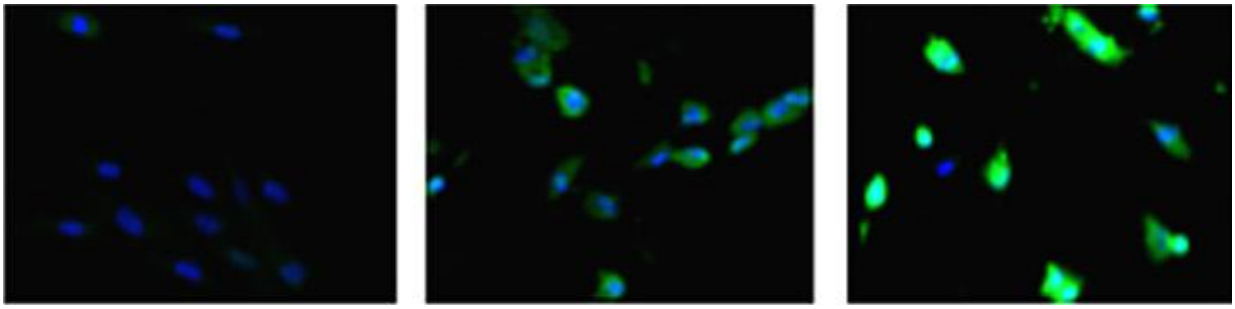
Formaldehyde damages proteins, not just DNA

September 29 2016, by David Orenstein



Human lung fibroblast cells were left alone on the left, exposed to formaldehyde for 1 hour in the middle and 3 hours on the right. The greater amount of green shows greater amounts of protein damage. Credit: Zhitkovich, et. al.

The capacity of formaldehyde, a chemical frequently used in manufactured goods such as automotive parts and wood products, to damage DNA, interfere with cell replication and cause cancer inspired new federal regulations this summer. But a new study in the *American Journal of Pathology* finds that the substance may pose a broader threat to health than previously thought by injuring cells in another way.

"We think formaldehyde is a much more dangerous toxicant in the sense that it is not only damaging DNA but there is also extensive damage to proteins," said corresponding author Anatoly Zhitkovich, Professor of Pathology and Laboratory Medicine in the Warren Alpert Medical

School of Brown University. "On one hand, damage to proteins in the nucleus could impair the stress responses to and repair of DNA damage, and on the other hand accumulation of damaged proteins could contribute directly to malfunctioning and killing of cells."

The findings may substantiate questions about whether formaldehyde adversely affects the nervous system, as has been seen in some animal studies, Zhitkovich said.

Protein problems

In several experiments described in the new paper, Zhitkovich's team at Brown showed that exposure of three types of human lung cells to formaldehyde set off a sequence of damage and cellular responses similar to what happens when cells are exposed to excessive heat. They saw tell-tale indications of widespread accumulation of damaged proteins. These indications were the appearance of a specific set of protective processes that try to clean up the damaged proteins before their buildup could kill the cells.

Zhitkovich first got the idea that formaldehyde might damage proteins when his laboratory was studying how cells respond to formaldehyde's DNA damage. Their data showed that a key anticancer protein in this response was reduced at high doses when its presence should be scaling up to meet the increasing formaldehyde exposure.

In the new study Zhitkovich, lead author Sara Ortega-Atienza and co-authors Blazej Rubis and Caitlin McCarthy therefore looked for signs of protein damage and saw them clearly. They observed that after brief formaldehyde exposures, cells exhibited a massive polyubiquitination, a process of marking damaged proteins for disposal, lest they accumulate. Shortly after the polyubiquitination process began, they then observed the heat shock response as a new set of proteins joined the massive

cleanup effort.

Ultimately many of the cells died, despite the activation of cell's defense responses. In an experiment where they purposely disabled one of the key heat shock response proteins, cells were even more likely to die.

Neither the polyubiquitination response nor the heat shock response occurred in control cells that did not have any contact with formaldehyde. Meanwhile, the scientists also subjected cells to substances known to damage DNA but not proteins, and found that this didn't unleash the polyubiquitination or heat shock responses. That suggests that those reactions were not responses to formaldehyde's DNA damage.

The next set of questions

Zhitkovich said the findings might explain why formaldehyde may be toxic to the nervous system. Neurons don't divide or replicate DNA, so they aren't as vulnerable to the kind of damage formaldehyde does to DNA. But they are especially vulnerable to accumulations of damaged and misfolded proteins – that's what happens in Alzheimer's and some other disease, for example – and that's exactly what Zhitkovich's team has found formaldehyde causes in cells. Animal studies, he noted, have shown that formaldehyde exposure undermines brain functions such as memory and learning.

To directly test this hypothesis, his group has begun formaldehyde exposure experiments with human neurons in the lab, he said.

Zhitkovich's team is also investigating whether formaldehyde damages particular types of proteins or whether it is toxic to them across the board.

And as a member of Brown's community of researchers on the biology of aging, he is also interested in studying whether long-term, low-level exposure to formaldehyde – which cells actually make themselves – could lead to a deleterious buildup of damaged proteins as cells get older.

For now, though, this study has already broken new ground by showing that formaldehyde is not just a threat to DNA, Zhitkovich said.

"Cells are dealing with two injuries instead of just one," he said.

More information: Sara Ortega-Atienza et al. Formaldehyde Is a Potent Proteotoxic Stressor Causing Rapid Heat Shock Factor Protein 1 Activation and Lys48-Linked Polyubiquitination of Proteins, *The American Journal of Pathology* (2016). DOI: 10.1016/j.ajpath.2016.06.022

Provided by Brown University