The code for survival: Cells fight stress by reprogramming a system of RNA modifications

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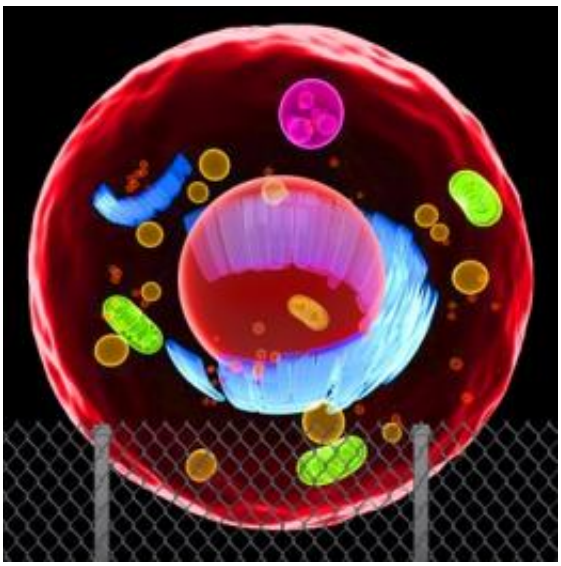

Graphic: Christine Daniloff

(PhysOrg.com) -- When cells are exposed to life-threatening stresses, they take quick action to save themselves. Among other defenses, they start manufacturing proteins that perform critical tasks such as repairing DNA.

Researchers at MIT and the University of Albany have now discovered one way that cells boost production of such proteins. In the Dec. 16 issue of PLoS Genetics, they report that when under stress, cells reprogram a

complicated system of chemical modifications of the RNA molecules that read the genetic code and deliver protein building blocks.

This mechanism is likely involved in cell responses not only to stressful stimuli, such as exposure to toxic chemicals and radiation, but also to hormones, growth factors and nutrients, says Peter Dedon, MIT professor of biological engineering and a senior author of the paper. Dedon is now studying how bacteria use this system to respond to the stress of being attacked by human white blood cells, which may help researchers develop new antibiotics that knock out those defense systems.

From DNA to proteins

DNA is the master orchestrator of every cell's activity, but because it cannot leave the cell nucleus, it needs an array of helper molecules to carry out its instructions. Genes — sequences of nucleic acids that code for a specific protein — are copied into messenger RNA (mRNA), which carries the protein blueprint from the nucleus to cell structures called ribosomes, where proteins are assembled. The genetic code in mRNA is "read" on the ribosome as a series of three-letter sequences, each of which calls for a specific amino acid (the building blocks of proteins).

Those amino acids are delivered to the ribosome by another type of RNA, transfer RNA (tRNA). Like other types of RNA, tRNA consists of a sequence of four main ribonucleosides — adenosine, guanosine, cytidine and uridine. However, after tRNA is synthesized, those ribonucleosides usually undergo dozens of chemical modifications that alter the tRNA structure and function.

A few years ago, Thomas Begley, a former MIT postdoctoral associate who is now an associate professor at the University of Albany, found

that for yeast to survive treatment with a toxic chemical, they require the action of enzymes that modify tRNA.

One of these genes codes for an enzyme that attaches a methyl group (a carbon atom bound to three hydrogen atoms) to ribonucleoside bases. That modification improves the efficiency of protein synthesis at the ribosome, specifically for proteins that contain many units of the amino acid arginine. After searching the yeast genome for genes rich in arginine, Begley found that those genes are critical to the cell's defenses against the original toxic agent. Modifying the tRNAs needed to produce those proteins allows the cell to synthesize the proteins faster and more accurately, allowing cells to mount a more effective defense against the toxic chemical, says Begley.

Patterns of response

In the research reported in the *PLoS Genetics* paper, Begley and Dedon teamed up to examine all 25 tRNA modifications found in yeast. (Most organisms have between 20 and 40.) Dedon's lab developed a way to use mass spectrometry, which can identify the structure of unknown compounds by analyzing their mass, to measure levels of all 25 tRNA modifications at once. The researchers then treated yeast cells with one of four toxic chemicals — MMS (an agent that attaches methyl groups), hydrogen peroxide, arsenic or bleach.

After treatment, levels of the different tRNA modifications increased or decreased, depending on the chemical. Using a multivariate statistical analysis, the researchers looked for patterns, and, for each type of chemical and the dose of the chemical, they identified a characteristic response or signature. As a powerful demonstration of the importance of specific RNA modifications to cell survival, the researchers knocked out individual proteins that synthesize the modifications found to change significantly for each chemical, and showed that the cells became more

susceptible to killing by the chemical. Studying the genes most influenced by those tRNA modifications could lead to clues to how cells cope with life-threatening stresses.

Tao Pan, professor of biochemistry and molecular biophysics at the University of Chicago, says the study overturns a long-held assumption that a tRNA molecule stays in the same modified state throughout its lifetime. “Previously it was believed that tRNA modification is static. This paper shows that under stress, the level of modification can continually change,” says Pan. “The next thing is to understand how and why cells do it.”

Dedon and Begley now plan to investigate the role of tRNA modifications in human cells. Previous studies have suggested that such modifications may suppress tumor development, and understanding those systems better could lead to new cancer diagnostics, according to Begley. “For example, if cells have a certain collection of tRNA modifications, that could indicate a pre-disease state,” he says.

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