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Researchers show that fibrosis can be stopped, cured and reversed

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University of California, San Diego researchers have proven in animal studies that fibrosis in the liver can be not only stopped, but reversed. Their discovery, to be published in *PLoS Online* on December 26, opens the door to treating and curing conditions that lead to excessive tissue scarring such as viral hepatitis, fatty liver disease, cirrhosis, pulmonary fibrosis, scleroderma and burns.

Six years ago, the UC San Diego School of Medicine research team discovered the cause of the excess fibrous tissue growth that leads to liver fibrosis and cirrhosis, and developed a way to block excess scar tissue in mice. At that time, the best hope seemed to be future development of a therapy that would prevent or stop damage in patients suffering from the excessive scarring related to liver or lung disease or severe burns.

In their current study, Martina Buck, Ph.D., assistant professor of medicine at UCSD and the Veterans Affairs San Diego Healthcare System, and Mario Chojkier, M.D., UCSD professor of medicine and liver specialist at the VA, show that by blocking a protein linked to overproduction of scar tissue, they can not only stop the progression of fibrosis in mice, but reverse some of the cell damage that already occurred.

In response to liver injury – for example, cirrhosis caused by alcohol – hepatic stellate cell (HSC) activated by oxidative stress results in large amounts of collagen. Collagen is necessary to heal wounds, but excessive

collagen causes scars in tissues. In this paper, the researchers showed that activation of a protein called RSK results in HSC activation and is critical for the progression of liver fibrosis. They theorized that the RSK pathway would be a potential therapeutic target, and developed an RSK inhibitory peptide to block activation of RSK.

The scientists used mice with severe liver fibrosis – similar to the condition in humans with cirrhosis of the liver – that was induced by chronic treatment with a liver toxin known to cause liver damage. The animals, which continued on the liver toxin, were given the RSK-inhibitory peptide. The peptide inhibited RSK activation, which stopped the HSC from proliferating. The peptide also directly activated the caspase or “executioner" protein, which killed the cells producing liver cirrhosis but not the normal cells.

“All control mice had severe liver fibrosis, while all mice that received the RSK-inhibitory peptide had minimal or no liver fibrosis,” said Buck.

Buck explained that the excessive collagen response is blocked by the RSK-inhibitory peptide, but isn’t harmful to the liver. “The cells continue to do their normal, healing work but their excess proliferation is controlled,” Buck said. “Remarkably, the death of HSC may also allow recovery from liver injury and reversal of liver fibrosis.”

The researchers found a similar activation of RSK in activated HSC in humans with severe liver fibrosis but not in control livers, suggesting that this pathway is also relevant in human liver fibrosis. Liver biopsies from patients with liver fibrosis also showed activated RSK.

The study expands on work reported in 2001 in the journal *Molecular Cell* announcing that a team led by Buck had found that a small piece of an important regulatory protein called C/EBP beta was responsible for fibrous tissue growth, or excessive scar tissue following injury or illness.

When normal scarring goes awry, excessive build-up of fibrous tissue can produce disfiguring scars or clog vital internal organs and lead to serious complications. Buck and colleagues developed a mutated protein that stopped this excessive fibrous tissue growth.

“Six years ago, we showed a way to prevent or stop the excessive scarring in animal models,” said Buck. “Our latest finding proves that we can actually reverse the damage.”

Worldwide, almost 800,000 people die from liver cirrhosis each year, and there is currently no treatment for it. Excessive tissue repair in chronic liver disease induced by viral, toxic, immunologic and metabolic disorders all result in excessive scar tissue, and could benefit from therapy developed from the UCSD researchers’ findings.

Source: University of California - San Diego

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