Too much of a good thing may lead to too much of a liver as well

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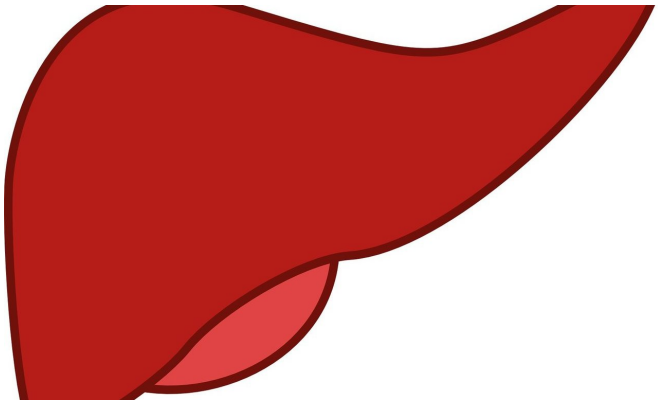

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All life is challenged by oxidants—reactive molecules or compounds that remove electrons from other molecules—often with adverse effect, commonly referred to as oxidative stress. Consequently, all organisms have evolved specialized antioxidant defenses. In humans and other multicellular animals, that defense depends upon a protein called NRF2 and its inhibitor, KEAP1.

In a new study, published February 24, 2020 in the *Journal of Hepatology*, a team of scientists, led by postdoctoral fellows Feng He, Ph.D., and Laura Antonucci, Ph.D., and senior author Michael Karin, Ph.D., Distinguished Professor of Pharmacology and Pathology at University of California San Diego School of Medicine, suggest prolonged exposure to NRF2 and KEAP1 may contribute to enlargement of the liver and fatty liver diseases.

NRF2 (Nuclear factor erythroid 2-related factor 2) is the master regulator of the antioxidant response. When cells are healthy and unstressed by oxidants, levels of NRF2 are kept low by KEAP1 (Kelch-like ECH-associated protein 1), which is constantly degrading NRF2.

But in response to oxidative stress, KEAP1 is inactivated, releasing NRF2 from its inhibitory grip. NRF2 levels subsequently build within the cell with the protein entering the nucleus, where it stimulates expression of numerous genes that code for enzymes and other proteins that detoxify harmful oxidants.

"By being able to reduce the devastating impact of oxidative stress, the KEAP1-NRF2 system has long been thought to protect us from cancer and aging," said Karin. "And much effort has been dedicated to the development of NRF2 activators for cancer prevention and age-related diseases. Many such compounds are being sold at health food stores as anti-aging remedies."

But research in recent years has found that several cancers, including liver and lung cancers, harbor mutations that decouple NRF2 from KEAP1, suggesting that persistent NRF2 activation may not be such a good thing after all. Some researchers now believe cancer cells may actually use NRF2 to protect themselves from radiation and chemotherapeutics.

Using a new mouse model whose liver cells express a KEAP1-resistant form of NRF2, Karin and collaborators found that persistent activation of NRF2 in these mice resulted in rapid and dramatic enlargement of the liver, known as hepatomegaly. In humans, hepatomegaly can appear after insulin overdosing, exposure to various toxins, certain viral and bacterial infections or as an indicator of an underlying disease, such as cirrhosis and liver cancer.

Because NRF2-induced hepatomegaly is similar to insulin-induced hepatomegaly, which relies upon activation of a protein kinase called AKT, the research team investigated the involvement of insulin and AKT in NRF2-induced hepatomegaly.

Although no evidence for excessive insulin

production was uncovered, the scientists found that AKT (otherwise known as Protein kinase B) was activated in livers expressing the degradation-resistant form of NRF2. The scientists also discovered that inhibiting AKT produced complete reversal of hepatomegaly and rapid restoration of normal liver size and physiology in the mice. And that chronic NRF2 activation causes persistent production of growth factors that activate AKT.

Working with co-corresponding author Beicheng Sun, MD, a liver surgeon at Nanjing University Medical School in China, the team also reported that human hepatomegaly that is caused by either toxin exposure or autoimmune hepatitis also entails NRF2 activation, enhanced growth factor signaling and stimulation of AKT activity.

In addition to liver enlargement, the scientists said persistent NRF2 activation produced excessive fat and glycogen accumulation, suggesting that NRF2 may also be involved in fatty liver disease, such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis—common metabolic disorders affecting millions of Americans.

The new findings, said Karin, suggest that AKT inhibitors, some of which have already been evaluated in humans for their anti-cancer activity, may be effective in the treatment and reversal of hepatomegaly, which affects more than 200 million persons worldwide.

More information: Feng He et al. NRF2 Activates Growth Factor Genes and Downstream AKT Signaling to Induce Mouse and Human Hepatomegaly, *Journal of Hepatology* (2020). DOI: 10.1016/j.jhep.2020.01.023

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