Scientists tie DNA repair to key cell signaling network

June 15 2012

University of Texas Medical Branch at Galveston researchers have found a surprising connection between a key DNA-repair process and a cellular signaling network linked to aging, heart disease, cancer and other chronic conditions. The discovery promises to open up an important new area of research — one that could ultimately yield novel treatments for a wide variety of diseases.

"This is a totally new concept — it goes against current dogma about the role of DNA repair," said UTMB professor Istvan Boldogh, senior author of a paper on the work now online in the *Journal of Biological Chemistry*. "We couldn't believe it ourselves, but the data convinced us."

Boldogh and his colleagues came up with the idea of a link between DNA repair and cellular signaling after a close examination of the relationship between DNA damage and cell death produced unexpected results. Conventional DNA-repair dogma holds that a cell's lifespan is determined by the amount of accumulated DNA damage it suffers — the overall corruption of genetic information stored in sequences of molecules called bases, which form the "rungs" of the DNA double helix. The cells used in Boldogh's study were especially vulnerable to damage because they lacked a key enzyme that repairs the DNA base guanine. According to dogma, this should have shortened the cells' lives; instead, they actually lived longer than expected. This made Boldogh wonder if another factor was involved in reducing the lifespan of normal cells.

"We proposed the hypothesis that instead of the accumulation of damaged guanine in DNA causing ill effects, what is significant is the release of a DNA-repair byproduct that somehow activates processes that shorten the lifespan of cells," Boldogh said.

The researchers knew just where to look to find this hypothetical repair byproduct. The majority of DNA damage is caused by ubiquitous reactive oxygen species, very chemically active molecules created as byproducts of respiration. When DNA meets reactive oxygen species, one of the most common results is the transformation of the DNA base guanine into a molecule called 8-oxoguanine, which can produce mutations in genes.

To protect the integrity of the genetic code, cells remove 8-oxoguanine from their DNA with a repair enzyme called OGG1. OGG1 does its job by attaching to a damaged base, cutting it free from the DNA molecule, and then releasing it. Boldogh and his collaborators found that their key byproduct was being produced just after this repair process was completed. Analyzing test-tube, cell-culture and mouse experimental data, they realized that immediately after being released by OGG1, 8-oxoguanine reunites with the repair enzyme, attaching at a bonding site different from the one used previously. And the resulting 8-oxoguanine-OGG1 complex, they found, has the ability to activate the powerful Ras signaling pathways, some of the most important biochemical networks in the cell.

"Ras family proteins are involved in almost every cell function: metabolism, activation of genes, growth signals, inflammation signals, apoptosis," Boldogh said. "Because it activates Ras pathways, the release of 8-oxoguanine in DNA base repair could be a master regulator of many very basic processes."

According to Boldogh, learning to control this "master regulator," could

result in profound consequences for biomedical science and human health. "The ability to regulate 8-oxoguanine excision may give us the ability to prevent the inflammation that's key to a number of chronic diseases — arthritis, atherosclerosis, Alzheimer's and others," he said. "We believe it may even enable us to extend lifespan, or at least healthy lifespan, which would be a very big achievement. Possibilities like that make us believe that this discovery is going to be very significant."

Provided by University of Texas Medical Branch at Galveston