment can be targeted to those patients most likely to respond.”

The Albert Einstein Cancer Center (AECC) is a National Institutes of Health–designated Myelodysplastic Syndromes Center of Excellence and serves as a national referral center for people with this disorder. “Our patients have access to more advanced therapies than are provided in the practice community,” says Dr. Verma. Einstein’s MDS research is supported by the NIH, the AECC and private donors. (See pages 3 and 4.)

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare but often fatal cancer. Einstein scientists led by Samir Parekh, M.D., assistant professor in the department of medicine (oncology), have identified clusters of genes in MCL cells with too much or too little methylation. Dr. Parekh and colleagues have shown that epigenetic drug combinations can reactivate tumor-suppressor genes in MCL cells. Such drug combinations might one day be used in addition to chemotherapies now in use against MCL.

Esophageal cancer

Cancer doesn’t develop overnight. The process often involves dozens of mutations and epigenetic changes that occur over many years. Dr. Verma is using HELP to track the epigenetic changes that occur when a condition known as Barrett’s esophagus (caused mainly by the acid reflux of chronic, severe heartburn) develops into often-fatal esophageal cancer.

“He’s dealing with the evolution of this cancer in the same way that developmental biologists deal with the development of an organism,” says Dr. Greally. “In an animal, you might go from a tadpole to a frog. In this cancer you go from inflammation through different stages until you get to a deadly cancer. We hope the pattern of epigenetic marks will tell us which patients with Barrett’s esophagus might be most at risk for developing esophageal cancer so that early treatment can be initiated.”

Q&A: Myelodysplastic Syndrome

Q: What causes myelodysplastic syndrome?

A: Some causes of MDS are unavoidable: advancing age, gender (it’s more common in men) and genes. But we can control one major MDS risk factor: smoking. Most of us know that smoking causes lung, mouth and throat cancers. We’re less aware that cancer-causing chemicals in tobacco smoke enter the bloodstream and can affect many parts of the body.
Blood Boosters

Patients with MDS and acute myeloid leukemia (AML) often develop thrombocytopenia, a deficiency of blood platelets. Platelets are necessary for the prevention of bleeding, and thrombocytopenia can be life-threatening in these patients. A new drug was recently approved for treating thrombocytopenia in people with hepatitis C. The drug works by stimulating the bone marrow to produce new blood cells. Researchers led by Ulrich Steidl, M.D., Ph.D., assistant professor in the department of cell biology and the Diane and Arthur B. Belfer Faculty Scholar in Cancer Research, have now shown that the drug effectively and safely boosts platelets in patients with MDS and AML. The study was published in the October 2009 issue of Blood. A clinical trial with this drug will be initiated soon.

New, Improved Inflammation Model

In one in five patients with inflammatory bowel disease (IBD), the condition progresses to colorectal cancer. Chronic inflammation is thought to be the main culprit when IBD morphs into cancer. But just how inflammation leads to tumor development hasn’t been clear. Now, AECC researchers led by Elaine Lin, Ph.D., assistant professor in the department of medicine oncology, have created a mouse model in which chronic inflammation spontaneously develops in the colon, followed by cancer in the inflamed regions. The novel mouse model has revealed a previously unrecognized molecular pathway that plays a key role when chronic inflammation gives rise to tumors, according to a study Dr. Lin and her colleagues published in the February 2010 issue of the American Journal of Pathology.

Reining In Runaway Cell Growth

In normal cells, a tumor-suppressing protein called the retinoblastoma protein (pRb) silences certain genes, preventing uncontrolled growth and division of cells. But when pRb is inactivated, the genes it normally silences turn on—resulting in cell proliferation and tumors. One way to halt cell growth would be to silence pRb’s target genes when pRb is inactivated. Liang Zhu, M.D., Ph.D., and his colleagues have done just that; by disabling Skp2, a cancer gene normally kept in check by pRB, they were able to prevent tumors from developing in mice that lacked pRB. Their findings, published in the January 2010 issue of Nature Genetics, suggest that Skp2 might be a good target for drugs that could treat or prevent tumors when pRB can’t do its cancer-control job.

ON THE WEB

To learn more about the Albert Einstein Cancer Center, please visit www.einstein.yu.edu/cancer.

AECC ADVANCES: COLLABORATING AGAINST CANCER

Research collaboration was the watchword at the 2010 Albert Einstein Cancer Center Advances retreat, held in May. Jeffrey Segall, Ph.D., professor of anatomy and structural biology and the Betty and Sheldon Feinberg Senior Faculty Scholar in Cancer Research, encouraged the 110 attendees from many different Einstein departments to look for opportunities to collaborate with their colleagues. Affirming the importance of teamwork in research, AECC director Dr. I. David Goldman reminded center members of the importance the National Cancer Institute assigns to the synergy of collaborative research when evaluating cancer centers. Dr. Goldman thanked the AECC’s generous supporters, acknowledging a recent $500,000 gift from Myles P. Dempsey Sr. and his wife, Jane, that will help fund pilot projects aimed at developing new approaches to diagnosing and treating breast cancer.

Among the attendees at the AECC Advances meeting were, from left: Rose Dempsey Dahlman; John S. Condeelis, Ph.D., the Judith and Burton P. Resnick Chair in Translational Research and coleader of the AECC’s Breast Cancer Working Group; Jeffrey W. Pollard, Ph.D., the Louis Goldstein Swan Chair in Women’s Cancer Research; Dr. Goldman; Jane A. Dempsey; Myles P. Dempsey Sr., founder and chairman of Tech Air, a leading regional provider of industrial, medical, and specialty gases; Myles P. Dempsey Jr., president of Tech Air; and Joseph A. Sparano, M.D., coleader of the Breast Cancer Working Group. (Dempsey family members not pictured: Marilyn Dempsey, Craig Dalhman, Katy Dempsey Haley, Kevin Haley, Kelly Dempsey Connolly, Mark Connolly, Jennifer Dempsey Torre and Edward Torre.)
NOTABLE GIFTS AND GRANTS

The Albert Einstein Cancer Center gratefully acknowledges the generosity of the following individuals and organizations whose support is critical to advancing its mission.

Einstein Overseer Linda Altman and her husband, Earle Altman, have made a commitment of $1,250,000 to support the laboratory of Steven Libutti, M.D., professor in the departments of surgery and of genetics and associate director for clinical services at the AECC. Dr. Libutti is studying how substances produced by tumors encourage angiogenesis (blood vessel growth)—which allows tumors to thrive and spread—and how it can be blocked.

Einstein Overseer Arthur Hershaft and his wife, Janet Hershaft, have pledged $500,000 to establish an shRNA functional genomics facility at Einstein. ShRNA stands for “small hairpin RNA,” a sequence of RNA that makes a tight hairpin turn that can be used to turn off the expression of specific genes. The new facility will enable Einstein researchers to identify the genes responsible for cancer and other potentially life-threatening diseases.

Gabrielle’s Angel Foundation for Cancer Research has donated $225,000 to support the research of Ulrich Steidl, M.D., Ph.D., the Diane and Arthur B. Belfer Faculty Scholar in Cancer Research, on acute myeloid leukemia, with a particular focus on leukemia stem cells. (See page 3.)

The Kimmel Foundation for Cancer Research has awarded a $200,000 Kimmel Scholar Award to Matthew Gamble, Ph.D., assistant professor of pharmacology. Dr. Gamble is one of 15 young U.S. scientists selected this year by the prestigious Kimmel Scholar Program. He is studying two families of proteins that interact abnormally in cancer—research that may lead to more targeted drug treatments.

EVENTS

Einstein’s Cancer Research Advisory Board hosts events during the year that bring together people interested in supporting the work of the Albert Einstein Cancer Center with distinguished Einstein faculty members who share the latest developments in cancer research.

Friends and supporters of the Albert Einstein Cancer Center attended a cocktail reception hosted by Zina and Andy Klang on June 17 at the Trump National Golf Club in Briarcliff Manor, NY.

Following introductory remarks by Allen M. Spiegel, M.D., Einstein’s Marilyn and Stanley M. Katz Dean, Dr. I. David Goldman, the AECC director and Susan Resnick Fisher Professor, gave an overview of new center initiatives. John S. Condeelis, Ph.D., codirector of Einstein’s Gruss Lipper Biophotonics Center and the Judith and Burton P. Resnick Chair in Translational Research, then discussed his pioneering research into the problem of tumor cell invasion and metastasis. His presentation was followed by a thoughtful question-and-answer session.

“It was inspiring to hear about the progress Dr. Condeelis and his colleagues are making in gaining new insights into how cancer spreads,” said Ms. Klang.

“There is exciting research going on at our cancer center. It’s so important for us to spread the word about the advances being made in AECC laboratories,” said Einstein Overseer Marilyn Katz, chair of the Cancer Research Advisory Board. “We are extremely grateful to Zina and Andy for making tonight’s enlightening and informative program possible.”

To learn more about supporting the work of the Albert Einstein Cancer Center, please contact:

IRA LIPSON
Director of Institutional Advancement
Albert Einstein College of Medicine
Jack and Pearl Resnick Campus
1300 Morris Park Avenue, Mazer 725
Bronx, NY 10461
718.430.2371
ira.lipson@einstein.yu.edu

ALBERT EINSTEIN CANCER CENTER

Our mission: to promote and carry out research that will yield insights into the origins of cancer and lead to effective new approaches for preventing, diagnosing and treating malignant diseases

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