Cells defend themselves from viruses, bacteria with armor of protein errors

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When cells are confronted with an invading virus or bacteria or exposed to an irritating chemical, they protect themselves by going off their DNA recipe and inserting the wrong amino acid into new proteins to defend them against damage, scientists have discovered.

These "regulated errors" comprise a novel non-genetic mechanism by which cells can rapidly make important proteins more resistant to attack when stressed, said Tao Pan, Professor of Biochemistry and Molecular Biology at the University of Chicago. A team of 18 scientists from the University of Chicago and the National Institute of Allergy and Infectious Disease led by Pan and Jonathan Yewdell published the findings Thursday in the journal *Nature*.

"This mechanism allows every protein to get some protection," Pan said. "The genetic code is considered untouchable, but this is a non-genetic strategy used in cells to create a bodyguard for proteins."

Proteins are constructed through a process called translation where cellular elements use the genetic code to guide the assembly of building blocks called amino acids into the correct sequence. First, a copy of the DNA, called messenger RNA, is made and transferred to a cellular structure called a ribosome. Transfer RNAs (tRNA), one for each of the 20 amino acids used in building proteins, read the messenger RNA code and bring the proper amino acids to the ribosome, where they are bonded together to form a complete protein.

Each tRNA can be attached to only one of 20 amino acids, a specificity that prevents errors during the construction of proteins. In artificial laboratory preparations, scientists have observed that only one out of every 10,000 amino acids is placed into a protein incorrectly, and thus protein errors were thought to be exceptionally rare.

But Jeffrey Goodenbour, University of Chicago graduate student and co-lead author along with Nir Netzer of the NIAID, decided to look at how often tRNA errors, called misacylations, occurred in live cells. After developing a novel technique for measuring these errors, published for the first time in this paper, the authors were surprised to find a much higher error rate in those cells for the amino acid methionine. As high as one out of every 100 methionines was incorrectly placed in proteins, they found.

When the cells were stressed by exposure to a virus, bacteria or a toxic chemical such as hydrogen peroxide, that error rate went even higher, as up to 10 percent of methionines placed into new proteins were different from what the gene specified.

"That was 1,000 times more than the textbook says should be there," Pan said.

Further experiments revealed that it was always the same amino acid, methionine, placed incorrectly into new proteins. Methionine is one of only two amino acids to carry sulfur atoms on its side chains, a feature that allows it to neutralize dangerous molecules called reactive oxygen species (ROS) that form inside an infected or stressed cell. ROS can damage proteins through a chemical process called oxidation, but methionine can be oxidized (and restored through a process called reduction) without being permanently damaged.

"The idea is that methionine can protect you from having oxidation of

the active site of protein, which would ultimately completely block function of the protein," Goodenbour said. "You end up reducing the total reactive oxygen species load in the cell. It's a very interesting mechanism."

Cells normally put methionines near important parts of a protein to protect those segments from being damaged by reactive oxygen species. When the cell is under stress, and the amount of ROS increases, the number of methionine "errors" is ramped up tenfold, allowing new proteins to be even more resistant to attack.

"Think of a boxing match," Pan said. "If you put methionine close to active site, the reactive oxygen species has to get past it to get to the active site residues for oxidization. You've put something right in front of it so a protein can take a hit. If you have a lot of methionines, to knock this protein out will take many, many hits. So this is a strategy used in cells to create a bodyguard for a protein."

A remaining puzzle is to determine why extra protective methionines are not encoded as part of the DNA in the first place, instead of being left to the post-genetic random placement described in this paper. Pan suggests that random placement of the amino acids makes proteins even more resistant to attack, since no two are created alike.

"This sounds chaotic and doesn't make a lot of sense according to the textbook," Pan said. "But this way the cells can always ensure that a subset of these proteins is somewhat less sensitive to the extra hits. I think that's the most important part of this - to make every protein molecule different - and you cannot do this genetically."

Source: University of Chicago Medical Center