

The Puzzle of Pancreatitis

It's not easy to breed a mouse prone to a chronic human disease, but Dafna Bar-Sagi, Ph.D., Chairwoman of the Department of Biochemistry, and her colleagues have for the first time mimicked chronic pancreatitis in laboratory animals.

The result is a revealing window on chronic inflammation, a chain of biochemical events equivalent to a wound that never heals.

Dr. Bar-Sagi's mice share the genetic defect that makes some people's bodies produce hyperactive trypsin, an important enzyme in the digestive process. This in turn causes ongoing turmoil in the pancreas, the organ responsible for insulin and digestive enzyme production, two important features of how our bodies process food for energy.

Chronic inflammation in the pancreas is like a permanent injury. An excess of trypsin causes pain, sluggish digestion, and eventually useless fibrous tissue throughout the organ, as well as permanently blocked or stalled ducts that normally convey digestive enzymes. Pancreatitis doesn't kill its sufferers, but it increases a person's chances of developing pancreatic cancer, often a fatal disease.

The puzzle of chronic pancreatitis is that it doesn't always lead to pancreatic cancer. This suggests to Dr. Bar-Sagi and her colleagues that the inflammation alone cannot give rise to cancer. "The question we try to answer," she says, "is 'What in addition to the chronic inflammation causes cancer?'"

Other conditions are known to give the pancreas trouble. People who abuse



alcohol have a higher likelihood of pancreatic cancer. Obesity is also thought to predispose people to pancreatic disease and cancer. Dr. Bar-Sagi's laboratory also is establishing mouse populations with obesity and the equivalent of alcohol abuse. "There's inflammation and there's inflammation," she points out. Studying the three types that afflict the pancreas—obesity, alcohol abuse, and the genetic defect in trypsin—may reveal areas of overlap. Answers about what eventually causes pancreatic cancer may lie in the common ground among various forms of inflammation.

An expert on cellular growth and renewal, Dr. Bar-Sagi has already homed in on the spatial effects of chronic inflammation in the pancreas. "We've observed that only tissues in the vicinity of inflammatory secretions are destroyed and subject to the cascade of changes that lead to cancer," she says. This insight has

led to studying spatial consequences of inflammation in a cell culture system.

The laboratory is also now able to study changes occurring in single pancreatic ducts of the mice with pancreatitis. Pancreatic cancer almost always originates in ductal tissue.

Jon Mallen-St. Clair, an M.D.-Ph.D. student in the laboratory, is excited by what the team has learned already. "In addition to cellular changes, we're looking at histone and chromatin modifications," he says. This means that the laboratory is studying the ways that the very gene sequences of living mice are altered during

pancreatitis. "There may be a pattern evident at the molecular level," adds Mallen-St. Clair.

The mouse model, which was described in a study published last year in the journal *Gastroenterology*, has yielded new ways of understanding how the wound that never heals leads to a serious form of cancer. But there is a hitch. "Especially for inflammatory diseases," Dr. Bar-Sagi notes, "if we want to establish parallel conditions in mice, they're not going to be very robust."

By this she means that what takes decades in the human body plays out differently in the much shorter life span of a mouse. Some of her lab's animals will, within two years, end up with what resembles human chronic pancreatitis. Some of them may adapt to their artificially created symptoms. There is much to learn from their tissues, she says. But the question always remains: how faithfully does it mimic what happens in humans? "A mouse model of chronic disease is always shades of gray," she says. "With patience and smarts, we may use the model to help sort out what gives rise to pancreatic cancer." ●

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