Scientists make critical end-stage liver discovery

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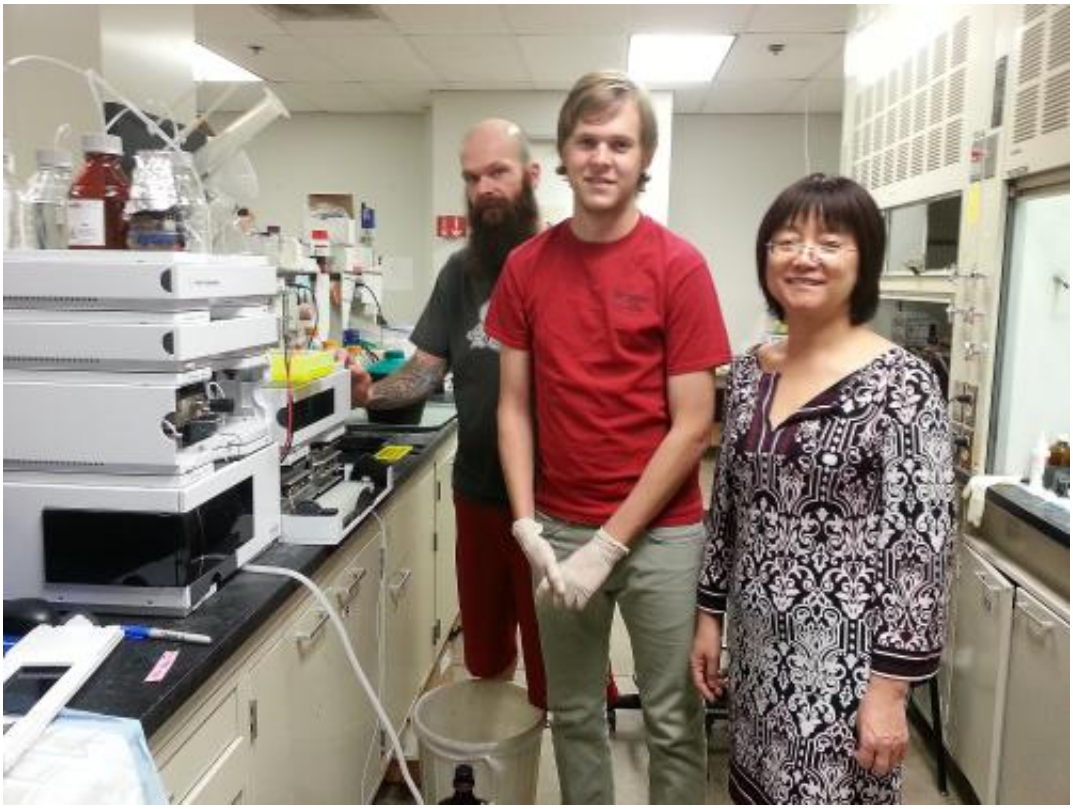

Donna Zhang with graduate student Bryan Harder (middle) and collaborator and Assistant Professor of Pharmacology Eli Chapman (left). Zhang's research group studies the molecular mechanisms cells use to protect themselves from damage caused by toxicants and carcinogens. Credit: Daniel Stolte/UANews

(Medical Xpress)—A team of researchers in the University of Arizona's College of Pharmacy has discovered a molecular pathway that could be

key to creating new therapeutics that would slow or even reverse the progression of end-stage liver disease.

Although cirrhosis of the liver is most commonly associated with alcohol or drug abuse, the condition – marked by scar tissue replacing healthy liver tissue – also can result from viral hepatitis, obesity and diabetes, as well as certain inherited diseases. According to the National Institutes of Health, cirrhosis is the 12th leading cause of death by disease in the U.S.

As with many other human pathologic conditions, end-stage liver disease goes hand in hand with oxidative stress, which refers to damage inflicted to biological tissues by reactive oxygen molecules. Such molecules, also called free radicals, occur naturally as a byproduct of metabolic processes in the body and are associated with many chronic diseases including cancer, diabetes, neurodegenerative and cardiovascular diseases.

"Cells keep oxidative stress under control through various mechanisms," said Donna Zhang, a professor in the UA Department of Pharmacology and Toxicology, explaining that most of these mechanisms involve Nrf2, a protein present in virtually every cell that acts as a molecular switch. Nrf2 activates various biochemical mechanisms inside the cell that capture reactive oxygen molecules or dispose of damaged cellular components before they can cause more trouble. The antioxidants found in many fruits and vegetables exert their healthful benefits by capturing reactive oxygen molecules.

Under normal, healthy conditions, when no oxidative stress response is needed, an enzyme called Keap1 constantly chews up Nrf2, keeping its level low.

"Then, under stress from reactive oxygen molecules, or when you eat antioxidants from certain plants like broccoli sprouts, it prevents Keap

from eating up Nrf2, allowing it to accumulate in the cell," Zhang explained. "Nrf2 then activates the cellular antioxidant response. That is how antioxidants work."

Donna Zhang is especially interested in how antioxidants found in plants help cells fight stress from reactive oxygen molecules. Credit: Daniel Stolte/UANews

According to conventional wisdom, our bodies turn on their Nrf2-mediated protection pathway when subjected to high oxidative stress to limit the damage from the destructive oxygen compounds. During liver cirrhosis, Nrf2 should be induced by oxidative stress, but for reasons unclear until this study, this does not happen.

"This was a puzzle before we did our study," she said. "Somehow the

protective mechanism mediated by Nrf2 is compromised by another factor, other than Keap1, in liver cirrhosis."

Adding to the mystery is the fact that drugs aimed at inhibiting Keap from chewing up Nrf2 have proven ineffective in a cirrhotic liver.

When Zhang and her colleagues studied tissue samples from a human cirrhotic liver, they discovered the reason behind the inexplicably low Nrf2 levels in the face of rampant oxidative stress.

It turned out that another enzyme chews up Nrf2 and prevents the much-needed antioxidant response, exacerbating the disease process. That protein, Hrd1, is part of the cells' garbage disposal – it specializes in destroying misfolded proteins before they can accumulate and damage cell components.

Under normal conditions, Hrd1 levels are low, so it does not interfere much with Nrf2, explained Zhang. As liver cirrhosis progresses, excessive inflammation triggers the garbage-mediated stress response and Hrd1 becomes very abundant and begins chewing up Nrf2.

The discovery could change the way scientists develop therapeutics, as it provides a new target for future drugs. In laboratory experiments, Zhang and her colleagues were able to restore Nrf2 levels in cirrhotic liver tissue by inactivating Hrd1, effectively reversing liver cirrhosis in mice.

"Previous efforts only focused on the Keap protein and tried to prevent it from breaking down Nrf2," Zhang said. "Now we know there is a second player in the game – Hrd1 – that we need to inhibit in order to restore Nrf2 levels.

"Boosting Nrf2 is good for protection in general, which is why you should always eat your broccoli," she stressed.

More information: "Hrd1 suppresses Nrf2-mediated cellular protection during liver cirrhosis." Tongde Wu, et al. *Genes & Dev*. 2014. 28: 708-722. Published in Advance March 17, 2014, DOI: 10.1101/gad.238246.114

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