World-first discovery of protein that causes liver disease brings hope for new treatments

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Professor Jacob George and Doctor Mohammed Eslam at the Westmead Institute have shown that variations in the interferon lambda 3 protein cause tissue damage in the liver. Credit: Westmead Institute for Medical Research

In a world-first discovery, scientists at Sydney's Westmead Institute for Medical Research have identified a protein that causes liver fibrosis (scarring), paving the way for new treatments for liver disease to be developed.

For the first time, researchers have unequivocally shown that variations in the interferon lambda 3 (IFNL3) protein are responsible for tissue damage in the liver.

The international team, led by Professor Jacob George and Doctor Mohammed Eslam at the Westmead Institute, had previously identified that the common genetic variations associated with liver fibrosis were located on chromosome 19 between the IFNL3 and IFNL4 genes.

Building on this research in their latest study, the team analysed liver samples from 2000 patients with Hepatitis C, using state-of-the art genetic and functional analysis, to determine the specific IFNL protein responsible for liver fibrosis.

The research demonstrated that following injury, there is increased migration of inflammatory cells from blood to the liver, increasing IFNL3 secretion and liver damage.

Notably, this response is determined to a great extent by an individual's inherited genetic makeup.

Lead author of the study, Professor Jacob George, said this was a significant outcome that will help to predict risk of liver disease for individuals, enabling early intervention and lifestyle changes.

"Liver disease is now the fifth most common cause of death in Australia, affecting 6 million Australians, and with significant financial cost to the health system.

"We have designed a diagnostic tool based on our discoveries, which is freely available for all doctors to use, to aid in predicting liver fibrosis risk.

"This test will help to determine whether an individual is at high risk of developing liver fibrosis, or whether a patient's liver disease will progress rapidly or slowly, based on their genetic makeup.

"This important discovery will play a vital role in reducing the burden of liver disease into the future," Professor George said.

Co-lead author, Doctor Mohammed Eslam, said this discovery holds great promise for the development of effective therapeutic treatments for liver disease.

"There is an urgent need for a safe pharmacologic therapy that can prevent of regress the progression of liver damage. There are currently no treatments available for patients with advanced fibrosis, and liver transplantation is the only treatment for liver failure.

"Now that we've identified IFNL3 as the cause of liver scarring, we can work towards developing novel treatments specifically targeting this gene.

"This could be medicine targeting IFNL3 that is tailored to an individual's genetic makeup, but could also include modifying usual treatment depending on whether a patient has IFNL3 risk genes.

"Our results show that it is possible to develop new targeted treatments for liver fibrosis and possibly even scarring in other organs such as the heart, lung and kidneys."

Dr Eslam said these outcomes fulfil several promises in the modern era of precision medicine.

"Firstly, it brings us closer to the goal of personalised medicine. Secondly, we have a better understand of biology and the way the human

body works. Finally, we are a step closer to developing novel potential treatments for liver disease," Dr Eslam concluded.

The research team will now extend their work to further understand the fundamental mechanisms of how IFNL3 contributes to liver disease progression and to translate these discoveries into new therapeutic treatments.

The results of the study were published online in the *Nature Genetics* journal on 10 April 2017.

More information: Mohammed Eslam et al, IFN-λ3, not IFN-λ4, likely mediates IFNL3–IFNL4 haplotype–dependent hepatic inflammation and fibrosis, *Nature Genetics* (2017). DOI: 10.1038/ng.3836

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