Study finds new pathway for treating non-alcoholic fatty liver disease

Researchers from the University of South Carolina, Duke University, University of Alabama at Birmingham and Metabolon Inc. Research Triangle Park have discovered a new way to treat non-alcoholic fatty liver disease—a condition that affects up to 25 percent of the population and may lead to cirrhosis and eventually liver cancer or failure. The study was published in *Free Radical Biology & Medicine*, a top scientific journal in the field of oxidative stress and medicine.

The team found that a protein (TRPV4), which is a part of the body’s defense system, is able to activate the release of a gas (nitric oxide). This gas then blocks one of the enzymes (CYP2E1) that is a major contributor to non-alcoholic liver disease and its progression. TRPV4 is already known to protect against cardiovascular abnormalities.

Now that this protein’s capacity to block the development of non-alcoholic fatty liver disease has been discovered, the next step is to harness its preventive and treatment abilities. According to the authors, a new generation of TRPV4 agonists can now be tested to improve outcomes related to non-alcoholic fatty liver disease. The agonist is a chemical that will bind to this protein and activate the release of nitric oxide to block the harmful enzyme. Once the appropriate agonist is identified, it can be incorporated into medication for clinical treatment.

“There are currently no clinically proven drugs to treat non-alcoholic fatty liver disease,” says Saurabh Chatterjee, an associate professor of environmental health sciences at USC’s Arnold School of Public Health and the director of the Environmental Health and Disease Laboratory where the research took place. “Our goal is to find novel pathways in the liver that will result in a cure, and this internal defense mechanism within the liver offers a very promising route.”

In addition to revealing the benefits of activating TRPV4, the researchers also warn against the obstruction of this critical protein. Inhibiting TRPV4 can enhance hepatotoxicity (i.e., liver damage caused by chemicals), which can result from acetaminophen or alcohol consumption.

Non-alcoholic fatty liver disease occurs when there is a buildup of extra fat in the liver (i.e., more that 5-10 percent of the liver’s total weight) coupled with lobular inflammation that is not caused by alcohol. Affecting both children and adults, this disease tends to occur in individuals who are obese or overweight, have diabetes, or high cholesterol or triglycerides; however, some people develop non-alcoholic fatty liver disease without any of these risk factors. Healthy liver function is important because it processes food and drink into energy and nutrients while removing harmful substances from blood.

This groundbreaking research has the potential to have a significant impact for both individuals and public health. “This type of research, which seeks novel pathways for treatment of diseases for which there are currently no therapeutic options is vitally important,” says collaborator and USC Vice President for Research Prakash Nagarkatti. “It opens doors that lead to the breakthroughs patients rely on to improve outcomes, enhance quality of life and even save lives.”
*The study was led by Ratanesh Seth, a postdoctoral fellow at the USC Arnold School of Public Health with collaborative inputs from Suvarthi Das (USC Arnold School of Public Health), Diptadip Dattaroy (USC Arnold School of Public Health), Varun Chandrashekaran (USC Arnold School of Public Health), Firas Alhasson (USC Arnold School of Public Health), Gregory Michelotti (Metabolon Inc. Research Triangle Park), Mitzi Nagarkatti (USC School of Medicine), Prakash Nagarkatti (USC School of Medicine), Anna Mae Diehl (Duke University School of Medicine), Darwin P. Bell (University of Alabama at Birmingham), Wolfgang Liedtke (Duke University School of Medicine), Saurabh Chatterjee (USC Arnold School of Public Health, Principal Investigator).

Funding: This work has been supported by NIH Pathway to Independence Award, R00ES019875 and P01AT003961 to Saurabh Chatterjee, US Department of Defense (W81XWH-13-1-0299 and a Harrington Discovery Institute (Cleveland OH) Scholar-Innovator Award to Wolfgang Liedtke. R01DK053792 to Anna Mae Diehl, P01AT003961, P20GM103641, R01AT006888, R01ES019313, R01MH094755 and VA Merit Award BX001357 to Mitzi Nagarkatti and Prakash S. Nagarkatti.