Discovery provides new insight into severe liver disease

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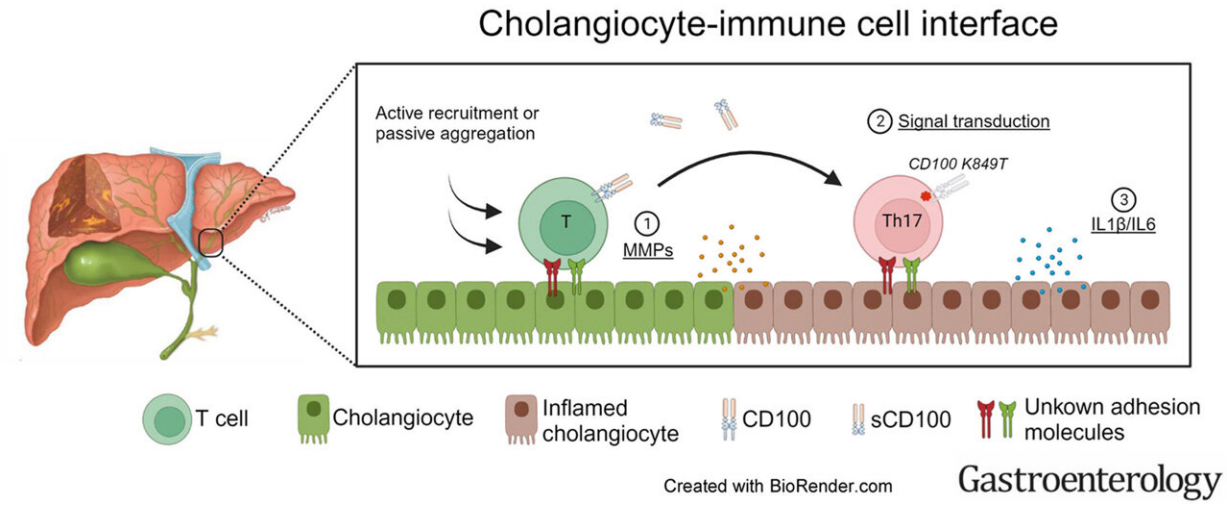

Graphical abstract. Credit: *Gastroenterology* (2023). DOI: 10.1053/j.gastro.2023.11.283

Primary sclerosing cholangitis (PSC) is a severe and chronic liver disease. It affects men more than women, and most people who are diagnosed with PSC are between 30 and 40 years old.

"There is no effective treatment for PSC. The disease is therefore the leading indication for liver transplantation in both Norway and the Nordic countries," says Xiaojun Jiang. She is a researcher at the Norwegian PSC Research Center (NoPSC) at the University of Oslo and

Oslo University Hospital.

PSC is characterized by inflammation in the bile ducts, which is a system of tubes both in and around the liver. The bile ducts carry bile from the liver to the small intestine. Bile is an important part of our digestive system and helps to break down and absorb fats from the food we eat.

The inflammation causes scar tissue to form in the bile ducts, making them narrow. This leads to a build-up of bile that gradually causes serious liver damage.

The cause of the disease is still unclear. The aim of NoPSC is to drive the search for understanding the disease and ultimately finding a cure for PSC patients. The Center has increased the understanding of mechanisms underlying disease development.

What we do know is that PSC is an autoimmune disease, meaning that the immune system, instead of protecting us from infections, attacks and damages cells in the body.

But what makes the immune system attack the body and cause inflammation in the bile ducts?

An interaction between the immune cells and the cells in the bile ducts

The bile ducts are lined with cells called cholangiocytes. They form the tubes that allow bile to be transported through the biliary system. In a new study, researchers at NoPSC have discovered that something occurs when these cells in the bile ducts encounter the immune cells in the liver.

"There is an interaction between the cells in the bile ducts and the immune cells that initiates an inflammatory process in the immune cells," Espen Melum, professor at NoPSC and the Research Institute for Internal Medicine, says.

"For some unknown reason, the immune cells of a person with PSC go to the bile ducts and interact with these cholangiocytes. It is as if they are trying to attack the wall of the tube," Jiang adds.

Thus, the interaction between the different cells causes the immune cells to become pathogenic. This, in turn, causes an inflammatory process that develops into liver disease over time.

The discovery, published in *Gastroenterology*, provides an important new research direction.

"Now that we know that this interaction between the immune cells and the cholangiocytes is important for the development of PSC, we can focus on that interface further," Jiang says. "We believe that if we could block the link between the immune cells and the cholangiocytes, we will be able to resolve the inflammation in the biliary system and hopefully prevent PSC from developing."

Part of the scientific puzzle

Melum emphasizes that despite not translating into clinical practice directly, this study is important in providing a fundamental understanding of PSC.

"Basic research lays the groundwork. Without understanding these types of processes, we won't be able to develop an effective treatment," he says and explains further, "New discoveries point us towards which disease mechanisms are at play. By understanding these types of disease

mechanisms better, we can potentially find novel therapeutic targets for use in treatment."

"This study is like a piece in the scientific puzzle."

Researchers at the NoPSC center have been studying the disease for over 30 years. In 2021, they found a genetic mutation for PSC in a family where several members have the liver disease.

"We found a mutation that causes PSC, and then we inserted the mutation into mice and saw that they were more prone to liver disease," Melum explains.

However, as it turns out, not all patients with PSC have this genetic mutation.

Relevance for all PSC patients

This new study is based on the previous findings.

The genetic mutation is expressed in the immune cells in the liver. When the inflammatory process starts in the immune cells, specific pathogenic cells develop, which are common in patients with PSC.

Jiang points out that these findings are well-documented.

So, even in individuals without a genetic mutation, this interaction can occur and create inflammation in the bile ducts, according to the researcher.

"We believe that this also applies to individuals who do not have the genetic mutation. Because it is the interaction with the cholangiocytes that triggers the development of pathogenic cells commonly found in

PSC," she says.

"Our study shows that the research we have done on the family with PSC, therefore, is relevant for all PSC patients," Jiang adds.

According to Jiang, the researchers at NoPSC describe PSC as a black box, meaning there is so much about the disease that we still do not know.

"However, I feel the mutation we have found is like a window on top of the box. Moreover, this new study uncovers something real that we can see through the window, something that is relevant to the disease. This gives us hope that we will find a cure for the patients," she says.

More information: Xiaojun Jiang et al, Cholangiocytes Modulate CD100 Expression in the Liver and Facilitate Pathogenic T-Helper 17 Cell Differentiation, *Gastroenterology* (2023). DOI: 10.1053/j.gastro.2023.11.283

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