MIT CEHS NEWSLETTER

Supported by NIH NIEHS Center Core Grant P30-ES002109

Massachusetts Institute of Technology
Center for Environmental Health Sciences

Fall/Winter 2012

Research team uncovers a new cellular stress response mechanism

As published in the NIEHS Environmental Factor, Article by Melissa Kerr on August 2012

In a recently published study, *(http://www.ncbi.nlm.nih.gov/pubmed/22760636)* a team of NIEHS-funded researchers applied innovative technologies to discover a step-wise process in the mechanisms of cell defense against toxic chemicals. They report that when introduced into a stress-inducing environment, the cell attempts to fortify its defenses by modifying a unique program that drives the makeup of its proteins. The findings appeared in the July 3 issue of Nature Communications.

Lead researcher on the team, Peter Dedon, M.D., Ph.D., *(http://web.mit.edu/be/people/dedon.shtml)* is a professor of toxicology and biological engineering at the Massachusetts Institute of Technology (MIT). The team included first author Clement Chan, Ph.D., of MIT, and 2006 NIEHS Outstanding New Environmental Scientist awardee Thomas Begley, Ph.D., *(http://www.albany.edu/cancergenomics/faculty/tbegley/tbegley.html)* a cancer biologist at the College of Nanoscale Science and Engineering (CNSE) at the University at Albany, along with colleagues from MIT and CNSE.

Dedon and Begley's research team has focused on RNA mechanisms that control protein expression within a cell. By delineating thep mechanisms of cellular response to stress, the team's research advances understanding of potential targets for attenuating the damaging effects that toxicants and other stressors may have on a cell.

"If you understand the mechanism, then you can design interventions," Dedon explained. "For example, what if we develop ways to block or interrupt the toxic effects of the chronic inflammation?" Inflammation has been implicated in aging and a range of diseases, including cancer.

Protein factory

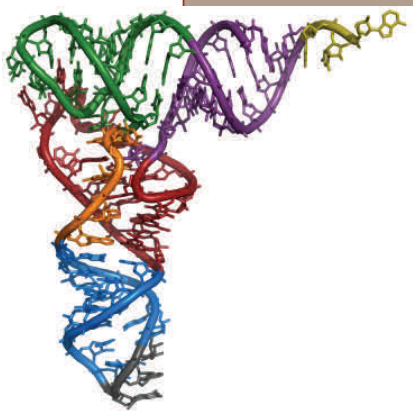
Proteins are major players within a cell, and the amino acids that make up proteins are specified by the information encoded within a cell's genes. The process of building proteins, called translation, occurs in the ribosome and consists of transfer ribonucleic acids (tRNA) binding to messenger RNA (mRNA).

Each tRNA carries a particular amino acid, which corresponds to one or more three-base sequences on the mRNA called codons. Other translational enzymes string the amino acids together to make a protein. A key to the research team's latest work is that different codons for an amino acid are not used equally, with emergency response genes containing biased distributions of specific codons.

Genetic emergency response

The team has now discovered that cells coordinate codon biases in genes with changes in tRNA structure, to adapt the construction of proteins needed for a cell to defend against toxic exposures. Dedon explained, "In the end, a stepwise mechanism leads to selective expression of proteins that you need to survive."

In earlier work reported in 2010, the team exposed yeast cells to different toxic chemicals, including bleach and hydrogen peroxide, both made by human immune cells. They described a cellular response in which a set of two-dozen tRNA structural modifications reprogram following toxicant exposure. They also found that if the cell did not have the ability to change the tRNA modifications, it would not be able to defend itself. This new study built on those findings by focusing on oxidative stress caused by hydrogen peroxide and a specific tRNA modification called m5C (see text box).



X-ray structure of a tRNA molecule found in yeast.
Image: Yikrazuul/wikipedia

Dedon's and Begley's team has found that there are particular patterns of tRNA modification that are markers for toxicant exposure and this may match patterns of codon distribution in groups of genes needed to respond to each toxicant. The authors concluded the paper by writing, "The variety of RNA modifications in the tRNA…suggest[s] a mechanism capable of fine tuning the translational response to virtually any cell stimulus."

The researchers plan to expand their studies of tRNA. If there were some way to control the reprogramming of these tRNA modifications, it could enhance cellular survival. The team also plans to investigate the mechanisms of cancer development in more detail, since certain tRNA-modifying proteins appear to control tumor growth.

http://www.niehs.nih.gov/news/newsletter/2012/8/science-stress/index.htm

In This Issue

Upcoming Events

CEHS "Open House" to be held on January 11th 2013

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Robert S. Harris Lecture to be held on April 25th 2013

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CEHS Poster Session to be held on May 10th 2013

PROFESSOR RIBBECK RECEIVED THE 2013 JOHN KENDREW YOUNG SCIENTIST AWARD

Professor **Katharina Ribbeck** received the 2013 John Kendrew Young Scientist Award (JKA) this past December 2012 This award is given by the European Molecular Biology Laboratory (EMBL) to recognize exceptional biological science scientists in the early stage of their career.

Congratulations to Postdoctoral Associates in the Tannenbaum Laboratory for receiving the American Cancer Society Awards. Dr. **Kun Lu** (pictured on the bottom right) won first place in the postdoctoral oral presentation while Dr. **Uthpala Seneviratne** (pictured on the bottom left) won first place for postdoctoral poster category.

Uthpala Seneviratne

Kun Lu

Congratulations to Emeritus **Gerald Wogan** for receiving the Princess Chulabhorn Gold Medal for research in services to the developing world at the Seventh International Princes Congress "Cancer: From Basic Research to Cure" in Bangkok, Thailand this past December 2012.

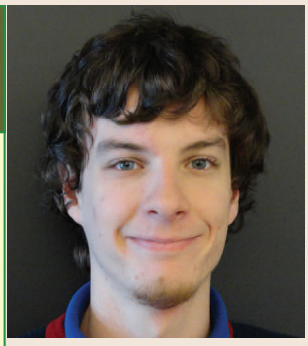
PROFESSOR SAMSON RECEIVED ELLISON MEDICAL FOUNDATION AWARD

Professor **Leona D. Samson** has been awarded the Ellison Medical Foundation Senior Scholar Award. This award supports biomedical research in aging. This project seeks to further investigate the role of Aag-initiated base excision repair and Parp1 in inflammation mediated tissue damage.

Congratulations to Associate Professor **Bevin P. Engelward** and former center faculty member **Jacquelyn Yanch** on having their EHP low-does radiation paper selected as one of the best MIT news stories of 2012!

http://web.mit.edu/newsoffice/2012/prolonged-radiation-exposure-0515.html

Welcome new HQ Staff



We are delighted to introduce a new staff of the Center Headquarters, **Thomas Cardran**, NEU IT coop Asst. System Administrator. Tom is located in room 56-669 and can be reached via email tcardran@mit.edu or by phone 617-452-3431. Tom's coop period will be through June 2013. Please join us in welcoming Tom to the Center!

WELCOME new Center member

We are pleased to announce **Robert G. Croy** as a new Center research member effective November 1, 2012. Dr. Croy will oversee the CEHS Imaging Facilities Core. He is located in room 56-669A and can be reached via email rgcroy@mit.edu or by phone 617-253-6729. Please contact Dr. Croy if you need access or training on the equipment in the Imaging Facilities Core.

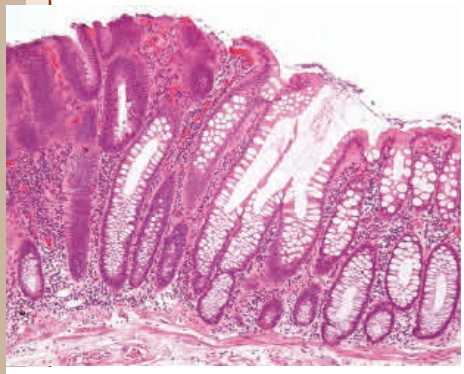
CEHS Second Featured Article

Five CEHS Laboratories Tackle the Relationship between Inflammation and Colon Cancer

Adapted from articles by Anne Trafton, MIT News Office published online on June 11 and 13, 2012.

Colon cancer is the third most prevalent cancer among men and women in the United States. A wealth of information suggests that inflammation is strongly involved in the development of the disease. For example, people with inflammatory bowel diseases are at higher risk, as are people who suffer certain chronic bacterial infections. Two studies by CEHS researchers have shed light on the factors that contribute to this disease, which directly affects over 1.2 million Americans.

Appearing in the June 11 online edition of the *Journal of Clinical Investigation,* CEHS research scientists Jennifer Calvo, Lisiane Meira, and former CEHS Director Leona Samson probed the DNA repair pathways that protect mice from DNA damage produced by inflammation – this DNA damage presumably helps initiate or promote the transformation of normal colonic cells into tumor cells. The team identified three enzymes critical to repairing this damage. Previous studies have shown that humans produce widely varying amounts of one of the enzymes, so the findings offer a possible explanation for why some IBD patients are more likely to develop colon cancer, Samson says. Measuring these enzyme levels in a particular patient could help predict that patient's risk of colon cancer. "All other things being equal, if the same inflammatory response is present in the colon of different individuals, but they have differences in DNA-repair capability, they're probably going to respond differently," says Samson.



This micrograph shows a colorectal adenoma a benign form of cancer that can turn malignant.

Photo:- Image: Wikipedia/Nephrom

Repair failure and disease

The Samson lab has previously shown that inflammation forms reactive molecules to produce a specific type of DNA damage that favors colon cancer development in mice. In that study, the researchers found that a DNA repair enzyme called AAG was necessary to repair this type of damage, known as etheno-base lesions. Mice lacking AAG were much more susceptible to inflammation-induced colon cancer. In the new study, Samson and colleagues looked at the effects of two additional DNA-repair enzymes, ALKBH2 and ALKBH3, which were previously shown to be involved in repairing etheno-base lesions. The researchers induced inflammation by treating the mice with a chemical called dextran sodium sulfate (DSS), which destroys the mucosal lining of the intestines, allowing bacteria to reach the epithelial cells and provoke an inflammatory response. Following such inflammation, mice missing both ALKBH2 and ALKBH3 were much more susceptible to colon cancer than normal mice; the results were even direr among mice missing all three DNA repair enzymes. After analyzing tissue samples, the researchers discovered that all of the mice had initially experienced similar extensive colon damage, but mice with at least one of the three DNA repair enzymes were able to repair most or all of the tissue damage. Mice lacking all three enzymes couldn't perform any tissue repair whatsoever.

The Yin Yang of the immune system

Whereas the Calvo et al. study used a chemical irritant to create inflammation, a complementary CEHS study used *Helicobacter hepaticus*, a bacterium similar to the bacterium that causes stomach ulcers and cancer in humans. The first author of the paper, which was published in the June 11 online issue of the *Proceedings of the National Academy of Sciences* was CEHS scientist Aswin Mangerich, working with CEHS deputy director Peter Dedon and CEHS faculty members Steven Tannenbaum, James Fox, and Gerald Wogan. For the past 30 years, Tannenbaum has led a group of researchers dedicated to studying the link between chronic inflammation and cancer. When the body's immune system detects pathogens or cell damage, it activates an influx of macrophages and neutrophils. These cells engulf bacteria, dead cells and debris. As part of this process, the cells produce highly reactive chemicals that help degrade the bacteria. Unfortunately the localized chemical warfare between the immune system cells and the bacterial targets can result in collateral damage to normal colon cells and, if sustained over a long period, that damage can lead to cancer. In the new MIT study, the researchers analyzed mice that were infected *with H. hepaticus*, which causes the mice to develop a condition similar to inflammatory bowel disease in humans.

Over the course of 20 weeks, the mice developed chronic infections of the liver and colon, with some of the mice developing colon cancer. Throughout the 20-week period, the researchers measured various types of damage to DNA, RNA and proteins. They also examined tissue damage and measured which genes were turned on and off as the infection progressed. One of their key findings was that the liver and colon responded differently to infection. The colon neutrophils, for example, selectively secreted hypochlorous acid, which significantly damages proteins, DNA and RNA by adding a chlorine atom to them. The hypochlorous acid is meant to kill bacteria, but it also leaks into surrounding tissue and damages the epithelial cells of the colon. The researchers found that levels of one of the chlorine-damage products in DNA and RNA, 5-chlorocytosine, correlated well with the severity of the inflammation, which could allow them to predict the risk of chronic inflammation in patients with infections of the colon, liver or stomach. Another difference the researchers found between the colon and the liver was that DNA repair systems became more active in the liver but less active in the colon, even though both were experiencing DNA damage. "It's possible that we have kind of a double whammy [in the colon] -- you have this bacterium that suppresses DNA repair, at the same time that you have all this DNA damage happening in the tissue as a result of the immune response to the bacterium," said Dedon, offering an explanation for how inflammation promotes colon cancer in this model.

The news articles of these stories can be found here:

http://web.mit.edu/newsoffice/2012/colon-cancer-0614.html

http://web.mit.edu/newsoffice/2012/cancer-inflammation-h-pylori-0611.html

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CEHS Third Featured Article

Weapon-wielding marine microbes may protect populations from foes

In some populations, natural antibiotics are produced by a few individuals whose closets relatives carry genes conferring resistance.

Article by Denise Brehn on September 6, 2012

Competition is a strong driving force of evolution for organisms of all sizes: Those individuals best equipped to obtain resources adapt and reproduce, while others may fall by the wayside. Many organisms — mammals, birds and insects, for instance — also form cooperative social structures that allow resources to be defended and shared within a population.

But surprisingly, even microbes, which are thought to thrive only when able to win the battle for resources against those nearest to them, have a somewhat sophisticated social structure that relies on cooperation, according to MIT scientists. These researchers have recently found evidence that some ocean microbes wield chemical weapons that are harmless to close relatives within their own population, but deadly to outsiders.

The weapons are natural antibiotics produced by a few individuals whose closest relatives carry genes that make them resistant. The researchers believe that the few antibiotic producers are acting as protectors of the many, using the antibiotics to defend the population from competitors or to attack neighboring populations.

Prof. Martin Polz (left) and postdoc Otto Cordero examine a petri dish of Vibrio bacteria. Photo: James M. Long, MIT

"We can't know what the environmental interactions really are, because microbes are too small for us to observe them in action," says Professor Martin Polz of MIT's Department of Civil and Environmental Engineering (CEE), lead investigator on a study appearing in this week's issue of the journal Science. "But we think the antibiotics. play a role in fending off competitors. Of course, those competitors could also produce antibiotics. It's a potential arms race out there."

A population of ocean microbes is defined by genetic likeness and shared ecological activities, such as their preferred microhabitat — say, free-floating or attached to algae — or their ability to harvest a particular substance. Because close relatives within populations have very similar if not identical resource requirements, they must by necessity also be strong competitors with one another.

This makes cooperation involving antibiotics doubly surprising, because the ability to produce antibiotics is a classic example of a "selfish" gene that ought to increase the fitness — or reproductive rate — of the individual carrying the gene. In a strictly competitive environment, the microbe would use this advantage against its closest relatives. But now it looks as if this competition is modulated by social interactions where antibiotics produced by a few individuals act as "public goods": items that benefit the group, rather than just the individual.

This differentiation of populations into individuals that produce antibiotics and those that are resistant is one of the first demonstrations that microbial populations engage in a division of labor by social role. This observation also provides an explanation for why so many genes are patchily distributed across genomes of closely related microbes. At least some of these genes may be responsible for creating tightly knit social units of bacteria in the wild.

"It's easy to imagine bacteria in the environment as selfish creatures capable only of reproducing as fast as conditions allow, without any social organization," says Otto Cordero, a CEE postdoc who is a first author on the Science paper. "But that is the mind-blowing part: Bacterial wars are organized along the lines of populations, which are groups of closely related individuals with similar ecological activities."

The study also uncovers an untapped source of antibiotics that could have the potential to aid in the fight against human bacterial pathogens, which are rapidly developing resistance to the few antibiotics in use — nearly all of which are produced by soil-living bacteria. "This paper [shows] that bacteria work together in complex relationships that have largely been underappreciated by the research community as a whole," says Gerry Wright, a professor of biochemistry and biomedical sciences and director of the Michael G. DeGroote Institute for Infectious Disease Research at McMaster University. He adds, "The impact on our understanding of resistance is critical. … This work is really important in showing that we can, in fact, study these big questions in populations of natural bacteria, and we can learn something important about how we use antibiotics and avoid resistance in the clinic."

To obtain these findings, the researchers tested about 35,000 interactions among pairs of 185 strains of Vibrionaceae bacteria populations taken from the ocean. They found that 44 percent of the strains were able to inhibit the growth of at least one other strain and 86 percent were inhibited by at least one other strain. They then used genomic analysis to determine genetic kinship.

http://web.mit.edu/newsoffice/2012/natural-microbe-antibiotic-0906.html