Stress responder is a first responder in helping repair DNA damage and avoiding cancer

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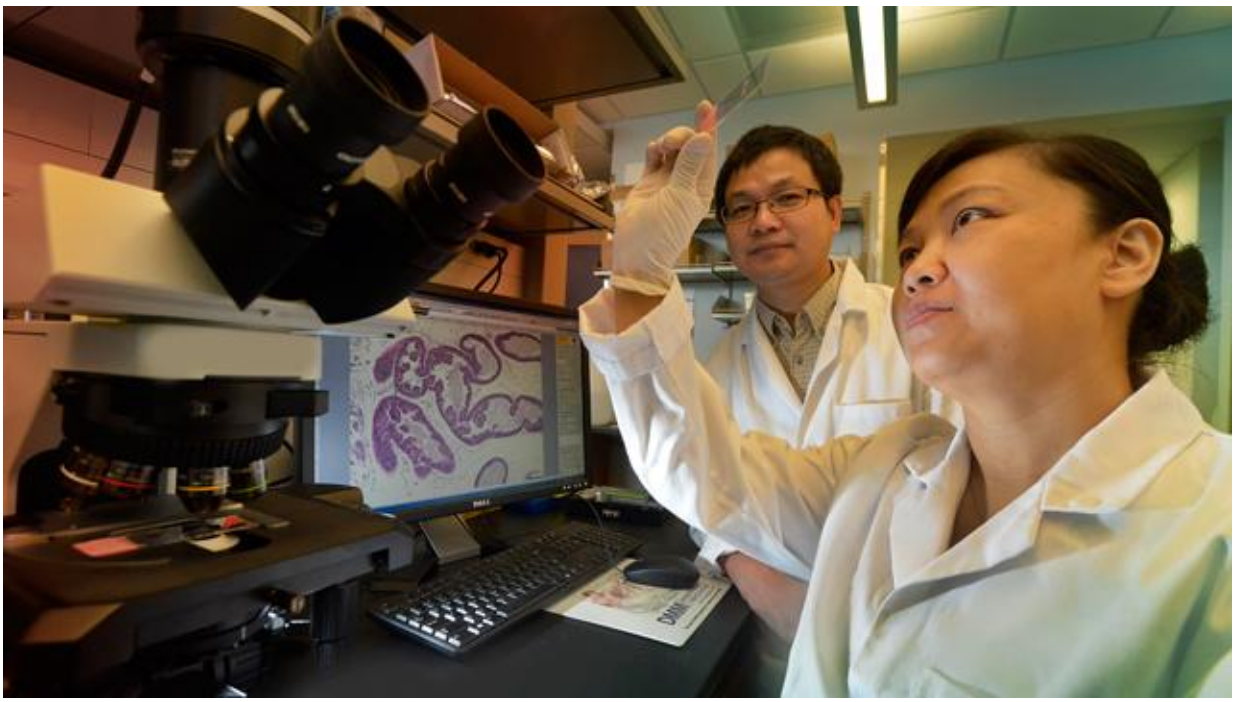

Dr. Chunhong Yan is a molecular biologist at the Georgia Regent University Cancer Center and the Department of Biochemistry and Molecular Biology at the Medical College of Georgia at GRU. Credit: Phil Jones

DNA damage increases the risk of cancer, and researchers have found that a protein, known to rally when cells get stressed, plays a critical,

early step in its repair.

In the rapid, complex scenario that enables a cell to repair DNA damage or die, ATF3, or activating transcription factor 3, appears to be a true first responder, increasing its levels then finding and binding to another protein, Tip60, which will ultimately help attract a swarm of other proteins to the damage site.

"This protein is a so-called stress responder, so when a cell senses stress, such as DNA damage, this protein can be induced," said Dr. Chunhong Yan, molecular biologist at the Georgia Regent University Cancer Center and the Department of Biochemistry and Molecular Biology at the Medical College of Georgia at GRU.

"One of the things we found is that ATF3 can bind to the Tip60 protein and promote the DNA damage repair function," said Yan, corresponding author of the study published in the journal *Nature Communications*.

Like its partner Tip60, ATF3 is expressed at low levels until cells get stressed, and DNA mutation is one of the most common cell stressors. ATF3 then finds and binds to Tip60, increasing the usually unstable protein's stability and level of expression. "If you look at the DNA under the microscope, you will see the damage site somehow labeled by this protein," Yan said. Tip60, in turn, modifies the protein ATM, helping it form a sort of scaffold where other worker bee proteins soon assemble.

While it may take years for a cell to recognize DNA damage, once it does, the response occurs within minutes. One of the early arrivals to the ATM scaffold is p53, a known and powerful tumor suppressor. Once on the scene, p53 helps assess whether or not the damage is repairable. If not, it triggers cell suicide. If the damage is fixable, it will arrest cell proliferation and help start the repair.

There is clearly a protein connection. When researchers knock ATF3 down, Tip60 activation and ATM signaling both go down. Cells start accumulating DNA damage and become more vulnerable to additional stress, setting the stage for cancer and other problems. Previously there was no known relationship between ATF3 and Tip60.

Many factors, including sunlight, even chemotherapy, can cause DNA mutations. Mutations can even occur in the normal process of a cell multiplying, as cells do commonly in areas such as the skin and gastrointestinal tract, and tend to increase with aging. Cancer itself can cause additional mutations as it morphs to try to escape whatever treatment is being used against it. In fact, DNA repair likely is a constant in the body that works well most of the time. "That is why understanding DNA damage response is so important," said Yan.

In human cancer cells, the researchers have shown that ATF3's role precedes previously known steps. Future studies include finding a drug that could help cells make even more of this stress responder as a possible adjunct cancer therapy.

"We want to find a drug that can increase expression of this ATF3 in the body, and this increased ATF3 can promote Tip60 activity and overall promote cell response to DNA damage," Yan said. The body naturally increases ATF3 levels in response to stress, including chemotherapy. In fact, many of the older cancer drugs intentionally damage DNA in an effort to promote cancer cell death. Now that ATF3's connection to DNA repair has been made, that synergy likely explains another way chemotherapy works. However, additional study is needed to find a more targeted ATF3 activator without the numerous, known side effects of chemotherapy or other known stressors, Yan said.

While the protein ATF3 was known to be a stress responder, just how it responded has mostly remained a mystery. "We really don't know much

about this protein," said Yan said. A decade ago, his research team found that ATF3 directly regulates the tumor suppressor p53.

"A next logical step is how can we make more ATF3?" While it's not yet done clinically, in his lab, Yan has measured ATF3 levels in the tissue of cancer patients and found the levels are low and/or that the ATF3 gene itself is mutated. One day, measuring ATF3 levels might also help predict who is at highest risk for cancer, he said.

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