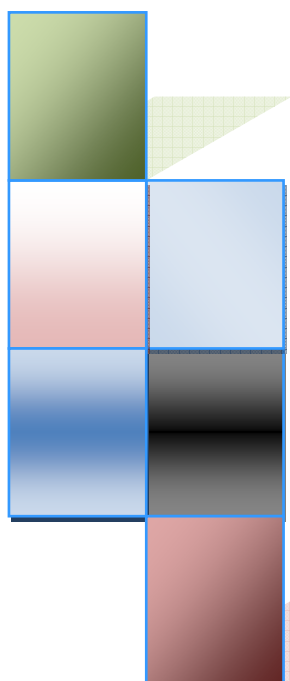


NanoCinna
Pharmacogenomics Center

Genomics News

Archive Dec 2010 – Apr 2011



5th Floor, No.56, Azimi St. Phase 1, Shahrak Ekbatan. Tehran-Iran
Tel: + 98-2144654896, +98-21-44654490
Fax: +98-21-44654896
www.nanocinna.net

Contents	Page
Mechanism that controls cell movement linked to tumors becoming more aggressive	3
New Gene for Childhood Cancer Neuroblastoma is Discovered	4
Nanostart AG: Successful Exit in the US	5
Gene duplication detected in depression	6
Protein protects cancer cells from oxidative stress	7
Detecting Cancer Early	8
Your Genome in Minutes: New Technology could Slash Sequencing Time	9
Genome of extinct Siberian human sheds new light on modern human origins	10
Mammalian aging process linked to overactive cellular pathway	12
Age doesn't matter: New genes are as essential as ancient ones	13
Researchers Illuminate Genetic Code for a Form of Pancreatic Cancer	14
Researchers believe EMT is the Dominant Program in Human Colon Cancer	15
Fat Associated With Chemical Changes in DNA That May Help Explain Obesity-Related Disease	16
DAXX/ATRX, MEN1, and mTOR Pathway Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors	18
Study in Mice Uncovers Pathway Critical for UV-Induced Melanoma	19
Strand-specific Transcriptome Profiling with Directly Labeled RNA	21
Researchers use Cell "Profiling" to Detect Abnormalities -- Including Cancer	22
NIH Researchers Extend use of Gene Therapy to Treat a Soft Tissue Tumor	23
Exiqon Announces 2011 Grant Program for MicroRNA Research	24
Scientists Find Key Protein That Suppresses Prostate Cancer Growth in the Laboratory	25
Method of DNA repair linked to higher likelihood of genetic mutation	26
Whole Genome Sequencing used to Help Inform Cancer Therapy	27
How disordered proteins spread from cell to cell, potentially spreading disease	29
Gene fuelled transporter causes breast cancer cells to self-destruct	31
York U researchers uncovering how ovarian cancer resists chemotherapy	32
Gene expression to distinguish metastasizing from non-metastasizing head and neck cancers	33
Discovery and Annotation of Small Proteins Using Genomics, Proteomics and Computational Approaches	34
Novel mechanism for control of gene expression revealed	35
Combination Overcomes Breast Cancer Resistance to Herceptin	36
Gene That Mediates Response to Key Cancer Drugs Frequently Mutated in Young Leukemia Patients Who Relapse	38

Contents	Page
Researchers develop new cancer treatment	40
New computer-based system can distinguish similar secondary tumours	41
Scientists Discover a Way to Kill Off Tumors in Cancer Treatment Breakthrough	42
Tumors Resistant to Radiation Therapy May Be Controlled by the MET Oncogene	43
Common Variant of P53 Tumor Suppressor Gene Linked to Increased Inflammatory Responses	44
Stress Signal in Cancer Cells Triggers Similar Response in Other Cells, Aiding Tumor Growth	45
DNA of 50 Breast Cancer Patients Decoded	46

Mechanism that controls cell movement linked to tumors becoming more aggressive

Dec 01, 2010

Athens, Ga. – Researchers at the University of Georgia have discovered a central switch that controls whether cells move or remain stationary. The misregulation of this switch may play a role in the increased movement of tumor cells and in the aggressiveness of tumors themselves.

"Malignant cancer arises when cancer cells acquire the ability to move away from their primary tissue location," said Natalia Starostina assistant research scientist in the UGA department of cellular biology and lead author of the research. "The control of cell movement is a fundamental aspect of animal development, and defects in cell movements can have devastating results ranging from tumor metastasis to vascular disease. " The movement of cells requires the "remodeling" of a supporting cell structure called the actin cytoskeleton. Starostina's research focused on how actin remodeling is controlled and how this regulates the movement of cancer cells.

The study was just published in the journal *Developmental Cell*. In addition to Starostina, other authors include Jennifer Simpliciano, undergraduate student; Michael McGuirk, lab technician; and Edward Kipreos, head of the lab. Cellular biology is a division of biological sciences in the Franklin College of Arts and Sciences.

The research by Kipreos' group focused on an unlikely source to control cell movement, a CKI protein. CKIs were originally identified as inhibitors of the cell cycle that function in the nucleus to prevent cells from dividing. Surprisingly, in the last few years, scientists noticed that certain very aggressive tumor cells had high levels of CKI in the cytoplasm, which is the part of the cell surrounding the nucleus. Kipreos' team discovered that a protein known as LRR-1 degrades a CKI called p21 specifically in the cytoplasm of human cells. If LRR-1 is inactivated, then p21 accumulates in the cytoplasm, where it induces the remodeling of the actin cytoskeleton and increases cell movement. One unique aspect of this discovery is that LRR-1 only affects p21 levels in the cytoplasm (where p21 regulates the actin cytoskeleton) but not in the nucleus (where p21 inhibits cell division). "The finding that LRR-1 controls p21 levels only in the cytoplasm was unexpected," said Kipreos, who also is a researcher in the UGA Cancer Center.

The accumulation of p21 in the cytoplasm causes the rearrangement of the actin cytoskeleton so that rod-like filaments made of actin are broken down, and the released actin is relocated to the periphery of cells where it promotes cell movement.

"While it was known that p21 is involved in remodeling the cytoskeleton, nobody had looked at its effects on cell motility," said Kipreos.

Scientists had previously observed that the accumulation of cytoplasmic p21 in a number of human cancers is associated with high tumor grade and poor prognosis. The Kipreos team's research shows that tumor cells with cytoplasmic CKI have increased movement, suggesting the reason these tumor cells are more aggressive is because their enhanced cell movements lead to metastasis in which the cancer spreads through the body.

"This work provides a key insight into how the movement of cells is controlled and explains why cancers with high cytoplasmic CKI levels are so aggressive," said Kipreos.

The team's initial breakthrough in linking LRR-1 to the degradation of CKI came from studying the small roundworm *Caenorhabditis elegans*. They found that in the worm LRR-1 specifically degrades the nuclear form of CKI to allow cells to divide.

"We thought it was very interesting that in worms, LRR-1 degrades a CKI in the nucleus to regulate cell division, while in humans, it degrades a CKI in the cytoplasm to control cell movement," said Starostina. Exactly how the new information might be used to develop diagnostics or therapies to treat cancer awaits development. But the discovery of this new regulatory pathway gives researchers a target that could one day allow them to slow the spread of tumors or halt cancer cells in their tracks.

**For more information about the UGA department of cellular biology, see <http://www.uga.edu/cellbio/>.
For more information about the UGA Cancer Center, see <http://www.uga.edu/cancercenter>.**

New Gene for Childhood Cancer Neuroblastoma is Discovered

Dec 03, 2010

Pediatric cancer researchers have identified variations in a gene as important contributors to neuroblastoma, the most common solid cancer of early childhood. The study team, led by researchers at The Children's Hospital of Philadelphia, found that common variants in the LMO1 gene increase the risk of developing an aggressive form of neuroblastoma, and also mark the gene for continuing to drive the cancer's progression once it forms.

The study appears online in *Nature*. A cancer of the sympathetic nervous system that usually occurs as a solid tumor in the abdomen, neuroblastoma accounts for 10 percent of childhood cancer deaths.

"Although genes closely related to LMO1 have previously been implicated in other cancers, this gene was not previously suspected to have a role in neuroblastoma," said study leader John M. Maris, M.D., director of the Center for Childhood Cancer Research at The Children's Hospital of Philadelphia. "We found that in addition to putting a child at risk of developing neuroblastoma, it acts as an oncogene - driving the biological changes that make tumors grow and spread throughout the body. "Although direct clinical applications are not immediate, Maris added, investigating this oncogene may suggest targets for developing more effective neuroblastoma treatments.

Maris collaborated with Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia, and co-senior author on the study, as well as with a large team of international investigators in performing a genome-wide association study (GWAS). They analyzed DNA samples from 2,251 patients (most of which were provided by the multicenter Children's Oncology Group) along with 6,097 control samples.

The researchers found a significant association between neuroblastoma and the LMO1 gene, located on chromosome 11, detecting the strongest signal among patients with the most aggressive form of the disease. This portion of the study identified SNPs, changes in a single letter within the DNA sequence, which predispose a child to developing neuroblastoma.

The study team then searched for copy number alterations - duplications or deletions of stretches of DNA - across the whole genome in neuroblastoma cancer cells. Again, the LMO1 gene displayed abnormal changes: duplicated sections of DNA that tended to occur in a significant percentage of tumors. "The normal role of the LMO1 gene is mainly to regulate gene transcription in the nervous system," said Maris. In gene transcription, DNA-encoded information is converted to RNA, part of the process by which a gene carries out biological functions. "The abnormalities we have found in this gene result in abnormally increased activity, driving an overproduction of cells into a tumor."

To further investigate the gene's role, the researchers used genetic tools to decrease LMO1's activity, and showed that this inhibited the growth of neuroblastoma cells in culture. Increasing LMO1 gene expression had the opposite effect, causing tumor cells to proliferate.

Because other genes in the LMO family are known to be active in acute leukemias, other researchers have been investigating potential anti-leukemia drugs to target portions of the LMO pathway. However, added Maris, using this knowledge to develop treatments for either leukemia or neuroblastoma will require much further work.

In the meantime, Maris suggests, the current research suggests that GWAS studies, already widely employed to identify common gene variants that confer disease risk, may also have another benefit, in indicating that the same genetic region may have a strong impact on cancer progression. "The real potential of studies like this may be in discovering new therapeutic targets."

Hakonarson agrees, adding that, "This is a prime example in which integrative genomics, combining SNP discovery arrays with gene expression arrays and other functional approaches, holds great promise in expanding our knowledge base for translating genetic discovery to clinical uses."

Further Information: <http://www.chop.edu>

Nanostart AG: Successful Exit in the US

Dec 02, 2010

FRANKFURT, Germany & SALT LAKE CITY, (BUSINESS WIRE)

Nanostart holding BioMicro has sold its remaining assets for a profit to US diagnostics company IRIS for 3.2 million US dollars. The asset sold is an analysis product line that automatically performs high-performance tests on the genetic material of somatic cells. With this transaction, the remaining assets of BioMicro have now been successfully sold. In March of this past year, BioMicro sold its main product – the entire MAUI system line – to global leader Roche within the framework of an asset deal.

A portion of revenues from the transaction will be entered as net income on the 2010 annual financial statement. The remaining portion will be applied to the first half of 2011. With an 8.4 percent holding in BioMicro, Nanostart will receive a corresponding disbursement from the transaction. Upon completion of the upcoming payments, the exit of BioMicro from the Nanostart portfolio will have reached a successful conclusion.

Nanostart CEO Marco Beckmann observes: "The shareholding in this highly innovative company has paid off for us. The transaction marks yet another successful exit and confirms our position as the world's leading nanotechnology investor. With the sale of BioMicro assets to a life science company, Nanostart has achieved its objective."

Further Information: <http://www.nanostart.de>

Gene duplication detected in depression

Dec 01, 2010

Finding by CHOP researchers points to disruptions in brain signaling networks

A large genetic study of people with major depression has found that a duplicated region of DNA on chromosome 5 predisposes people to the disorder. The gene involved plays an important role in the development of nerve cells, adding to evidence that disruptions in neurotransmission networks form a biological basis for depression. "The copy number variations we discovered were exclusive to people with depression, and were located in a gene region important in signaling among brain cells," said study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "This finding extends work by other researchers suggesting that disruptions in neurotransmitter networks in the brain are an underlying cause of major depressive disorders." The study appears online today in Public Library of Science One (*PLoS One*). The current research is the first large-scale genome-wide study of copy number variation (CNV) in major depressive disorder (MDD), a major psychiatric and behavioral disorder affecting an estimated 16 percent of the U.S. population. CNVs are deletions or duplications of segments of DNA. While a specific CNV is relatively rare in a population, it often exerts a strong effect on an individual who harbors the CNV in their genes.

Hakonarson's group conducted a whole-genome scan of DNA from 1,693 patients with MDD, mainly from a European database, and from 4,506 control subjects. The researchers identified 12 CNVs exclusive to MDD cases. Their most notable finding was a large duplication of DNA segments on chromosome 5q35.1, a CNV shared by five unrelated patients and not observed in healthy controls. Residing at that location is the gene *SLIT3*, which is involved in axon development. The axon is the portion of a neuron that carries nerve impulses away from the cell body. Hakonarson added that he plans follow-up studies with more refined sequencing technology, in which he expects to identify many more CNVs and possibly other types of mutations in the *SLIT3* gene, as well as in other functionally related genes that may predispose to depression. Further studies may also reveal how strongly CNVs at *SLIT3* and other related genes contribute to the risk of depression. "Clinical applications for our discoveries are still in the future, but it may be possible at some point to incorporate these findings into personalized medicine," Hakonarson said. "Identifying causative genes may suggest future targets for drug development, and may also help us predict a person's future risk of developing depression," he added. Hakonarson's group used genotype data from the Genetic Association Information Network and from the database of Genotype and Phenotype (dbGaP) of the National Institutes of Health. Funding for the study came from an Institutional Development Award from The Children's Hospital of Philadelphia and from a Research Development Award from the Cotswold Foundation. "Duplication of the *SLIT3* Locus on 5q35.1 Predisposes to Major Depressive Disorder," *PLoS One*, published online Dec. 1, 2010.

About The Children's Hospital of Philadelphia: The Children's Hospital of Philadelphia was founded in 1855 as the nation's first pediatric hospital. Through its long-standing commitment to providing exceptional patient care, training new generations of pediatric healthcare professionals and pioneering major research initiatives, Children's Hospital has fostered many discoveries that have benefited children worldwide. Its pediatric research program is among the largest in the country, ranking third in National Institutes of Health funding. In addition, its unique family-centered care and public service programs have brought the 460-bed hospital recognition as a leading advocate for children and adolescents.

For more information, visit <http://www.chop.edu>.

Protein protects cancer cells from oxidative stress

Dec 01, 2010

High levels of a protein called thioredoxin-like 2 helps protect cancer cells from the oxidative stress that they generate as they grow and invade tissues throughout the body, said a consortium of researchers led by those at Baylor College of Medicine (www.bcm.edu) in a report in the *Journal of Clinical Investigation* (<http://www.jci.org>).

When Dr. Ning-Hui Cheng (<http://www.bcm.edu/cnrc/faculty/index.cfm?pmid=9524>), an instructor at the USDA/ARS Children's Nutrition Research Center (<http://www.bcm.edu/cnrc/>) at Baylor College of Medicine and Texas Children's Hospital, and his colleague Dr. Xiaojiang Cui (then at BCM and now at the John Wayne Cancer Institute in Santa Monica, Calif.) looked for the protein in human breast cancer cells, they found it exists there at high levels. When they removed the protein from the cancer cells, the levels of oxidative stress (called reactive oxygen species or ROS) increased and an important signaling activity called NF-kB were reduced. As a result, the cells ceased growing and invading.

"They did not thrive. Cancer cells can use this as a weapon to keep oxidative stress at a level that is toxic to normal cells but can be tolerated by cancer cells," he said. This ability to withstand oxidative stress is one reason cancer cells can resist anti-cancer drugs, he said.

"Our data show that this protein is highly expressed in cancer cells lines and in patients," he said. This makes thioredoxin-like 2 (also called glutaredoxin 3) a promising target of future drug development, said Cheng.

"We could use an inhibitor to reduce the levels of the protective protein. When the reactive oxygen species levels go up, it kills the cancer," he said. He thinks this protein plays an important role in the spread of cancer or metastasis.

The protein is essential for normal growth in developmental stages, he said. Mice bred to lack this protein die before birth.

"Cells that lack this protein cannot survive," he said. "The difference is that cancer cells produce too much and they survive as well.

He and his colleagues have found high levels of protein in other cancers as well. In future studies, they hope to find out whether the protein causes cancer or just maintains it. Others who took part in this work include Bolanle A. Bukoye, Adrian Lee and Jian Huang of BCM; Ying Qu and Bingya Liu of Shanghai Jiaotong University School of Medicine; Jinhua Wang, Miyung Shin-Sim, Armando E. Giuliano and Partha S. Ray of the John Wayne Cancer Institute in Santa Monica, California; Hua Guo and Ning Zhang, of Tianjin Medical University in China; Xin Lin and Peng Huang, of The University of Texas MD Anderson Cancer Center, and John W. Martens of Erasmus Medical Center in Rotterdam, The Netherlands.

Funding for this work came from the Susan B. Komen Breast Cancer Foundation, the Avon Foundation, Del Webb Foundation, and The United States Department of Agriculture/Agricultural Research Service under a cooperation agreement.

When the embargo lifts, this report is available at <http://www.jci.org/>.

For more information on basic science research at Baylor College of Medicine, please log on to www.bcm.edu/fromthelab.

Detecting Cancer Early

Feb 09, 2010

The earlier the doctor finds the tumor, the better the patient's chances of recovery. A new testing method aims to detect the disease in its initial stages. The technology is based on a microfluidic chip with tiny channels in which a blood sample from the patient circulates. The chip traces marker proteins which are indicative of cancer. The measured concentration of the tumor marker in the blood will help doctors to diagnose the disease at an early stage.

Similar testing systems already exist but their measurements are not very precise and they can only detect molecules that are present in the blood in large quantities. What's more, the tests have to be carried out in a laboratory, which is time-consuming and costly.

A project funded by the German Ministry of Education and Research and coordinated by the Fraunhofer FIT aims to improve matters. Biofunctionalized nanoparticles developed by research scientists at the Fraunhofer Institute for Silicate Research ISC in Würzburg are the key element in the new sensor. "We have improved the detection limit compared with the present state of the art by a factor of one hundred," explains Dr. Jörn Probst, Head of the Business Unit Life Science at the ISC. "Whereas previously a hundred molecules were needed in a certain quantity of blood to detect tumor markers, we now need only one. This means that diseases can be diagnosed much earlier than with present methods."

But how does the biosensor integrated in the chip register the few biomolecules swimming around in the blood that are indicative of a certain disease? "We have placed antibody-occupied nanoparticles on the sensor electrode which fish out the relevant proteins. For this purpose, we repeatedly pump the blood across the electrode surface. As with a river, the flow is fastest in mid-channel and the water runs more slowly near the bank. We have therefore made a sort of fishing rod using nanoparticles which registers the antibodies in the middle of the blood flow where most proteins swim by per unit of time.« If an antibody catches the matching protein, a tumor marker, the electrical charge distribution shifts and this is picked up by the electrode."

The researcher groups are now developing a first demonstrator combining four independent single-molecule-sensitive biosensors. The experts are also working on the simultaneous detection of several tumor markers, which will increase the clarity of tests. The system will be ready to enter the market in a few years' time.

Disclaimer: This article is not intended to provide medical advice, diagnosis or treatment. Views expressed here do not necessarily reflect those of ScienceDaily or its staff.

Your Genome in Minutes: New Technology could Slash Sequencing Time

Dec 22, 2010

Scientists from Imperial College London are developing technology that could ultimately sequence a person's genome in mere minutes, at a fraction of the cost of current commercial techniques.

The researchers have patented an early prototype technology that they believe could lead to an ultrafast commercial DNA sequencing tool within ten years. Their work is described in a study published this month in the journal 'Nano Letters' and it is supported by the Wellcome Trust Translational Award and the Corrigan Foundation.

The research suggests that scientists could eventually sequence an entire genome in a single lab procedure, whereas at present it can only be sequenced after being broken into pieces in a highly complex and time-consuming process. Fast and inexpensive genome sequencing could allow ordinary people to unlock the secrets of their own DNA, revealing their personal susceptibility to diseases such as Alzheimer's, diabetes and cancer. Medical professionals are already using genome sequencing to understand population-wide health issues and research ways to tailor individualized treatments or preventions.

Dr Joshua Edel, one of the authors on the study from the Department of Chemistry at Imperial College London, said: "Compared with current technology, this device could lead to much cheaper sequencing: just a few dollars, compared with \$1m to sequence an entire genome in 2007. We haven't tried it on a whole genome yet but our initial experiments suggest that you could theoretically do a complete scan of the 3,165 million bases in the human genome within minutes, providing huge benefits for medical tests, or DNA profiles for police and security work. It should be significantly faster and more reliable, and would be easy to scale up to create a device with the capacity to read up to 10 million bases per second, versus the typical 10 bases per second you get with the present day single molecule real-time techniques."

In the new study, the researchers demonstrated that it is possible to propel a DNA strand at high speed through a tiny 50 nanometre (nm) hole - or nanopore - cut in a silicon chip, using an electrical charge. As the strand emerges from the back of the chip, its coding sequence (bases A, C, T or G) is read by a 'tunnelling electrode junction'. This 2 nm gap between two wires supports an electrical current that interacts with the distinct electrical signal from each base code. A powerful computer can then interpret the base code's signal to construct the genome sequence, making it possible to combine all these well-documented techniques for the first time.

Sequencing using nanopores has long been considered the next big development for DNA technology, thanks to its potential for high speed and high-capacity sequencing. However, designs for an accurate and fast reader have not been demonstrated until now.

Further Information: <http://www.imperial.ac.uk>

Genome of extinct Siberian human sheds new light on modern human origins

Dec 22, 2010

The sequencing of the nuclear genome from an ancient finger bone found in a Siberian cave shows that the cave dwellers were neither Neandertals nor modern humans.

An international team of researchers led by Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig (Germany) has sequenced the nuclear genome from a finger bone of an extinct hominin that is at least 30,000 years old and was excavated by archaeologists from the Russian Academy of Sciences in Denisova Cave in southern Siberia, Russia, in 2008. A team at Harvard Medical School led the population-genetics analysis.

These findings are published in the December 23 issue of *Nature*.

Earlier this year Svante Pääbo and his colleagues showed that the mitochondrial DNA from the finger bone displayed an unusual sequence suggesting that it came from an unknown ancient hominin form. Now, using techniques the researchers developed to sequence the Neandertal genome earlier this year, they have sequenced the nuclear genome from the bone.

The researchers found that the individual was female and came from a group of hominins that shared an ancient origin with Neandertals, but subsequently diverged. They call this group of hominins Denisovans. Unlike Neandertals, Denisovans did not contribute genes to all present-day Eurasians. However, Denisovans share an elevated number of genetic variants with modern-day Papua New Guinean populations, suggesting that there was interbreeding between Denisovans and the ancestors of Melanesians.

In addition, a Denisovan tooth found in the same cave shows a morphology that is distinct from Neandertals and modern humans and resembles much older hominin forms. Bence Viola, a scientist at the Max Planck Institute of Evolutionary Anthropology comments, "The tooth is just amazing. It allows us to connect the morphological and genetic information."

David Reich, an associate professor at Harvard Medical School who led the population genetic analysis, says, "The fact that Denisovans were discovered in Southern Siberia but contributed genetic material to modern human populations from New Guinea suggests that Denisovans may have been widespread in Asia during the Late Pleistocene."

According to Svante Pääbo of the Max Planck Institute of Evolutionary Anthropology, "In combination with the Neandertal genome sequence, the Denisovan genome suggests a complex picture of genetic interactions between our ancestors and different ancient hominin groups."

Mammalian aging process linked to overactive cellular pathway

Dec 22, 2010

Whitehead Institute researchers have linked hyperactivity in the mechanistic target of rapamycin complex 1 (mTORC1) cellular pathway, to reduced ketone production, which is a well-defined physiological trait of aging in mice.

Their results are reported in the December 23 edition of the journal *Nature*.

"This is the first paper that genetically shows that the mTORC1 pathway in mammals affects an aging phenotype," says Whitehead Institute Member David Sabatini. "It provides us with a molecular framework to study an aging-related process in deeper detail." When we think of aging, sagging skin, dimmed vision, and fragile bones come to mind. But Sabatini's lab is more interested in the cellular changes that occur as organisms age. One cellular pathway, the mTORC1 pathway, is known to coordinate cell growth with nutrient availability and other growth factors. Previous research has shown that when this pathway is inhibited, a variety of animals, including worms, flies, and mice tend to live longer.

Although an increased lifespan suggests that mTORC1 is involved in aging, it fails to clarify mTORC1's precise role in the process. In fact, lifespan is a poor proxy for studying aging, as it is not always a cause of death. One well-defined trait of aging is a decrease in ketogenesis, or the ability to produce ketones. During sleep or other times of low carbohydrate intake, the liver converts fatty acids to ketones, which are vital sources of energy during fasting, especially for the heart and brain. As animals age, their ability to produce ketones as a response to fasting declines. The cause of this phenomenon remains unknown. To determine whether mTORC1 mediates ketogenesis in mice, Shomit Sengupta, a former graduate student in Sabatini's lab and first author on the *Nature* paper, studied the effects of induced hyperactivity in the mTORC1 pathway in the livers of fasting mice. He found that while most blood and liver metabolite levels did not change significantly, ketone levels fell. After establishing that activating the mTORC1 pathway decreases ketogenesis, Sengupta tried to find exactly where mTORC1 was acting. Knowing that peroxisome proliferator-activated receptor alpha (PPAR-alpha) is an activator of liver ketogenesis, Sengupta attempted to jumpstart the process by stimulating PPAR-alpha. Interestingly, ketone levels failed to increase—a clear indication that that mTORC1 was thwarting PPAR-alpha.

"That now places mTORC1 as the master regulator of ketogenesis," says Sengupta, who is now a Research Fellow at Harvard Medical School. "It could be one of many inputs for PPAR alpha – that's unclear right now. But mTORC1 is sufficient and necessary to suppress PPAR-alpha and ketogenesis." Connecting mTORC1 to the aging-related decline in ketogenesis was the next step. If mTORC1 activation is responsible for lower ketone levels caused by aging, turning on mTORC1 in older mice should not affect their already low ketone levels – it would be like trying to turn off a light switch that is already off. So Sengupta compared the ketone production of old and young mice during fasting. While turning on the mTORC1 pathway during fasting reduced ketone production in the young mice, the old mice maintained the same, low ketone levels. And when the mTORC1 pathway was turned off in very young mice that were subsequently aged, these older mice did not experience the decline in ketogenesis found in normal mice. Their ketogenesis levels were similar to younger mice, confirming that continual inhibition of the mTORC1 pathway prevented the aging-induced decline in ketone production. It might follow that suppressing mTORC1 could slow aging, and indeed, some have suggested that the drug rapamycin, an mTOR inhibitor used to treat cancer and to prevent organ transplant rejection, might have anti-aging properties. "Rapamycin definitely has lots of anti-aging hype," says Sabatini, who is also a professor of biology at MIT and a Howard Hughes Medical Institute (HHMI) investigator. "Having worked with that molecule a lot, I'm not sure I would take it for long periods of time, just for slowing down aging."

Instead Sabatini is focused on a host of more practical questions, including why ketogenesis is suppressed by aging and how aging serves to activate mTORC1.

"We know enough of what's upstream of mTORC1 that I think now we can test different components and ask which one is sort of acting funny in its aged state," says Sabatini.

Age doesn't matter: New genes are as essential as ancient ones

Dec 22, 2010

New genes that have evolved in species as little as one million years ago – a virtual blink in evolutionary history – can be just as essential for life as ancient genes, startling new research has discovered.

Evolutionary biologists have long proposed that the genes most important to life are ancient and conserved, handed down from species to species as the "bread and butter" of biology. New genes that arise as species split off from their ancestors were thought to serve less critical roles – the "vinegar" that adds flavor to the core genes.

But when nearly 200 new genes in the fruit fly species *Drosophila melanogaster* were individually silenced in laboratory experiments at the University of Chicago, more than 30 percent of the knockdowns were found to kill the fly. The study, published December 17 in *Science*, suggests that new genes are equally important for the successful development and survival of an organism as older genes.

"A new gene is as essential as any other gene; the importance of a gene is independent of its age," said Manyuan Long, PhD, Professor of Ecology & Evolution and senior author of the paper. "New genes are no longer just vinegar, they are now equally likely to be butter and bread. We were shocked."

The study used technology called RNA interference to permanently block the transcription of each targeted gene into its functional product from the beginning of a fly's life. Of the 195 young genes tested, 59 were lethal (30 percent), causing the fly to die during its development. When the same method was applied to a sample of older genes, a statistically similar figure was found: 86 of 245 genes (35 percent) were lethal when silenced.

Because the young genes tested only appeared between 1 and 35 million years ago, the data suggests that new genes with new functions can become an essential part of a species' biology much faster than previously thought. A new gene may become indispensable by forming interactions with older genes that control important functions, said Sidi Chen, University of Chicago graduate student and first author of the study.

"New genes come in and quickly interact with older genes, and if that interaction is favorable by helping the organism survive or reproduce better, it is favored by natural selection and stays in the genome," Chen said. "After a while, it becomes essential, and the organism literally cannot live without the gene any more. It's something like love: You fall in love with someone and then you cannot live without them."

The indispensable nature of new genes also questions long-held beliefs about the shared features of development across different species. In 1866, German zoologist Ernst Haeckel famously hypothesized that "ontogeny recapitulates phylogeny" after observing that the early steps of development are shared by animals as different as fly and man.

Biologists subsequently predicted and confirmed that the same ancient, essential genes would be the conductors of this early development in all species. This principle enabled the use of model organisms, including flies, mice, and rats, to be used for research on the mechanisms of human disease.

Intriguingly, in the new study, deleting many of the new genes causes flies to die during middle or late stages of development, while older genes were lethal during early development. So while ancient genes essential for the early steps of development are shared, newer genes unique to each species may take over the later developmental stages that make each species unique. For example, many new genes in the study were found to be involved with metamorphosis, the mid-life stage that drastically transforms the body plan in animals.

"This may change the way we view the developmental program," Long said. "Each species has a different species-specific developmental program shaped by natural selection, and we can no longer say that from *Drosophila* to humans the development of different organisms is just encoded by the same genetic program. The story is much more complicated than what we used to believe."

As such, a full understanding of biological diversity may require a new focus on genes unique to each organism.

"I think it has important implications on human health," Chen said. "Animal models have proven to be very useful and important for dissecting human disease. But if our intuition is correct, some important health information for humans will reside in the unique parts of the human genome."

The newfound importance of young genes and unique developmental programs may have a dramatic impact on the field, Long said. The discovery will also inspire new research directions examining how quickly new genes can become essential and their exact role in species-specific development.

"Biologists have long assumed, quite reasonably, that ancient genes have survived natural selection because they are essential to life and that new genes are generally less critical to an organism's development," said Irene Eckstrand, PhD, who manages Dr. Long's and other evolutionary biology grants at the National Institutes of Health. "This important study suggests that this assumption is flawed, unlocking new questions that could lead to a deeper understanding of evolutionary processes and their impact on human health."

Researchers Illuminate Genetic Code for a Form of Pancreatic Cancer

Jan 21, 2011

Through a grant provided by the Caring for Carcinoid Foundation, researchers at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center have discovered several key mutations in pancreatic neuroendocrine tumors.

This significant finding holds the promise of improving patient diagnosis and treatment and brings the neuroendocrine cancer community closer to a cure. Neuroendocrine cancers affect approximately 100,000 patients in the United States, including, according to published reports, Steve Jobs, CEO of Apple Inc.

Dr. Nickolas Papadopoulos, Ph.D., associate professor at Johns Hopkins Kimmel Cancer Center and lead researcher on this project recognized the support of the Caring for Carcinoid Foundation. "We are very grateful to the Foundation for funding this research. Without their visionary support, this project would not have been possible. We look forward to continuing our work to advance treatment options for neuroendocrine cancer patients," says Dr. Papadopoulos.

Papadopoulos and his team uncovered the set of genetic alterations present among patients with non-functional pancreatic neuroendocrine tumors. They also uncovered a prognostic set of mutations and a rapid way of prioritizing patients for treatments with mTOR inhibiting drugs.

Papadopoulos says, "One of the most significant things we have learned is that each patient with this form of pancreatic cancer has a unique genetic code that predicts how aggressive the disease is and how sensitive it is to specific treatments." Dr. Papadopoulos and his team found that in patients with non-functional pancreatic neuroendocrine tumors, those with specific mutations lived at least 10 years from diagnosis, while more than 60% of patients without these mutations died within five years of diagnosis.

These findings, published online in Science Express on January 20, 2011, suggest new approaches for treating patients with pancreatic neuroendocrine tumors. With few treatment options currently available for pancreatic neuroendocrine tumor patients, these findings represent important advances toward improving treatment options for these patients.

Of these breakthroughs, CFCF Founder and metastatic carcinoid cancer survivor Nancy Lindholm says, "This research finding represents a monumental leap forward in understanding the underlying mechanism of neuroendocrine cancer. Thanks to the phenomenal work of Dr. Papadopoulos and his team, we are one step closer to a cure. I am grateful to the commitment and dedication of the Caring for Carcinoid Foundation community for supporting researchers like Dr. Papadopoulos and making these insights possible. I hope this news brings reviewed optimism and courage to everyone living with carcinoid, pancreatic neuroendocrine, and related neuroendocrine cancers".

The significant findings of Papadopoulos and his team lays the framework for further genomic and drug pathway studies, and visibly demonstrates the progress that is possible through funded research of rare cancers.

For more information, visit <http://www.technologynetworks.com>

Researchers believe EMT is the Dominant Program in Human Colon Cancer

Jan 21, 2011

Traditionally Colon Cancer has long been thought of as heterogeneous, therefore making it difficult to identify unifying molecular hypotheses explaining the biology and behavior of the disease. To help combat this problem researchers at Merck have attempted to uncover unbiased, native biological traits that might underpin colon cancer.

The work, which appears in BioMed Centrals Medical Genomics Journal, details how unsupervised microarray data analysis was carried out on 326 human colon cancer samples, to discover the first principal component (PC1) of the most variable set of genes. It was discovered that the most dominant pattern of intrinsic gene expression in colon cancer (PC1) was tightly correlated with the EMT signature-- both in gene identity and directionality.

This data demonstrates that the biology underpinning the native, molecular classification of human colon cancer was clarified through the lens of comprehensive transcriptome analysis.

Abstract:

Background: Colon cancer has been classically described by clinicopathologic features that permit the prediction of outcome only after surgical resection and staging. Methods: We performed an unsupervised analysis of microarray data from 326 colon cancers to identify the first principal component (PC1) of the most variable set of genes. PC1 deciphered two primary, intrinsic molecular subtypes of colon cancer that predicted disease progression and recurrence. Results: Here we report that the most dominant pattern of intrinsic gene expression in colon cancer (PC1) was tightly correlated (Pearson $R = 0.92$, $P < 10^{-135}$) with the EMT signature-- both in gene identity and directionality. In a global micro-RNA screen, we further identified the most anti-correlated microRNA with PC1 as MiR200, known to regulate EMT. Conclusions: These data demonstrate that the biology underpinning the native, molecular classification of human colon cancer--previously thought to be highly heterogeneous--was clarified through the lens of comprehensive transcriptome analysis.

To read the full paper, entitled 'EMT is the Dominant Program in Human Colon Cancer' please visit: <http://www.biomedcentral.com/1755-8794/4/9/abstract>

Fat Associated With Chemical Changes in DNA That May Help Explain Obesity-Related Disease

Jan 24, 2011

Fat appears to associate with some distinctive chemical changes in the DNA -- a finding that may help explain why obesity can increase the risk for chronic problems such as cardiovascular disease and diabetes, researchers report.

The finding, published in *BMC Medicine*, may one day help identify those at risk and reduce it, according to Dr. Xiaoling Wang, genetic epidemiologist at the Medical College of Georgia's Georgia Prevention Institute.

"Losing fat is very difficult; we know that. We also know it causes many diseases so we want to identify and target pathways to reduce those diseases," Wang said.

Fat used to be viewed as essentially padding and a ready energy source but scientists are learning it's more like a factory that makes chemicals and compounds such as hormones and proteins. Studies comparing two groups of obese versus lean teens found higher levels of chemical change, or methylation, in a portion of the UBASH3A gene and lower levels in part of the TRIM3 gene.

Both genes are known to have roles in regulating the immune system, which is often dysregulated in obese individuals. Dysregulation can result in a level of chronic inflammation that contributes to diseases such as cardiovascular disease, diabetes and cancer. Methylation can impact immune function by affecting gene expression levels which ultimately impacts downstream functions of the proteins produced by genes.

"You need to know disease pathways to find novel medications," Wang said. "We generally know they have a dysregulation of the immune function, but we didn't know the specific site." She believes she found at least two sites in the UBASH3A and TRIM3 gene. Her initial search was broad: a genome-wide screen of seven obese and seven lean teens that enabled her to identify genes most different between the two. She ranked the differences and, in a much larger study of 46 obese and 46 lean controls, looked at the same sites in the top six genes and found again the distinctive methylation pattern in UBASH3A and TRIM3.

Wang now wants to clarify whether fat causes the DNA changes or vice versa and confirm that the changes contribute to the immune dysfunction associated with obesity.

She notes that because obesity does not always lead to related diseases, it's important to have a way to not just intervene, but to identify those most at risk. Factors such as fitness, body shape and environment probably are also predictors for related disease.

"... (T)he public health message of 'eat less and exercise more' appears to have fallen on deaf ears," Drs. Paul W. Franks and Charlotte Ling of Sweden's Skåne University Hospital, Lund University write in an accompanying editorial. "Thus, despite the apparently simple explanation and remedy for obesity, this knowledge is not enough. We are saddled with a challenge, which is to unravel the mechanisms by which obesity emerges and to understand how its presence causes disease and death, with the hope that somewhere within the details hides the solution to the problem." They note that Wang's study provides "tentative evidence" that DNA methylation at the two gene sites may be implicated in obesity-related disease.

DAXX/ATRX, MEN1, and mTOR Pathway Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors

Jan 20, 2011

Pancreatic Neuroendocrine Tumors (PanNETs) are a rare but clinically important form of pancreatic neoplasia. To explore the genetic basis of PanNETs, we determined the exomic sequences of ten nonfamilial PanNETs and then screened the most commonly mutated genes in 58 additional PanNETs. The most frequently mutated genes specify proteins implicated in chromatin remodeling: 44% of the tumors had somatic inactivating mutations in MEN-1, which encodes menin, a component of a histone methyltransferase complex; and 43% had mutations in genes encoding either of the two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain associated protein) and ATRX (alpha thalassemia/mental retardation syndrome X-linked). Clinically, mutations in the MEN1 and DAXX/ATRX genes were associated with better prognosis. We also found mutations in genes in the mTOR (mammalian target of rapamycin) pathway in 14% of the tumors, a finding that could potentially be used to stratify patients for treatment with mTOR inhibitors .

for more information visit <http://www.sciencemag.org>

Study in Mice Uncovers Pathway Critical for UV-Induced Melanoma

Jan 20, 2011

Scientists have made an unanticipated discovery in mice that interferon-gamma, a type of protein primarily used by the immune system for intercellular communication, acts as a promoter for the deadly form of skin cancer known as melanoma.

This finding resulted from a series of experiments designed to understand how solar ultraviolet (UV) radiation causes melanoma. The results of this study suggest that interferon-gamma, which has been thought to contribute to an innate defense system against cancer, under some circumstances may promote melanoma and incite the development of tumors. The work, led by researchers from the National Cancer Institute (NCI), part of the National Institutes of Health, appeared online in *Nature*, Jan. 19, 2011 .

Cutaneous melanoma is a highly aggressive and frequently drug-resistant cancer with rising incidence rates. The major environmental risk factor for melanoma is UV radiation exposure, usually from the sun, with the highest risk associated with intermittent burning doses, especially during childhood .

Over the past 10 years, the researchers used genetically engineered mice first to prove, and then to try to understand, the connection between exposure to UV radiation and the initiation of melanoma. The current work was the latest attempt to define the molecular mechanisms of this cause and effect relationship. The results of this study offer the possibility that the inhibition of interferon-gamma immediately after sunburn might block the carcinogenic activation of the skin's pigment-producing cells, known as melanocytes, making it a potentially effective preventive strategy against UV radiation-induced melanoma, according to the scientists .

The key to the experiments, led by Glenn Merlino, Ph.D., Laboratory of Cancer Biology and Genetics, NCI, and research fellow and first author M. Raza Zaidi, Ph.D., was the development of a unique genetically engineered mouse in which the melanocytes were exclusively labeled with a green fluorescent protein. This fluorescent tag allowed visual tracking and specific purification of melanocytes from the mouse skin. For the first time this enabled researchers to evaluate the response of melanocytes to UV radiation exposure while residing in the natural skin environment of a living animal .

The researchers observed that UV radiation doses equivalent to what would cause sunburn in human skin resulted in increased numbers and movement of melanocytes within the mouse skin. A detailed analysis of gene expression changes associated with this melanocyte activation revealed abnormal expression of a number of genes known to be responsive to interferon-gamma .

When the function of interferon-gamma was inhibited at the time of UV radiation, the number of melanocytes and their movement remained normal, suggesting that interferon-gamma was responsible for the UV radiation-induced activation of the melanocytes .

The source of interferon-gamma within the skin was determined to be macrophages-cells that normally protect against infection-that had infiltrated the skin after UV exposure. The pro-melanoma potential of these macrophages was revealed when they were found to enhance the growth of melanomas when transplanted under the skin of mice .

This effect was abolished when interferon-gamma was blocked, corroborating its importance in promoting melanoma development. Moreover, when the scientists examined human melanoma tissue samples, they found interferon-gamma-producing macrophages in 70 percent of the tumors, supporting the idea that these macrophages can significantly contribute to the initiation and/or progression of human melanoma.

"We anticipate that this discovery may change how interferons are used in the clinic as anticancer agents," said Merlino. "Our findings raise the possibility that targeting the interferon-gamma pathway may represent a novel, less toxic therapeutic alternative for effective treatment of malignant melanoma patients, who currently have poor cure rates".

These studies were made possible through long-term collaborations with Edward De Fabo, Ph.D., and Frances Noonan, Ph.D., of George Washington University Medical Center, Washington, D.C.

Strand-specific Transcriptome Profiling with Directly Labeled RNA

Jan 17, 2011

Researchers at the Forsythe Institute and the University of Boston have developed an effective method using directly labelled RNA in hybridized microarrays to map transcriptome profiles specific to both coding strands of a bacterial genome.

With lower manufacturing cost, high spot density, and flexible probe design, genomic tiling microarrays are ideal for comprehensive transcriptome studies. Typically, transcriptome profiling using microarrays involves reverse transcription, which converts RNA to cDNA. The cDNA is then labeled and hybridized to the probes on the arrays, thus the RNA signals are detected indirectly. Reverse transcription is known to generate artifactual cDNA, in particular the synthesis of second-strand cDNA, leading to false discovery of antisense RNA. To address this issue, we have developed an effective method using RNA that is directly labeled, thus by-passing the cDNA generation. This paper describes this method and its application to the mapping of transcriptome profiles.

The paper, entitled 'Strand-specific transcriptome profiling with directly labeled RNA on genomic tiling microarrays', is freely available online through.

Researchers use Cell “Profiling” to Detect Abnormalities -- Including Cancer

Jan 28, 2011

An Ohio State University mathematician and his colleagues are finding ways to tell the difference between healthy cells and abnormal cells, such as cancer cells, based on the way the cells look and move.

They are creating mathematical equations that describe the shape and motion of single cells for laboratory analysis.

Though this research is in its early stages, it represents an entirely new way of identifying cell abnormalities, including cancer. It could one day be useful in gauging future stages of a disease -- for example, by detecting whether cancer cells are aggressive and likely to spread throughout the body, or metastasize.

In a paper published online in the *Bulletin of Mathematical Biology*, researchers describe a mathematical model which analyzes image sequences of single, live cells to determine abnormalities manifested in their shape and behavior. A brain tumor cell was one of the cell types they analyzed in the study.

Huseyin Coskun, visiting assistant professor of mathematics at Ohio State and leader of the project, described their novel approach as a first step toward developing mathematical tools for diagnosing cell abnormalities and for giving potential prognoses.

Because the technique would allow doctors to view how cancer cells behave under different physical or chemical conditions, it could also be used to test different treatment strategies for each individual patient -- such as determining the most efficient dose of chemotherapeutic agents or radiation -- or even to test entirely new treatments.

In addition, Coskun sees his technique as a tool for also pathologists, who typically look at photographs of biopsied cells to identify cancer and judge how advanced the cancer may be.

“A pathologist can diagnose cancer, but as far as predicting the future, they don’t have many tools at their disposal -- particularly if a cancer is in its early stages,” Coskun said. “That’s why I believe that one of the most important applications of this research is profiling cancer cells. Given a cell’s motion and its morphological changes, we want to be able to determine what’s happening inside the cell. If it looks like a cancer cell, and a particularly aggressive one, we would like to quantify how likely it is that the cancer cells will invade the body.”

In a very basic sense, diagnosing a “sick” cell such as a cancer cell by its appearance, motion, and behavior is analogous to diagnosing a sick human, he said. “When we get sick, our behavior changes.

We may stay in bed, sleep a lot -- maybe we are coughing or sneezing. These are basic symptoms that a doctor will consider to determine if we’re sick. Abnormalities oftentimes manifest themselves as behavioral changes in all living organisms. Therefore, a careful analysis of and profiling the behavioral patterns of single cells could provide valuable information.”

Cell motion is important for all life, he continued. White blood cells move when they attack microbes that have invaded the body. A wound heals when newly grown cells move in to close it. But something about aggressive cancer cells causes them to move from the tumor where they originated

into the blood stream, where they migrate to different organs and grow out of control. Living cells often change shape, expand, or contract, and Coskun believes that he and his colleagues

can create unique “personality profiles” of cancer cells.

Coskun and his colleague, Hasan Coskun, assistant professor of mathematics at Texas A&M University-Commerce, used a branch of physics called continuum mechanics to derive equations that describe cells’ appearance and behavior. They compared their model outcomes to findings from past cancer studies, which indicated that cancer cells are more deformable than normal cells.

The researchers discovered that their model results agree with those experimental findings.

Obtaining data from live cell image sequences to use as an input in the mathematical models is not easy. For this, Coskun collaborated with Hakan Ferhatosmanoglu, an associate professor, and his then-student, Ahmet Sacan, both of computer science and engineering at Ohio State. They created open source software called CellTrack to extract data from movies of cell motion. Given a movie of live cells under the microscope, CellTrack tracks individual cells, extracts data that can be used in the mathematical models, and provides other useful statistical information about the motion.

Huseyin Coskun acknowledged the current limits of his methodology. The researchers were able to show that their mathematical models can be applied to analyze single cell motion and obtain useful information. They were also able to hypothesize a biological explanation for very complex mechanism of cell motion based on their mathematical model outcomes. But he and his partners need many more high-resolution movies of healthy cells and cancer cells to build upon this initial work. That's why Coskun is setting up collaborations with medical researchers at Ohio State and other universities.

Coskun believes that mathematical techniques such as his are becoming more common in the biomedical sciences because they allow researchers to perform studies that would be too difficult, time-consuming or expensive in real life. He hopes his technique could be used to answer emerging questions in cell biology.

NIH Researchers Extend use of Gene Therapy to Treat a Soft Tissue Tumor

Feb 09, 2011

Results of an intermediate stage clinical trial of several dozen people provides evidence that a method that has worked for treating patients with metastatic melanoma can also work for patients with metastatic synovial cell sarcoma, one of the most common soft tissue tumors in adolescents and young adults.

This study is the first to use genetically modified immune cells, in a technique known as adoptive therapy, to cause cancer regression in patients with a solid cancer as opposed to melanoma. This approach represents a method for obtaining immune cells from any cancer patient and converting them into ones that can recognize cancer cells expressing the target antigen, NY-ESO-1, according to researchers at the National Cancer Institute.

NY-ESO-1 is a protein found in up to 50 percent of melanomas and cancers of the breast, prostate, esophagus, lung, and ovary, and in 80 percent of synovial sarcomas. "Since NY-ESO-1 is expressed in a substantial number of cancers, beside melanoma and synovial sarcoma, it is an attractive target for immune-based therapies against these cancers as well," said lead investigator Steven Rosenberg, M.D., Ph.D., chief of the Surgery Branch in NCI's Center for Cancer Research.

This work builds upon previously published results in patients with metastatic melanoma. Those studies showed that metastatic melanoma patients could be treated by infusion with their own genetically modified T cells, or white blood cells, that had receptors on their surfaces that recognized an antigen on the melanoma cells. In this study, 17 patients with synovial cell sarcoma or metastatic melanoma, whose tumors expressed NY-ESO-1, received therapy with their own immune cells engineered to express a T cell receptor capable of recognizing the NY-ESO-1 antigen. To perform this treatment, the investigators isolated normal white blood cells, called lymphocytes, from each patient's blood and modified these cells by inserting the gene encoding the anti-tumor T cell receptor into them. These genetically modified cells were then able to recognize and destroy NY-ESO-1-expressing cancer cells. The results showed tumor regression in four of the six patients with synovial cell sarcoma and in five of the 11 melanoma patients. A partial response that lasted 18 months was observed in one of the synovial cell sarcoma patients, while two of the melanoma patients demonstrated complete ongoing regression responses that lasted 20 months or longer, which for patients with these diseases, is significant.

"Now that we have shown that a patient's own cells genetically engineered to express a receptor against the NY-ESO-1 antigen can mediate tumor regression, we will be optimizing this treatment and extending it to the treatment of patients with other common cancers," said Rosenberg. The study appeared in the Jan. 31, 2011, issue of the Journal of Clinical Oncology.

Exiqon Announces 2011 Grant Program for MicroRNA Research

Feb 02, 2011

Company announces the launch of 2011 global research grant program, open to researchers from academic and non-profit institutions.

Exiqon A/S has announced the launch of its 2011 global research grant program, open to researchers from academic and non-profit institutions.

“We at Exiqon aim to support our customers around the world in their daily life at the laboratories and are proud of offering excellent products for identifying the role of microRNAs in developmental and pathological pathways. With this grant program we give them access to a cutting edge technology that cannot be missed in any research institution”, said Executive Vice President Sales & Marketing, Dr. Elisete Pedrollo.

The Exiqon Grant Program has been established with an internal seed funding of \$40,000 / €30.000 from which awards will be given to researchers to drive projects enhancing the understanding of how microRNA expression and function relates to normal cellular development, and/or disease-related cellular pathways.

Recipients will use Exiqon Grant Program awards for the purchase of any Exiqon microRNA product or service. Exiqon offers a complete product line for microRNA investigation, including products for RNA isolation, Microarray analysis, qRT-PCR analysis, Northern Blotting, In Situ Hybridization, and Knockdown studies. Exiqon also offers microRNA profiling services for both microarray and qRT-PCR analysis, complete with full sample QC and customized data analysis and reporting.

Researchers are invited to submit an abstract, outlining their research area, project goals, and proposed workflow no later than Monday, 28 February 2011. Award conveyance through the Exiqon Grant Program does not influence, and is not influenced by, any other existing or potential sources of project funding.

Scientists Find Key Protein That Suppresses Prostate Cancer Growth in the Laboratory

Feb 09, 2011

Cancer researchers have discovered an important protein, produced naturally inside cells, that appears to suppress the growth of prostate cancer cells in the laboratory. The findings, published in the journal Cancer Research, offer promising leads for research towards new treatments.

Prostate cancer is the most common cancer among men in the UK, with 37,500 men diagnosed with the disease every year. Many prostate cancers are slow growing, but in some cases the cancer is aggressive and spreads to other parts of the body, such as the bone. These cases are much more likely to be fatal.

In the new study, scientists at Imperial College London found that a protein called FUS inhibits the growth of prostate cancer cells in the laboratory, and activates pathways that lead to cell suicide. The researchers also looked for the FUS protein in samples from prostate cancer patients. They found that in patients with high levels of FUS, the cancer was less aggressive and was less likely to spread to the bone. Higher levels of FUS also correlated with longer survival. The results suggest that FUS might be a useful marker that can give doctors an indication of how aggressive a tumour will be. "At the moment, there's no way to say whether a prostate tumour will kill you or be fairly harmless," said Dr Charlotte Bevan, senior author of the study, from the Department of Surgery and Cancer at Imperial College London. "Current hormonal therapies only work for a limited time, and chemotherapy is often ineffective against prostate cancer, so there's a real need for new treatments. "These findings suggest that FUS might be able to suppress tumour growth and stop it from spreading to other parts of the body where it can be deadly. It's early stages yet but if further studies confirm these findings, then FUS might be a promising target for future therapies." Prostate cancer depends on male hormones to progress as these hormones stimulate the cancer cells to divide, enabling the tumour to grow. Treatments that reduce hormone levels or stop them from working are initially effective, but eventually the tumour stops responding to this treatment and becomes more aggressive.

Dr Bevan and her team began by exposing prostate cancer cells to male hormones and looking at how the levels of different proteins changed. They discovered that the hormones made the cells produce less of the FUS protein, and examined further whether FUS might influence cell growth by inserting extra copies of the gene for FUS into cells grown in culture. They found that making the cells produce more FUS led to a reduction in the number of cancer cells in the dish. Greg Brooke, first author of the study, from the Department of Surgery and Cancer at Imperial College London said: "Our study suggests that FUS is a crucial link that connects male hormones with cell division. The next step is to investigate whether FUS could be a useful test of how aggressive prostate cancer is. Then we might look for ways to boost FUS levels in patients to see if that would slow tumour growth or improve response to hormone therapy. "If FUS really is a tumour suppressor, it might also be involved in other cancers, such as breast cancer, which has significant similarities with prostate cancer." The study was funded by Prostate Action, the Medical Research Council, the Imperial College Experimental Cancer Medicine Centre (set up with a grant from Cancer Research UK and the Department of Health) and the Prostate Cancer Charity.

Method of DNA repair linked to higher likelihood of genetic mutation

Feb 15, 2011

Accurate transmission of genetic information requires the precise replication of DNA. Errors in DNA replication are common and nature has developed several cellular mechanisms for repairing these mistakes. Mutations, which can be deleterious (development of cancerous cells), or beneficial (evolutionary adaptation), arise from uncorrected errors. Researchers from Indiana University-Purdue University Indianapolis (U.S.A) and Umea^o University (Sweden) report that a method by which cells repair breaks in their DNA, known as Break-induced Replication (BIR), is up to 2,800 times more likely to cause genetic mutation than normal DNA synthesis. When one or many cells repair themselves using the efficient BIR method, accuracy is lost. These findings will publish next week in the online, open access journal *PLoS Biology*.

"When BIR occurs, instead of using a "band aid" to repair a chromosomal break, the broken piece invades another chromosome and initiates replication which happens at the wrong place and at the wrong time and probably with participation of wrong proteins," said Anna Malkova, Ph.D., Associate Professor of Biology at the School of Science at IUPUI, who led the study.

The researchers used yeast to investigate the level of mutagenesis associated with BIR and found that the process's proclivity to cause mutation was not effected by where in the DNA the repair was made. But why is BIR so inaccurate as compared to normal replication?

"We didn't find a smoking gun," said Malkova, also an adjunct associate professor of medical and molecular genetics at the Indiana University School of Medicine. "We think there are at least four changes to the replication machinery that might occur to create a perfect storm or synergy that make BIR repair so mutagenic."

For example, during BIR, the researchers found a dramatic increase in the concentration of nucleotides – the building blocks used to form DNA.

"Our findings strongly suggest that mutagenesis caused by BIR doesn't happen slowly, it occurs in surges – sudden bursts which may lead to cancer," said Malkova, who is a geneticist. "We plan to continue investigating BIR in the hope of finding clues as to why this means of cell repair is so likely to cause mutations. The ultimate goal, of course, is to prevent those mutations that cause cancer."

Whole Genome Sequencing used to Help Inform Cancer Therapy

Feb16, 2011

Physicians and researchers at Mayo Clinic in Arizona and the Translational Genomics Research Institute (TGen) have successfully completed sequencing both a single patient's normal and cancer cells - more than 6 billion DNA chemical bases.

While the whole genomes of several individuals or their cancers have been sequenced in recent years, this is believed to be among the first successful application of whole genome sequencing performed in support of the medical care of a specific cancer patient. A male patient with pancreatic cancer was the first patient at Mayo Clinic to have whole genome sequencing performed on both his tumor and non-cancerous cells as part of a clinical research project. By comparing the tumor DNA to the patient's normal DNA, researchers found genetic changes (mutations) that were important in helping inform doctors about how best to plan the patient's next treatment. This was a case of using a definable genetic change that could be linked to specific treatment, something believed to be a glimpse into the almost certain future of individualizing cancer care.

Mayo Clinic administered all the clinical aspects of the research. TGen performed the genetic sequencing.

While the Mayo-TGen sequencing was done as part of ongoing research, it signals a major step toward implementation of whole genome sequencing to support clinic treatment options. "This is a demonstration of the clinical utility of whole genome sequencing," said Keith Stewart, M.B., Dean of Research at Mayo Clinic. "As we do more and more of this, we will move closer and closer to personalized genetic medicine, which means using genetic information to minimize or prevent disease."

Details of this research, its results and implications for the future, will be included in an upcoming scientific paper.

Cost reductions start to make whole genome sequencing practical

In 2003, after 13 years and nearly \$2.7 billion, the government-funded international Human Genome Project deciphered the first entire human genome sequence. Continuing technological advances now allow scientists to evaluate the entire human genome at a fraction of the time and cost. "No one thought that this would be possible this soon, and the key now is to combine all medical and scientific information together," said Mitesh J. Borad, M.D., Assistant Professor of Medicine and oncology specialist at Mayo Clinic. "However, we are still very early in the process. A lot of questions will come out of this. But in the long run, this will only help." Other sequencing techniques — such as genome-wide association studies — are less expensive tests, but examine only selected portions of DNA. Whole genome sequencing (WGS) looks at the entire genome, giving scientists the most comprehensive view of the potential genetic origins of disease.

"Increasingly we will use information from an individual's DNA sequence to expand from today's attempts to define disease risk to actual disease management," said Jeffrey Trent, Ph.D., President and Research Director at TGen and the former Scientific Director of the federal government's National Human Genome Research Institute. "We recognize our lack of complete knowledge of many of the genetic changes we observe, and how exactly they will align with drugs for treatment. However, the use of new compounds for some leukemias and gastrointestinal tumors with defined genetic alterations is the prototype example of a genetic change matched to a targeted therapy providing profound clinical benefit. Our study is one of a handful now underway that is attempting to identify and then match a gene alteration to targeted agents."

Uncovering a precise origin of diseases

Performing genomic sequencing on cancerous tumors may provide clinicians with information to treat

cancer more precisely, especially for patients who are resistant to traditional treatments. Cancer is a disease often rooted in genetic mutations and can change a person's DNA. Essentially, WGS distills all the molecular ingredients that make up a person's genetics so physicians can pinpoint the root cause of a disease. The knowledge gained from this research should allow clinicians to design treatments to address many specific diseases. "Every step we take in research gets us closer to making this routine for cancer patients," said Rafael Fonseca, M.D., Deputy Director, Mayo Clinic Cancer Center in Arizona. "If we look in the not too distant future, this is a possibility for every cancer patient." At this point, start-up costs for WGS are still significant. Genetic sequencing of tumors requires immense technological and human resources. Once processes are developed and regularly implemented, the long-term costs of sequencing are expected to further drop. "Whole genome sequencing allows us to dig deeper into the genome than ever before by providing more information and increasing our probability of identifying an 'Achilles heel' not previously recognized by more conventional approaches," said John Carpten, Ph.D., Director of TGen's Integrated Cancer Genomics Division. "The long-term hope is that doctors will leverage this information to inform decisions about patient care in cancer, and beyond."

How disordered proteins spread from cell to cell, potentially spreading disease

Feb 18, 2011

One bad apple is all it takes to spoil the barrel. And one misfolded protein may be all that's necessary to corrupt other proteins, forming large aggregations linked to several incurable neurodegenerative diseases such as Huntington's, Parkinson's and Alzheimer's.

Stanford biology Professor Ron Kopito has shown that the mutant, misfolded protein responsible for Huntington's disease can move from cell to cell, recruiting normal proteins and forming aggregations in each cell it visits.

Knowing that this protein spends part of its time outside cells "opens up the possibility for therapeutics," he said. Kopito studies how such misfolded proteins get across a cell's membrane and into its cytoplasm, where they can interact with normal proteins. He is also investigating how these proteins move between neuronal cells.

The ability of these proteins to move from one cell to another could explain the way Huntington's disease spreads through the brain after starting in a specific region. Similar mechanisms may be involved in the progress of Parkinson's and Alzheimer's through the brain.

Kopito discussed his research on Friday, Feb. 18, at 8:00 a.m. Eastern, at the annual meeting of the American Association for the Advancement of Science in Washington, D.C.

Not all bad

Not all misfolded proteins are bad. The dogma used to be that all our proteins formed neat, well-folded structures, packed together in complexes with a large number of other proteins, Kopito said. But over the past 20 years, researchers have found that as much as 30 percent of our proteins never fold into stable structures. And even ordered proteins appear to have some disordered parts.

Disordered proteins are important for normal cellular functions. Unlike regular proteins, they only interact with one partner at a time. But they are much more dynamic, capable of several quick interactions with many different proteins. This makes them ideal for a lot of the standard communication that happens within a cell for its normal functioning, Kopito said.

But if some of our proteins are always disordered, how do our cells tell which proteins need to be properly folded, and which don't? "It's a big mystery," said Kopito, and one that he's studying. This question has implications for how people develop neurodegenerative diseases, all of which appear to be age-related.

Huntington's disease is caused by a specific mutated protein. But the body makes this mutant protein all your life, so why do you get the disease in later adulthood? Kopito said it's because the body's protective mechanisms stop doing their job as we get older. He said his lab hopes to determine what these mechanisms are.

A bad influence

But it's clear what happens when these mechanisms stop working – misfolded proteins start recruiting normal versions of the same protein and form large aggregations. The presence of these aggregations in neurons has been closely linked with several neurodegenerative diseases.

Kopito found that the mutant protein associated with Huntington's disease can leave one cell and enter another one, stirring up trouble in each new cell as it progresses down the line. The spread of the misfolded protein may explain how Huntington's progresses through the brain.

This disease, like Parkinson's and Alzheimer's, starts in one area of the brain and spreads to the rest of it. This is also similar to the spread of prions, the self-replicating proteins implicated in mad cow disease and, in humans, Creutzfeldt-Jakob disease. As the misfolded protein reaches more parts of the brain, it could be responsible for the progressive worsening of these diseases.

Now that we know that these misfolded proteins spend part of their time outside of cells, traveling from one cell to another, new drugs could target them there, Kopito said. This could help prevent or at least block the progression of these diseases.

Kopito is currently working to figure out how misfolded proteins get past cell membranes into cells in the first place. It is only once in the cell's cytoplasm that these proteins can recruit others. So these studies could help find ways to keep these mischief-makers away from the normal proteins.

He is also collaborating with biology professor Linqun Luo to track these proteins between cells in the well-mapped fruit fly nervous system. In the future, Kopito said he hopes to link his cell biology work to disease pathology in order to understand the role misfolded proteins play in human disease.

Gene fuelled transporter causes breast cancer cells to self-destruct

Scientists at Queen's have shown that they can deliver a gene directly into breast cancer cells causing them to self-destruct, using an innovative, miniscule gene transport system, according to research published today (28 February) in the International Journal of Pharmaceutics.

Using a transport system called a Designer Biomimetic Vector (DBV), Dr Helen McCarthy, from Queen's School of Pharmacy, funded by Breast Cancer Campaign, packaged a gene into a nanoparticle 400 times smaller than the width of a human hair, allowing it to be delivered straight into breast cancer cells in the laboratory. The gene called iNOS, is targeted specifically to breast cancer cells using the DBV where it forces the cells to produce poisonous nitric oxide; either killing the cells outright or making them more vulnerable to being destroyed by chemotherapy and radiotherapy. As this approach leaves normal healthy breast cells unaffected, this would overcome many of the toxic side effects of current treatments.

Further investigation is needed but it could be trialled in patients in as little as five years. Dr McCarthy's next step is to turn the nanoparticles into a dried powder that could be easily transported and reconstituted before being given to patients. Dr McCarthy said: "A major stumbling block to using gene therapy in the past has been the lack of an effective delivery system. Combining the Designer Biomimetic Vector with the iNOS gene has proved successful in killing breast cancer cells in the laboratory. In the long term, I see this being used to treat people with metastatic breast cancer that has spread to the bones, ideally administered before radiotherapy and chemotherapy. Dr Lisa Wilde, Research Information Senior Manager, Breast Cancer Campaign said: "Gene therapy could potentially be an exciting avenue for treating breast cancer. Although at an early stage, Dr McCarthy's laboratory research shows that this system for delivering toxic genes to tumour cells holds great promise and we look forward to seeing how it is translated into patients."

York U researchers uncovering how ovarian cancer resists chemotherapy

March 2, 2011

TORONTO – York University researchers have zeroed in on a genetic process that may allow ovarian cancer to resist chemotherapy.

Researchers in the university's Faculty of Science & Engineering studied a tiny strand of our genetic makeup known as a MicroRNA, involved in the regulation of gene expression. Cancer occurs when gene regulation goes haywire.

"Ovarian cancer is a very deadly disease because it's hard to detect," says biology professor Chun Peng, who co-authored the study. By the time it's diagnosed, usually it is in its late stages. And by that point there's really no way to treat the disease. Even when the disease is discovered in its early stages, chemotherapy doesn't always work," she says.

Peng was among a team of researchers that discovered a receptor, ALK7 that induces cell-death in epithelial ovarian cancer cells. They have now discerned that microRNA 376c targets this crucial receptor, inhibiting its expression and allowing ovarian cancer cells to thrive.

"Our evidence suggests that microRNA 376c is crucial to determining how a patient will respond to a chemotherapeutic agent," says Peng. "It allows cancer cells to survive by targeting the very process that kills them off," she says.

In examining tumours taken from patients who were non-responsive to chemotherapy, researchers found a higher expression of microRNA 376c and a much lower expression of ALK7.

Peng believes that this research is a step towards being able to make chemotherapy drugs more effective in the treatment of the disease.

"Further study is needed, but ultimately if we can introduce anti-microRNAs that would lower the level of those microRNAs that make cancer cells resistant to chemotherapeutic drugs, we will be able to make chemotherapy more effective against ovarian cancer," Peng says.

She urges women to educate themselves about the risk factors and symptoms of the disease. For more information, visit <http://www.ovariancanada.org> .

Peng is a world expert in the area of ovarian cancer and the molecular basis of complications in pregnancy. Her research on chemo-resistance has also contributed to knowledge and prediction of pre-eclampsia, a pregnancy disorder that is a leading cause of maternal and perinatal complications and death.

The article, "MicroRNA 376c enhances ovarian cancer cell survival by targeting activin receptor-like kinase 7: implications for chemoresistance," was published in the *Journal of Cell Science*.

Gene expression to distinguish metastasizing from non-metastasizing head and neck cancers

Feb 24, 2011

The validation of a test, based on gene expression and predicting the tumours that will metastasize in lymph nodes of head & neck cancers, was presented today at the 3rd International Conference on innovative approaches in Head and Neck Oncology (ICHNO), in Barcelona.

Dr Robert Takes, from the Radboud University Nijmegen Medical Centre, the Netherlands, reported results of a study involving 222 cases of oral or oropharyngeal cancer. The study was jointly led by scientists from Nijmegen and the University Medical Center Utrecht, and involved all eight head and neck oncological centres of the Netherlands. "Today, it is impossible with current diagnostic tools to detect small lymph node metastasis in patients with head and neck squamous cell carcinoma and therefore it is common practice to operate on the neck even if no metastases have been detected," said Dr Takes. "The majority of these operations is unnecessary because, in most cases, no metastases are present."

If the chance of metastasis could be predicted more accurately, the number of operations could be reduced. "In our study, determining gene expression changes in the primary tumour improved the distinction between tumours that do metastasize from those that don't," continued Dr Takes.

With an array containing a set of 825 relevant genes, identified in a prior study and suitable for clinical application, distinction between metastasizing and non-metastasizing tumours was possible. The test correctly predicted the absence of metastasis in 89% of the cases.

"This is the first biological test that was able to obtain a high level of accuracy and has been validated in multiple centres on a large cohort of patients," said Dr Takes.

"The possible reduction of unnecessary neck treatments in case of a negative test may result in decreased morbidity without deterioration of oncological outcomes. Also, in the remaining cases that still develop metastasis in the neck, salvage treatment is still possible," added Dr Takes.

This signature is an additional method to already existing means to assess the neck, like imaging techniques and sentinel node procedures. "One important message arising from the study is that the combination of biological (gene signature) and clinical factors did better than either alone," commented Prof Adrian Begg from the Netherlands Cancer Institute (NKI). "It thus appears that this signature is a useful addition which can help the decision on treatment policy."

"Treatment is usually mainly selected based on the anatomical extent of the primary tumour and its metastasis. Additional biological information on the behaviour of each individual tumour could result in a more tailored treatment resulting in better survival," said Dr Takes.

"Takes and colleagues have carried out an important and essential step in all studies on gene signatures," concluded Prof Begg, "namely to move on from the initial finding of potential prognostic or predictive significance to validation in an independent clinical series."

"We look forward to further validation and refinement of this approach which opens promising developments. In such studies it would still be useful to look at genome-wide expression, which would provide the opportunity to not only validate the present signature but also to look for even better ones."

Discovery and Annotation of Small Proteins Using Genomics, Proteomics and Computational Approaches

March 07, 2011

A study published in the journal *Genome Research* demonstrates that there are potential short open reading frame (sORF) candidates to be annotated in sequenced genomes and also described is an efficient strategy for discovery of sORFs in species with no genome annotation yet available.

Abstract

Small proteins (10-200 amino acids [aa] in length) encoded by short open reading frames (sORF) play important regulatory roles in various biological processes, including tumor progression, stress response, flowering, and hormone signaling. However, ab initio discovery of small proteins has been relatively overlooked. Recent advances in deep transcriptome sequencing make it possible to efficiently identify sORFs at the genome level. In this study, we obtained ~2.6 million expressed sequence tag (EST) reads from *Populus deltoides* leaf transcriptome and reconstructed full-length transcripts from the EST sequences. We identified an initial set of 12,852 sORFs encoding proteins of 10-200 aa in length. Three computational approaches were then used to enrich for bona fide protein-coding sORFs from the initial sORF set: (1) coding-potential prediction, (2) evolutionary conservation between *P. deltoides* and other plant species, and (3) gene family clustering within *P. deltoides*. As a result, a high-confidence sORF candidate set containing 1469 genes was obtained. Analysis of the protein domains, non-protein-coding RNA motifs, sequence length distribution, and protein mass spectrometry data supported this high-confidence sORF set. In the high-confidence sORF candidate set, known protein domains were identified in 1282 genes (higher-confidence sORF candidate set), out of which 611 genes, designated as highest-confidence candidate sORF set, were supported by proteomics data. Of the 611 highest-confidence candidate sORF genes, 56 were new to the current *Populus* genome annotation. This study not only demonstrates that there are potential sORF candidates to be annotated in sequenced genomes, but also presents an efficient strategy for discovery of sORFs in species with no genome annotation yet available.

The article is published online in *Genome Research* and is free to access.

Novel Mechanism for Control of Gene Expression Revealed

March 4, 2011

(Boston) – Dr. David Levin, Professor of Molecular & Cell Biology at Boston University Henry M. Goldman School of Dental Medicine and Professor of Microbiology at Boston University School of Medicine discovered recently a novel, evolutionarily conserved mechanism for the regulation of gene expression. The study describing this work titled, “Mpk1 MAPK Association with the Paf1 Complex Blocks Sen1-Mediated Premature Transcription Termination,” appears in the March 4 issue of *Cell*.

Normal cell growth, embryonic development, and responses to stress, require proper spatial and temporal control of gene expression. Studies on control of transcription (RNA biosynthesis) are typically centered on understanding how the RNA polymerase is recruited to the promoter, the control region of a gene. However, new work from Levin and postdoctoral fellow, Ki-Young Kim, has revealed the existence of a second level of control in a yeast model system.

They found that genes expressed solely under certain stress conditions are normally maintained in a silent state by a process called transcriptional attenuation. In attenuation, the RNA polymerase initiates transcription of the gene, but its progress is terminated prematurely by a termination complex that binds to the polymerase. Attenuation occurs commonly in bacteria, but was not previously known to operate in eukaryotic cells (those with a nucleus).

“In response to an inducing stress signal, attenuation must be overcome so that a target gene can be expressed,” said Levin. “The way that works in this instance is that an activating transcription factor, called Mpk1, serves double duty—it is first responsible for recruitment of the RNA polymerase to the promoter, but Mpk1 then binds to the transcribing polymerase to block association of the termination complex.”

Mutations in a human protein, called Senataxin, which is related to a component of the yeast termination complex, are responsible for causing juvenile-onset forms of ALS and ataxia, two neuromuscular degenerative diseases.

In their newest research, Levin and Kim show that the discovered attenuation mechanism is evolutionarily conserved in humans. “The findings of this research have broad implications that translate to human cells,” said Levin. “We know that when the key yeast proteins are replaced by their human counterparts, they are able to engage in the same interactions to exert control over attenuation.”

Levin believes that attenuation is actually a widespread phenomenon. “Approximately 10% of yeast genes appear to be under attenuation control, which suggests that it may also be common in humans,” said Levin. “This opens the door to the possibility of new approaches to therapeutic gene silencing, now that we know transcriptional attenuation operates in eukaryotic cells and that it’s a regulated process.”

Combination Overcomes Breast Cancer Resistance to Herceptin

Mar. 13, 2011

Breast cancer tumors take numerous paths to resist the targeted drug Herceptin, but a single roadblock at a crucial crossroads may restore a tumor's vulnerability to treatment, scientists at The University of Texas MD Anderson Cancer Center report on line at *Nature Medicine*.

Adding the drug saracatinib to Herceptin treatment shrinks previously resistant tumors by cutting off at least five different molecular pathways, each of which can resist, said senior author Dihua Yu, M.D., Ph.D., professor in MD Anderson's Department of Molecular and Cellular Oncology.

"Scientists have identified so many ways by which a tumor resists Herceptin that it raises an important issue for treatment," Yu said. "Will we have to give patients six drugs or 10 drugs to block them all? The side effects would be awful. Two pills are better. This combination is a promising therapy for those with Herceptin-resistant breast cancer."

Working in cell lines, mouse models of breast cancer and checking their work in human tumor samples, Yu and colleagues identified SRC, a known cancer-promoting protein, as the crucial common downstream component of multiple resistance pathways.

Saracatinib is an SRC inhibitor, thwarting that protein and allowing Herceptin to work again in tumors that have a high amount of the HER2 protein.

Only about 26 percent of women with HER2-positive breast cancer respond to Herceptin as single therapy. Between 40 and 60 percent respond to the drug when combined with other chemotherapy.

Combination is ready for clinical trials

Yu said saracatinib has been tested in phase I and phase II clinical trials as a single treatment against late-stage cancers. It has a favorable side effects profile.

"It didn't work as a single agent, but very few drugs work by themselves against late stage disease," Yu said. "Our experiments confirmed its lack of efficacy as a sole treatment. But combined with Herceptin, it's beautiful."

Another SRC inhibitor, dasatinib, has been approved by the U.S. Food and Drug Administration as an anti-cancer drug, but it has harsher side effects, said Siyuan Zhang, Ph.D., a postdoctoral fellow in Yu's lab and the paper's first author.

A tumor-suppressor's job

In 2004, Yu's lab discovered that loss of the tumor-suppressing gene known as PTEN led to Herceptin-resistant tumors. PTEN is a phosphatase -- a protein whose function is to strip phosphate chemical groups off of other molecules.

PTEN has two components, one to remove phosphate groups from lipids, and another to remove them from proteins. PTEN's target protein however, was unknown.

Zhang discovered that SRC is a PTEN target. With its phosphate groups, SRC is active. PTEN stifles SRC by peeling away the phosphates.

If PTEN loss leads to Herceptin resistance, and PTEN targets SRC, would that make SRC the culprit?

On the trail of SRC

In a series of experiments the researchers found:

SRC is active in breast cancer cells once vulnerable but now resistant to Herceptin and in cells that are resistant from the start.

Activation of SRC drives resistance to Herceptin. Tumors with low SRC levels treated by Herceptin shrunk to 20 percent of their original volume in 21 days while SRC-heavy tumors increased by nearly 400 percent over the same time in mouse experiments.

SRC activity correlates with patient response to Herceptin. Assessing SRC activation in samples of 57 human breast cancer tumors, the team found that more than 90 percent of tumors with low SRC responded compared with 40 percent of tumors with active SRC.

Patients with little active SRC had a median survival of 57.9 months compared with 34.2 months in those with high SRC activity.

SRC is activated by a number of receptor tyrosine kinases that cause resistance, including IGF-1R, EGFR, ERBB2, HER3, and Met, separate pathways that work through SRC. "Block SRC, and you reverse them all," Zhang said.

Crushing resistance

Combining Herceptin and saracatinib to treat resistant tumors in mice reduced tumor volume by 90 percent in 25 days. Herceptin alone kept tumor volume about the same during the same period, while control and saracatinib alone permitted growth of more than 200 percent.

The difference was more striking in tumors deficient in SRC's enemy, the PTEN tumor-suppressor. The combination reduced tumor volume by more than 90 percent while the two drugs alone allowed growth of between 200 and 400 percent.

Gene That Mediates Response to Key Cancer Drugs Frequently Mutated in Young Leukemia Patients Who Relapse

Mar. 15, 2011

Despite dramatically improved survival rates for childhood acute lymphoblastic leukemia (ALL), relapse remains a leading cause of death from the disease. Work led by St. Jude Children's Research Hospital investigators identified mutations in a gene named CREBBP that may help the cancer resist steroid treatment and fuel ALL's return.

CREBBP plays an important role in normal blood cell development, helping to switch other genes on and off. In this study, researchers found that 18.3 percent of the 71 relapsed-ALL patients carried alterations in the DNA sequence of CREBBP. In contrast, the gene's sequence was changed in just one of the 270 young leukemia patients whose cancer did not return.

Investigators say the gene is a potential indicator of relapse risk because of the high frequency of CREBBP mutations in relapsed patients and evidence the changes persisted from diagnosis or emerged at relapse from subpopulations of leukemia cells present from the beginning. Researchers also found evidence the changes occur in important regulatory regions of the gene and affect cell function, including how cancer cells respond to the steroids that play an important role in cancer treatment. The work appears in the March 10 issue of the scientific journal *Nature*.

"This study gives us further evidence that detailed genomic studies can identify important mutations that influence tumor response to treatment," said Charles Mullighan, M.D., Ph.D., assistant member of the St. Jude Department of Pathology. Mullighan and Jinghui Zhang, Ph.D., an associate member of the St. Jude Department of Computational Biology, are co-first authors. Mullighan is also the corresponding and senior author.

In the same issue of *Nature*, investigators also reported that deletions and deactivating mutations in CREBBP and a related gene known as EP300 occurred in about one-third of patients identified with one of the two most common subtypes of B-cell non-Hodgkin lymphoma. Mullighan is one of that study's five St. Jude co-authors.

Previous reports have linked deletions or chromosome rearrangements involving CREBBP to rare cases of acute leukemia. But this is the first study linking changes in the gene's DNA sequence to leukemia and lymphoma, cancers of the blood and bone marrow.

ALL is the most common childhood cancer. While ALL cure rates have climbed to 90 percent, the disease is often deadly if it returns. This study was designed to advance understanding of the biological basis of treatment failure. "The results of this study emphasize that there are additional genetic changes that help determine whether a child does well or relapses," Mullighan said.

The findings stem from the largest DNA sequencing project yet for ALL, which is diagnosed in about 3,000 U.S. children annually. Researchers from St. Jude and the National Cancer Institute tracked changes in 300 genes from 23 young ALL patients. For each gene, researchers compared the DNA makeup in the patient's normal cells with the sequence at diagnosis and relapse.

The effort turned up 52 non-inherited mutations in 32 genes, many for the first time. The group included four in CREBBP. When researchers checked another 341 young leukemia patients for alteration in CREBBP, they found that 13 of the 71 relapsed-ALL patients carried changes. In two more, pieces of CREBBP's DNA were deleted.

"The robust and accurate analytical method that we developed for processing such a large data volume made discovery of the CREBBP mutations possible," Zhang said. "This exciting finding illustrates that genomic sequencing can provide insight into not only disease initiation, but progression and prognosis as well."

Fourteen mutations were found scattered throughout CREBBP. The list includes an alteration also linked to Rubinstein-Taybi syndrome, a rare inherited multisystem developmental disorder, as well as mutations linked to the cell's steroid response. Four alterations occurred in the region of the gene that regulates DNA expression through a process of chemical modification known as acetylation. Working in mouse cells growing in the laboratory, researchers showed that CREBBP mutations disrupted acetylation of key DNA targets.

When researchers treated CREBBP-mutated leukemia cells growing in the laboratory with the steroid dexamethasone, a majority showed resistance to the drug. The study included cells from nine ALL subtypes. But researchers found most of the cells proved sensitive to another drug. That drug, vorinostat, uses a different mechanism to impact acetylation. Researchers now plan to test vorinostat in a mouse model of relapsed ALL.

Researchers develop new cancer treatment

Apr 5, 2011

Scientists from the School of Pharmacy at Queen's University Belfast and Almac Discovery Ltd have developed a new treatment for cancer which rather than attacking tumours directly, prevents the growth of new blood vessels in tumours, starving them of oxygen and nutrients, thereby preventing their growth.

Targeting tumour blood vessels is not a new concept, however, this drug attacks the blood vessels using an entirely different pathway and therefore could be useful for treating tumours which don't respond to or which are resistant to current therapies of this type.

Professor Tracy Robson and her research team at Queen's, in collaboration with researchers at Almac Discovery, developed a new drug to disrupt the tumour blood supply. They have demonstrated that this leads to highly effective inhibition of tumour growth in a number of models as reported this month in *Clinical Cancer Research*, a journal of the American Association for Cancer Research. Almac Discovery is developing the drug candidate and expects to start clinical trials within the next year.

Professor Tracy Robson from the School of Pharmacy at Queen's explains: "By understanding the anti-angiogenic potential of the natural protein, FKBPL, we have been able to develop small peptide-based drugs that could be delivered to prevent tumour growth by cutting off their blood supply. This is highly effective in models of prostate and breast cancer.

"However, this also has the potential for the treatment of any solid tumour and we're excited about continuing to work with Almac Discovery as this drug enters clinical trials."

Dr Stephen Barr, President and Managing Director of Almac Discovery said: "This is a first class example of a collaboration between a university and industry to produce a novel approach to cancer therapy that has a real chance of helping patients".

The Almac Discovery / Queen's University drug is currently undergoing preclinical development and may provide a first-in-class therapy for targeting tumour angiogenesis by an entirely different pathway to those agents currently approved.

Source: Almac Discovery Ltd

New computer-based system can distinguish similar secondary tumours

Apr 5, 2011

A new computer-based system discussed in the International Journal of Healthcare Technology and Management can distinguish between apparently similar secondary tumours and allow a cancer specialist to trace the metastases back to the site of the original cancer in the patient's body.

Cancer can spread through the body without the patient knowing that they had a primary tumour in the colon, lung, breast, prostate or other organ. When patients with metastatic cancer visit their doctor with symptoms it is then a difficult task to identify the tissue of origin of the cancer and so treat it accordingly. A European team has now tested software that can classify superficially identical tumours based on data obtained from a gene expression microarray analysis of biopsied tumour tissue. Given that metastatic cancer of unknown primary site (CUP) is one of the 10 most frequent cancer diagnoses worldwide the software could prove indispensable in treating cancer that has reached this stage.

Previous studies have shown that it is possible to distinguish between metastatic cancer tissues even though they look almost identical under the microscope by analysing them chemically using DNA micro-arrays. Unfortunately, such arrays, while widely used in research laboratories, are complex and expensive and not viable in the clinical setting of a hospital or oncology unit. Commonly, samples would have to be sent to specialist laboratories, which delays results and is expensive. A much simpler approach is to use automated software that can analyse tissues "in silico".

Torik Ayoubi of KU Leuven in Belgium and colleagues at the Maastricht University Medical Centre in The Netherlands have now tested the TCLASS software from <http://www.mastergenix.com/> on a random set of 100 metastatic cancers that make up part of the large Expression Project for Oncology and found that they could classify them according to their original cancer type just as accurately as any of the available laboratory tools. The advantage is that the TCLASS approach is extremely simple to implement and could potentially be further developed as a major diagnostic tool.

Scientists Discover a Way to Kill Off Tumors in Cancer Treatment Breakthrough

Apr. 4, 2011

Scientists from the School of Pharmacy at Queen's University Belfast and Almac Discovery Ltd have developed a new treatment for cancer which rather than attacking tumours directly, prevents the growth of new blood vessels in tumours, starving them of oxygen and nutrients, thereby preventing their growth.

Targeting tumour blood vessels is not a new concept, however, this drug attacks the blood vessels using an entirely different pathway and therefore could be useful for treating tumours which don't respond to or which are resistant to current therapies of this type.

Professor Tracy Robson and her research team at Queen's, in collaboration with researchers at Almac Discovery, developed a new drug to disrupt the tumour blood supply. They have demonstrated that this leads to highly effective inhibition of tumour growth in a number of models as reported this month in *Clinical Cancer Research*, a journal of the American Association for Cancer Research. Almac Discovery is developing the drug candidate and expects to start clinical trials within the next year.

Professor Tracy Robson from the School of Pharmacy at Queen's explains: "By understanding the anti-angiogenic potential of the natural protein, FKBPL, we have been able to develop small peptide-based drugs that could be delivered to prevent tumour growth by cutting off their blood supply. This is highly effective in models of prostate and breast cancer.

"However, this also has the potential for the treatment of any solid tumour and we're excited about continuing to work with Almac Discovery as this drug enters clinical trials."

Dr Stephen Barr, President and Managing Director of Almac Discovery said: "This is a first class example of a collaboration between a university and industry to produce a novel approach to cancer therapy that has a real chance of helping patients."

The Almac Discovery / Queen's University drug is currently undergoing preclinical development and may provide a first-in-class therapy for targeting tumour angiogenesis by an entirely different pathway to those agents currently approved.

Story Source:

The above story is reprinted (with editorial adaptations by *ScienceDaily* staff) from materials provided by Queen's University Belfast, via EurekAlert!, a service of AAAS.

Journal Reference:

1. A. Valentine, M. O'Rourke, A. Yakkundi, J. Worthington, M. Hookham, R. Bicknell, H. O. McCarthy, K. McClelland, L. McCallum, H. Dyer, H. McKeen, D. J. J. Waugh, J. Roberts, J. McGregor, G. Cotton, I. James, T. Harrison, D. G. Hirst, T. Robson. FKBPL and Peptide Derivatives: Novel Biological Agents That Inhibit Angiogenesis by a CD44-Dependent Mechanism. *Clinical Cancer Research*, 2011; 17 (5): 1044 DOI: 10.1158/1078-0432.CCR-10-2241

Tumors Resistant to Radiation Therapy May Be Controlled by the MET Oncogene

Apr. 4, 2011

Ionizing radiation treats many cancers effectively, but in some patients a few tumor cells become resistant to radiation and go on to cause relapse and metastasis. A growth factor-receptor protein called MET may be a key player in these cells' resistance to radiation, and drugs targeting MET may help to prevent radiation-induced metastasis, according to a study published online April 4th in the *Journal of the National Cancer Institute*.

The gene that encodes MET is known as a cancer-promoting gene, or oncogene. It is expressed at high levels in many cancers and is associated with metastasis. But the exact role it plays and how it may induce radiation-resistant tumor cells is unclear.

To explore the molecular mechanisms behind radioresistance, the group led by Carla Boccaccio, M.D. and Paolo M. Comoglio, M.D., of the Institute for Cancer Research at Candiolo, University of Turin Medical School, examined the expression of the MET gene and the activity of the MET protein in human cancer cell lines before and after exposure to ionizing radiation. They also observed the effect of radiation on two proteins that regulate MET--ataxia telangiectasia mutated (ATM) and nuclear factor kappa B or NF- κ B.

They found that after radiation treatment, MET expression increased up to fivefold due to activation of ATM and NF- κ B. The tumor cells that survived irradiation became more invasive than previously. Moreover, inhibiting MET counteracted this increased invasiveness and promoted death of the tumor cells (apoptosis). In mice, treatment with MET inhibitors, such as specific small-molecule kinase inhibitors, enhanced the effect of radiation, stopping growth or inducing shrinkage of tumors.

The authors conclude that ionizing radiation drives overexpression and activity of MET through the ATM and NF- κ B signaling pathways, making some tumor cells resistant to radiation and more invasive. They also conclude that drugs that inhibit MET might counter radiation resistance.

"This has important therapeutic implications," they write, "as it suggests that the combination of radiotherapy with MET inhibition can radiosensitize cancer cells."

In an accompanying editorial, Olga Guryanova M.D., Ph.D. and Shideng Bao, Ph.D., of the Lerner Research Institute at the Cleveland Clinic, Cleveland, Ohio, note that the study adds new details to emerging knowledge of the roles of MET and NF- κ B in therapeutic resistance. "The finding that NF- κ B activation is ATM dependent adds yet another vignette to the picture," they write.

The editorialists point out that the study also raises questions for future investigation. One step, they suggest, would be to test human tumor cells isolated from surgical specimens to confirm the results. Another would be to determine whether MET expression is elevated in cancer stem cells, which have shown resistance to radiation and chemotherapy in some studies.

"Augmenting the sensitivity of resistant cancer cells to conventional treatments has been the subject of great effort," they write. "Improved radiotherapy with radiosensitizers is expected to increase the efficacy of cancer treatment."

Story Source:

The above story is reprinted (with editorial adaptations by *ScienceDaily* staff) from materials provided by Journal of the National Cancer Institute, via EurekAlert!, a service of AAAS.

Journal Reference:

1. Francesca De Bacco, Paolo Luraghi, Enzo Medico, Gigliola Reato, Flavia Girolami, Timothy Perera, Pietro Gabriele, Paolo M. Comoglio, Carla Boccaccio. Induction of MET by Ionizing Radiation and Its Role in Radioresistance and Invasive Growth of Cancer. *Journal of the National Cancer Institute*, 2011; DOI: 10.1093/jnci/djr093

Common Variant of P53 Tumor Suppressor Gene Linked to Increased Inflammatory Responses

Apr. 4, 2011

New findings by Fox Chase Cancer Center researchers link a common variant of the powerful anticancer gene p53 to increased inflammatory responses following DNA damage. The results may help explain why African Americans, who more frequently possess this variant, tend to be more susceptible to certain kinds of inflammation-related diseases and cancers, such as type II diabetes and colorectal cancer.

Maureen Murphy, PhD, associate professor at Fox Chase, published the findings in the March issue of the journal *Molecular and Cellular Biology*, and presented the results at the AACR 102nd Annual Meeting 2011.

Murphy and her colleagues studied the DNA variation, or polymorphism, located at amino acid 72, or codon 72, in the p53 gene -- human beings can have either the proline or arginine amino acid at this location. The proline variant is more common in African Americans and other human populations originating from regions near the equator. The arginine and proline variants were known to affect p53's anticancer functions at the cellular level, but their role in living organisms had not been explored.

To find out how the polymorphisms influence p53's activity, the researchers genetically engineered mice to express either the proline or the arginine variant. In animals with the proline variant, DNA-damaging radiation triggered an increase in programmed cell death along with enhanced activation of inflammation genes.

"This study provides the first evidence that p53 and its polymorphisms play a role in inflammation," says Murphy. "Now we need to look at these variants and the risk of cancers associated with inflammation."

Tracing precisely how the proline variant increases activation of inflammation genes, the researchers found that the proline form of the gene interacts more with a DNA-binding protein complex called NF-kB, which regulates the immune response to infection and cellular stress. Consistently, Murphy and her colleagues found that mice with the proline variant responded more strongly to the challenge of DNA damage than did mice with the arginine variant.

Murphy suggests that the proline version may be more common in individuals living near the equator because it may help people fight the greater number of immune challenges presented by viruses and bacteria that thrive in the warmer temperatures near the equator.

Next, Murphy and her team will study whether the codon 72 polymorphisms influence animals' susceptibility to inflammation-associated cancers, such as colitis-associated colorectal cancer, prostate cancer, stomach cancer induced by *Helicobacter pylori* infection, and liver cancer caused by the hepatitis B virus.

Murphy notes that p53 mutations are seen in the majority of human cancers, a fact that lends particular significance to the research being pursued in her lab.

"The p53 tumor suppressor gene is the most important cancer-related gene," she says. "It responds to DNA damage and other stress by halting the cell cycle, helping to repair DNA. But, when the damage is too severe, or when the earliest pre-cancerous lesion forms, p53 initiates programmed cell death of that pre-cancerous cell."

This area of investigation was new for Murphy, who relied on guidance from colleagues with different scientific backgrounds to make rapid headway in her studies. Noting Fox Chase's collaborative environment, she says that "it wasn't so painful making the transition into making mouse models. I could not have done this research anyplace else."

Amanda Frank, Yan Zhou, Karthik Devarajan, and Andres Klein-Szanto from Fox Chase are co-authors on the study. Additional colleagues were from the University of Pennsylvania and the German Cancer Research Foundation.

Stress Signal in Cancer Cells Triggers Similar Response in Other Cells, Aiding Tumor Growth

Apr. 4, 2011

Researchers at the University of California, San Diego School of Medicine say a "stress response" mechanism used by normal cells to cope with harsh or demanding conditions is exploited by cancer cells, which transmit the same stress signal to surrounding cells, triggering an inflammatory response in them that can aid tumor growth.

The findings are reported by Maurizio Zanetti, MD, professor of medicine and director of the Laboratory of Immunology at the UC San Diego Moores Cancer Center, and colleagues, and published in the April 4 early online edition of *Proceedings of the National Academy of Sciences*.

The endoplasmic reticulum (ER) is the protein-making factory inside all cells. Increased physiological demands or disease conditions can sometimes cause proteins to misfold and accumulate in the ER. Cells typically respond by an ER stress response, which attempts to reset normal ER balance.

For normal cells, the ER stress response is transient. For tumor cells, it's life. Because they exist in an environment that's invariably difficult (their host is always trying to kill them, and oxygen and nutrient deprivation are frequent), tumor cells produce an on-going ER stress response, which helps them not only to survive, but to thrive.

According to Zanetti and colleagues, tumor cells generate "transmissible ER stress." Specifically, they induce bystander cells to issue a similar stress response, most notably nearby macrophages -- a type of white blood cell employed by the body's immune system to recognize and remove pathogens and cellular debris.

Recently, several laboratories, including some at UC San Diego, have underscored the crucial role of inflammation in promoting cancer growth. A consequence of "transmissible ER stress" points to "receiver" macrophages as an important source of inflammation, which serves as an environmental cue for cancer development.

"It's well-known that macrophages entering the tumor microenvironment lose the ability to aid the immune system in rejecting the tumor, and that they may actually play a role in actively suppressing anti-tumor immunity," said Zanetti. "We believe that transmissible ER stress could be an important initial tumor-derived signal that promotes the 'brainwashing' of macrophages in the tumor microenvironment. It could be the first event in a cascade that results in the commandeering of macrophages by the tumor."

If so, transmissible ER stress may represent a unifying mechanism that explains at least some of the earliest interactions between tumors and the immune system. "Our paper details the first evidence of this phenomenon," Zanetti said, adding that transmissible ER stress also presents a new, potential target for tumor-specific therapies and drugs.

"Our findings suggest that development of therapies targeted against the tumor ER stress response may be doubly effective," said Zanetti. "Such therapies would target not only the tumor's intrinsic ability to cope with microenvironmental insults, but, at the same time, would impede the tumor cells' ability to nullify the anti-tumor immune response, perhaps allowing our bodies to more easily fight off tumors."

Co-authors of the study are Navin R. Mahadevan and Jeffrey Rodvold, Laboratory of Immunology UC San Diego Moores Cancer Center and Biomedical Sciences Program; Homero Sepulveda, BD Biosciences, San Diego; Steven Rossi, UCSD Department of Pediatrics, Cancer Symptom Control Program; and Angela F. Drew, Department of Cancer and Cell Biology, University of Cincinnati.

Funding for this research came, in part, from grants from the UCSD Academic Senate, UCSD Medical Scientist Training Program and the National Institute on Drug Abuse.

<http://www.sciencedaily.com/releases/2011/03/110318102243.htm>

DNA of 50 Breast Cancer Patients Decoded

Apr. 3, 2011

In the single largest cancer genomics investigation reported to date, scientists have sequenced the whole genomes of tumors from 50 breast cancer patients and compared them to the matched DNA of the same patients' healthy cells. This comparison allowed researchers to find mutations that only occurred in the cancer cells.

They uncovered incredible complexity in the cancer genomes, but also got a glimpse of new routes toward personalized medicine. The work was presented at the American Association for Cancer Research 102nd Annual Meeting 2011.

In all, the tumors had more than 1,700 mutations, most of which were unique to the individual, says Matthew J. Ellis, MD, PhD, professor of medicine at Washington University School of Medicine in St. Louis and a lead investigator on the project.

"Cancer genomes are extraordinarily complicated," Ellis says. "This explains our difficulty in predicting outcomes and finding new treatments."

To undertake the massive task, Washington University oncologists and pathologists at the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine collaborated with the university's Genome Institute to sequence more than 10 trillion chemical bases of DNA -- repeating the sequencing of each patient's tumor and healthy DNA about 30 times to ensure accurate data.

"The computing facilities required to analyze this amount of data are similar in scale to those of the Large Hadron Collider, used to understand the workings of sub-atomic particles," Ellis says.

The DNA samples came from patients enrolled in a clinical trial that Ellis is leading for the American College of Surgeons Oncology Group. All patients in the trial had what is called estrogen-receptor-positive breast cancer. These cancer cells have receptors that bind to the hormone estrogen and help the tumors grow.

To slow tumor growth and make the tumors easier to remove, patients received estrogen-lowering drugs before surgery. But, for unknown reasons, this treatment does not always work. Twenty-four of the 50 tumor samples came from patients whose tumors were resistant to this treatment, and 26 came from patients whose tumors responded. Comparing the two groups might help explain why some estrogen-receptor-positive breast cancer patients do well with estrogen-lowering drugs and others poorly.

Confirming previous work, Ellis and colleagues found that two mutations were relatively common in many of the patients' cancers. One called PIK3CA is present in about 40 percent of breast cancers that express receptors for estrogen. Another called TP53 is present in about 20 percent.

Adding to this short list of common mutations, Ellis and colleagues found a third, MAP3K1, that controls programmed cell death and is disabled in about 10 percent of estrogen-receptor-positive breast cancers. The mutated gene allows cells that should die to continue living. Only two other genes, ATR and MYST3, harbored mutations that recurred at a similar frequency as MAP3K1 and were statistically significant.

"To get through this experiment and find only three additional gene mutations at the 10 percent recurrence level was a bit of a shock," Ellis says.

In addition, they found 21 genes that were also significantly mutated, but at much lower rates -- never appearing in more than two or three patients. Despite the relative rarity of these mutations, Ellis stresses their importance.

"Breast cancer is so common that mutations that recur at a 5 percent frequency level still involve many thousands of women," he says.

Ellis points out that some mutations that are rare in breast cancer may be common in other cancers and already have drugs designed to treat them.

"You may find the rare breast cancer patient whose tumor has a mutation that's more commonly found in leukemia, for example. So you might give that breast cancer patient a leukemia drug," Ellis says.

But such treatment is only possible when the cancer's genetics are known in advance. Ideally, Ellis says, the goal is to design treatments by sequencing the tumor genome when the cancer is first diagnosed.

"We get good therapeutic ideas from the genomic information," he says. "The near-term goal is to use information on whole genome sequencing to guide a personalized approach to the patient's treatment." This work builds on previous collaborations between Washington University oncologists and the Genome Institute. In a study published last year in *Nature*, they reported the complete tumor and normal DNA sequences of a woman with "triple-negative" breast cancer, a particularly aggressive type that is difficult to treat and more common in younger women and African-Americans.

While many mutations are rare or even unique to one patient, Ellis says quite a few can be classified on the basis of common biological effects and therefore could be considered together for a particular therapeutic approach.

Ellis looks to future work to help make sense of breast cancer's complexity. But these highly detailed genome maps are an important first step.

"At least we're reaching the limits of the complexity of the problem," he says. "It's not like looking into a telescope and wondering how far the universe goes. Ultimately, the universe of breast cancer is restricted by the size of the human genome."

Reference: Ellis et al. Breast cancer genome. Presented April 2, 2011, at the 102nd Annual Meeting of the American Association for Cancer Research in Orlando, Fla.

Ding L, Ellis MJ, Weinstock GM, Aft R, Watson M, Ley TJ, Wilson RK, Mardis ER et al. Cancer remodeling in a basal-like breast cancer metastasis and xenograft. *Nature*. April 15, 2010.

This work was supported by grants from the National Human Genome Research Institute, the Breast Cancer Research Foundation, the National Cancer Institute, Susan G. Komen for the Cure and Washington University School of Medicine.

Story Source:

The above story is reprinted (with editorial adaptations by *ScienceDaily* staff) from materials provided by Washington University School of Medicine. The original article was written by Julia Evangelou Strait.