

New research could lead to pharmacological treatments for chronic pancreatitis

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The pancreas is a tricky organ for researchers and surgeons alike because of its sensitivity. Tucked away in a hard-to-reach spot behind the stomach, it's in charge of secreting enzymes to help digest everything you eat. Even slightly puncturing the pancreas during surgery can cause it to begin digesting itself.

That may be in part why there is so little understanding of what causes pancreatitis, a fairly common and quite painful disorder of the gut.

"We try not to touch the pancreas," said Aida Habtezion, MD, assistant professor of gastroenterology and hepatology. "That's one of the reasons the field has not progressed much. We don't have much access to the pancreas. We especially don't want to touch it when it is inflamed with pancreatitis."

By working with animal models and cells retrieved from the few surgeries involving the human pancreas, Habtezion has spearheaded new research that provides insight for the first time into the molecular pathway that leads to [chronic pancreatitis](#), the debilitating, long-term form of the disease.

In a study published May 18 in *Nature Communications*, Habtezion and her colleagues found that blocking this pathway stops the progression of the uncontrolled growth of [scar tissue](#), or fibrosis, that's the hallmark of chronic pancreatitis.

"This is the first step to showing that you can alter the progression of this disease," said Habtezion, senior author of the study. The lead author is postdoctoral scholar Jing Xue, PhD.

Habtezion, a gastroenterologist with a background in immunology, splits her workdays between the lab and the hospital. Her interest in these patients has crossed over into her lab.

"Acute pancreatitis is one of the most common gastrointestinal admissions-related illnesses," she said. "Some people just have one or two episodes, and we never see them back." Others go on to develop chronic pancreatitis, which is a risk factor for [pancreatic](#) cancer.

No known cure

Chronic pancreatitis is marked by constant, severe stomach pain. There is no known cure and little treatment beyond narcotics to help control the pain. The disease destroys the ability of the pancreas to absorb nutrients, leading to nutritional deficiencies and malnutrition, along with the crippling nausea and diarrhea caused by the abdominal pain. Key contributors to the disease include excessive alcohol consumption, gallstones and genetic factors.

"My lab has been interested in the inflammatory responses associated with pancreatitis and in understanding the molecular pathways that may be targeted to alter the progression of the disease," Habtezion said.

It's generally understood that chronic pancreatitis is marked by the uncontrolled growth of scar tissue in the pancreas, slowly destroying the organ's ability to function. Just how this happens is less clear.

In previous research, Habtezion's lab has shown that macrophages, a type of immune cell in the body, play a role in the acute form of pancreatitis.

The goal of the new study was to determine the role of macrophages in the development of chronic pancreatitis from the acute form of the disease. Previous research has also shown that pancreatic stellate cells may play a role in fibrosis. These cells live in the pancreas and travel to injury sites when activated.

"Our most important finding was that there is cross-talk between macrophages and stellate cells," Habtezion said. "We identified this pathway." Next, they set out to determine if blocking this pathway would slow or stop fibrosis. This is where colleagues from Cedars-Sinai Medical Center—co-authors Stephen Pandol, MD, director of basic and translational [pancreas](#) research, and Ramachandran Murali, PhD, associate professor of biomedical sciences—helped out.

"Dr. Murali said, 'Oh, I have this agent that can block this receptor,'" Habtezion said. "He was developing the potential drug as treatment for another disease. We used this blocking peptide in both the animal models and the human cells."

When applied to the pathway, the pharmacological agent successfully slowed the fibrosis, she said.

"For the first time we can show that macrophages interact with pancreatic stellate cells via a particular immune pathway, and by targeting this pathway we show a decrease in chronic pancreatitis/fibrosis progression," she said. "This has great implication in a disease that has no active therapy with no known agents that can alter its natural devastating course."

Provided by Stanford University Medical Center

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