Logic and Lung Cancer

“Smoking damages mainly the lungs, so what better way to counteract that damage than to go in like the smoke itself—through the airways?” says Roman Perez-Soler, M.D., professor of medicine and oncology division chief. Dr. Perez-Soler and his co-investigator, Yiyu Zou, Ph.D., associate professor of medicine (oncology), are using this strategy against lung cancer, which kills about 150,000 Americans each year and is the leading cause of cancer death.

Lung cancer is so lethal because it has usually spread to other organs by the time it’s detected. But what if it could be found much earlier? “In smokers, cells in the bronchial epithelium [lung lining] are hit by carcinogen-laden smoke, which damages DNA,” explains Dr. Perez-Soler, who is also associate director of clinical research and co-leader of the Developmental Therapeutics Program at the Albert Einstein Cancer Center, and chair and chief of oncology at Montefiore Medical Center, the University Hospital and academic medical center for
lung cancer is the leading cause of cancer deaths among men and women in the United States. Cigarette smokers are at markedly increased risk of developing this disease. Unfortunately, by the time the disease can be diagnosed, most cases are not curable because the cancer is so far advanced.

Eliminating smoking will prevent the vast majority of lung cancers and other cancers that affect the upper airways. However, people who have already been exposed, and people who cannot or will not stop smoking, present formidable challenges. For them, we need to develop new approaches that detect lung tumors early enough to be cured by surgery or radiation.

This issue of Einstein Cancer Center News describes a collaborative project that brings together a multidisciplinary team of scientists focused on detecting and defining the early defects in genes that lead to lung cancer and designing a strategy for reversing these genetic changes. What is particularly novel about this approach is that it is noninvasive: both diagnosis and treatment are carried out via the respiratory airway. This project, led by Dr. Roman Perez-Soler, is an example of “translational” research at the Albert Einstein Cancer Center, where promising discoveries that originate in the lab are evaluated in mouse models and then translated into initiatives in humans.

Einstein. Damaged lung cells can linger in a premalignant state for many years. Things go wrong, he explains, when cells can no longer prevent bulky chemical units called methyl groups from inactivating tumor-suppressor genes that normally put a brake on cell division. These reversible changes to genes are referred to as “epigenetic,” in contrast to gene mutations that are permanent—and Drs. Perez-Soler and Zou hope to take advantage of that reversibility.

Follow the Smoke

Their novel therapy involves inhaling a “demethylating” drug called 5-azacytidine. Ideally, it will reactivate tumor-suppressor genes by stripping off the methyl groups that have silenced them. Inhalation therapy is an ideal approach for treating bronchial premalignant lesions and small cancers that have not yet spread: “The drug is toxic, but the doses delivered directly to the damaged tissue in this way are very small,” says Dr. Perez-Soler.

Last year the National Institutes of Health awarded the researchers a five-year, $2.5 million grant to develop this inhalation therapy, now being tested in mice for safety and efficacy. “After we determine the highest nontoxic dose, we’ll extrapolate to humans, write a clinical protocol and start treating patients at Montefiore,” says Dr. Perez-Soler.

Early Warning

The first people treated—probably beginning next year—will be patients with lung cancer whose therapy has failed. But the researchers’ ultimate aim is to intervene with inhaled 5-azacytidine at an earlier, premalignant stage. A technique developed by Simon D. Spivack, M.D., M.P.H., professor of medicine (pulmonary medicine), of epidemiology & population health and of genetics, will help identify those people most likely to benefit from the inhalation therapy. Dr. Spivack analyzes the DNA contained in exhaled breath, looking for genetic “signatures” indicating that someone is at high risk for lung cancer. Dr. Spivack is also chief of pulmonary medicine at Einstein and Montefiore, and co-director of the Montefiore Asthma Center.

John Greally, M.B., B.Ch., Ph.D., associate professor of genetics, of medicine (hematology) and of pediatrics, has developed a technique called the HELP assay that detects methyl groups at key locations in every human gene. The HELP assay will be used before and after inhalation therapy to reveal whether the therapy is having the desired demethylating effect on genes. Dr. Greally is also the Faculty Scholar for Epigenomics and attending physician in pediatrics at The Children’s Hospital at Montefiore.

Q: Do people exposed to secondhand smoke experience the same sort of gene silencing in their lung tissue as smokers do?

A: A study published in Mutagenesis earlier this year found similar DNA methylation patterns in lung tumors of smokers and of never-smokers exposed to secondhand tobacco smoke. But a smoker’s exposure to tobacco smoke is far greater and incurs a much higher cancer risk. Compared with never-smokers, people who currently smoke have a 15- to 20-fold increased risk of developing lung cancer, while a never-smoker chronically exposed to secondhand smoke has only about a 25 percent increased risk for lung cancer.
Cancer's Hearty Appetite

Ana Maria Cuervo, M.D., Ph.D.
Professor, Developmental and Molecular Biology
Professor, Anatomy and Structural Biology
Professor of Medicine (Gastroenterology & Liver Diseases)
The Robert and Renée Belfer Chair for the Study of Neurodegenerative Diseases
Albert Einstein College of Medicine

Cancer cells require energy in the form of glucose (sugar) to grow. How do they meet that need? A new study shows that they rev up autophagy (“self-eating”), in which cell compartments called lysosomes digest worn-out proteins and other damaged cellular components. Dr. Cuervo and her colleagues detected unusually high levels of one type of autophagy, chaperone-mediated autophagy, in cells from more than 40 types of human cancers—but not in healthy tissue. When they blocked this autophagy in mice, the cancer cells stopped dividing, and most died because they were no longer able to use sugar as fuel; the researchers observed dramatic tumor shrinkage and nearly nonexistent metastasis. The findings were published in Science Translational Medicine in 2011. Dr. Cuervo is working to identify or develop drugs that block autophagy.

Genes at Work

Robert H. Singer, Ph.D.
Professor and Co-Chair, Anatomy and Structural Biology
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Cell Biology
Co-director, Gruss Lipper Biophotonics Center
Albert Einstein College of Medicine

Dr. Singer and his colleagues recently watched, for the first time, the process of gene transcription, which occurs when a gene converts its DNA information into molecules of messenger RNA that then make the protein encoded by the gene. Proteins govern the body’s structure and function, and underlie cancer and many other diseases when mutated or present in aberrant amounts. When the scientists inserted DNA sequences into a gene in live yeast cells, RNA made from these sequences bound a green fluorescent protein; expression of the entire gene resulted in messenger RNA molecules visible under fluorescent light. The study was published in a 2011 issue of Science.

Reversing Resistance

Sridhar Mani, M.D.
Professor of Medicine (Oncology)
Professor of Genetics
The Miriam Mandel Faculty Scholar in Cancer Research
Albert Einstein College of Medicine
Attending Physician in Oncology
Montefiore Medical Center

How do cancers become resistant to anticancer drugs? One culprit may be the pregnane X receptor (PXR), a protein in the nucleus of cells that senses toxic substances and responds by mobilizing the cell’s detoxification mechanisms. By grafting human colon cancer cells into immunodeficient mice, Dr. Mani and his colleagues found that activated PXR not only resulted in drug resistance but also spurred tumor cells to multiply, invade and metastasize. The researchers also found that activation of PXR required fibroblast growth factor 19. Insights gleaned from this study could lead to improved treatments for colon and other cancers. The study was published in a 2011 issue of the Journal of Clinical Investigation.

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

updates

Welcome

Einstein recently recruited two experts on cancer stem cell biology.

Wenjun Guo, Ph.D., from the Whitehead Institute for Biomedical Research, studies the molecular mechanisms that control whether stem cells in mammary tissues remain dormant, multiply or differentiate into other types of cells. Dr. Guo came to Einstein in 2011 as an assistant professor of cell biology. One focus of his research will be breast cancer stem cells.

Keisuke Ito, M.D., Ph.D., from Harvard Medical School, arrived in 2012 as an assistant professor of cell biology and of medicine and serves as the director of scientific resources for the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research. Dr. Ito’s academic interests include the critical regulatory mechanisms in the controlled equilibrium of healthy and leukemia stem cells. His research focuses on developing more-effective drugs for patients with hematological malignancies.
The Helen and Irving Spatz Foundation has made a commitment of $1 million to support clinical trials in cancer. This investment will help Einstein investigators advance their efforts to find new and improved cancer treatments.

Funds totaling $215,659 were received from the Estate of Ruth Brandes for cancer research.

The Breast Cancer Research Foundation has renewed grants totaling $675,000 to support research studies by Rachel Hazan, Ph.D.; Susan Band Horwitz, Ph.D., the Rose C. Falkenstein Chair in Cancer Research, and Hayley M. McDaid, Ph.D.; and Thomas E. Rohan, M.D., Ph.D., the Atran Foundation Chair in Social Medicine.

The Avon Foundation for Women has awarded a grant of $125,000 to B.BOLD Buddies, a component of the Bronx Breast Oncology Living Daily (B.BOLD) program that offers one-on-one peer support for patients with breast cancer. B.BOLD is directed by Alyson B. Moadel, Ph.D., head of the Psychosocial Oncology Program at the AECC.

Our mission: to promote and conduct research that will elucidate the origins of cancer and lead to effective new approaches for the prevention, diagnosis and treatment of malignant diseases

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From left: Dean Allen M. Spiegel, M.D.; AECC Director I. David Goldman, M.D.; Overseers Kathy K. Weinberg and Samuel G. Weinberg; and Vern L. Schramm, Ph.D., the Ruth Merns Chair in Biochemistry.

Einstein National Women’s Division, and Overseer Samuel G. Weinberg at their Greenwich, CT, home.