Researchers identify a potential therapeutic target against cirrhosis and liver inflammation

July 28 2023

A new study by a team of the University of Barcelona could promote the design of drugs to treat these pathologies. Credit: University of Barcelona

The RNF41 protein could be a new therapeutic target in the fight against two chronic liver diseases: cirrhosis and liver inflammation. This is the conclusion of a study published in the journal *Science Translational*

Medicine led by researcher Pedro Melgar-Lesmes, from the Department of Biomedicine at the Faculty of Medicine and Health Sciences of the University of Barcelona.

This study could lead to the design of drugs that enhance the production of RNF41 protein in macrophages, defensive cells of the immune system that play an essential role in the response to liver damage and in the progression of chronic liver disease.

"This potential therapeutic target represents a new master regulator of the role of macrophages in the control of chronic liver diseases and other diseases characterized by inflammation and fibrosis," says Melgar-Lesmes.

"Our findings highlight that the regulation of innate immunity, and in particular macrophage activity, is essential to fight liver fibrosis and enhance liver regeneration."

What is the role of the RNF41 protein in liver fibrosis?

The study reveals that the expression of RNF41—a protein related to inflammatory processes—is lower in macrophages isolated from liver samples of patients with liver cirrhosis, regardless of the origin of the disease. In mice with liver fibrosis, the expression of the protein in liver macrophages is also reduced.

The team has found that a prolonged inflammation process in liver macrophage cell cultures leads to a decrease in RNF41 protein. "Therefore, chronic inflammation could be responsible for the reduction of RNF41 in macrophages," says Melgar-Lesmes.

In mice in which RNF41 protein function could be restored, results have shown enhanced elimination of fibrosis, reduced liver inflammation and increased liver regeneration.

An innovative methodology

To obtain these results, an innovative methodology based on the use of dendrimer-graphite nanoparticles (DGNP)—molecules with functional characteristics of interest in biomedicine—designed by the team has been used. In addition, the technique of specific isolation of macrophages, using magnetic spheres bound to antibodies (MACS), has also been applied. This has demonstrated that these nanoparticles are effective in selective gene therapy in inflamed macrophages in fibrotic liver.

In parallel, in vitro studies confirm that if RNF41 protein disappears in macrophages of fibrotic mouse livers, it triggers a storm of inflammatory cytokines that leads to increased fibrosis, liver damage and some mortality. "This tells us that RNF41 protein is necessary to overcome fibrosis and chronic inflammation in liver disease," says Melgar-Lesmes.

The team's future lines of research will focus on identifying which proteins control the RNF41 protein in macrophages. "This will allow us to design new drugs to increase the expression of this key protein in the regulation of the role of macrophages in inflammation and liver fibrosis," concludes Melgar-Lesmes.

More information: Alazne Moreno-Lanceta et al, RNF41 orchestrates macrophage-driven fibrosis resolution and hepatic regeneration, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.abq6225

Provided by University of Barcelona