Researchers provide world's first view of Type 1 diabetes as it unfolds

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A war is being waged in the pancreases of millions of people throughout the world. The siege leads to the development of type 1 diabetes and has been a battlefield largely hidden from view-- until now. Researchers at the La Jolla Institute for Allergy & Immunology have created the first cellular movies showing the destruction underlying type 1 diabetes in real-time in mouse models. This detailed, dynamic view will provide the worldwide scientific community insights into this disease process as never before possible and may profoundly affect future directions in type 1 diabetes research.

"We are presenting the first images at cellular resolution of type 1 diabetes as-it-unfolds," said Matthias von Herrath, M.D. one of the world's top type 1 diabetes researchers and director of the Diabetes Research Center at the La Jolla Institute for Allergy & Immunology. "Being able to view these insulin-producing cells while they interact in the pancreas, rather than in a static state under the microscope, will greatly enhance our ability – and that of the broader scientific community -- to find interventions for type 1 diabetes."

A paper on the team's scientific findings, along with the cellular movies taken by the researchers, were published online today in the *Journal of Clinical Investigation*. The movies are freely available and can be seen at http://www.jci.org/articles/view/59285 (movie links at end of paper). Ken Coppieters, Ph.D., formerly of the La Jolla Institute and now at Ghent University, Belgium, is first author on the study. Dr. von Herrath is senior author.

"This live imaging of the white blood cells that cause diabetes is quite remarkable," said George Eisenbarth, M.D., Ph.D., a prominent type 1 diabetes researcher and executive director of the Barbara Davis Center for Childhood Diabetes in Colorado. "These images provide critical information about the disease process, in particular showing us the reasons why the beta cell destruction (underlying type 1 diabetes) occurs very slowly over time. Such information may enable new approaches to stop the destruction process, with the ultimate goal being prevention."

The studies are illuminating cell processes that previously had to be extrapolated from photos, computer modeling or lab experiments. Bart Roep, M.D., Ph.D., a diabetes expert and professor at Leiden University Medical Center in the Netherlands, called the work a technological breakthrough. "I thought this was unfeasible (in vivo imaging of type 1 diabetes). But thankfully, they proved me wrong," he said. "These videos show the cellular interactions in incredible detail, things are moving. The information they have found thus far is amazing and this is just the beginning of the knowledge that can be gained through this technology."

Dr. Coppieters said the movies have provided a number of surprising insights. "We have drawn several scientific conclusions from these studies in mice that we believe will influence future therapeutic directions," he said. "We are continuing our studies and hope that other researchers will also find these movies valuable in enhancing their research efforts."

In the movies, objects resembling ants can be seen furiously scampering about looking for their prey. The "ants" are actually immune system T cells, the body's cellular soldiers. The "prey" is insulin-producing beta cells, which the T cells mistakenly attack and destroy, eventually leading to type 1 diabetes.

The groundbreaking studies were enabled through the use of a two-

photon microscope and a new procedure developed by Dr. von Herrath that allowed the microscope's use in the pancreas. The pancreas is a small, soft and difficult to access organ that has long presented special challenges for researchers. Up to this point, the scientific community has used the two-photon to study lymph nodes, the liver and other organs in vivo, but never the pancreas.

"The two-photon microscope enables researchers to "see" into living tissues at a much greater depth than conventional imaging methods," said Dr. von Herrath. "It uses intense pulses of light that enable us to monitor interactions of cells without destroying them."

The Brehm Coalition, a unique type 1 diabetes research collaboration, provided major funding for the two-photon microscope. The Juvenile Diabetes Research Foundation (JDRF) was a significant contributor to the research studies. "Dr. von Herrath was one of a very limited, select group of scientists chosen to receive funding through the JDRF Scholar Award program," said Richard Insel, M.D., the JDRF's chief scientific officer, noting the award targets high-risk, high-reward endeavors. "We are thrilled that Dr. von Herrath's research has provided new insights into the pathogenesis of type 1 diabetes that could lead to novel therapeutic approaches. This is just the kind of pioneering research that the Scholar Award was designed to encourage."

Dr. Coppieters said the as-it-happens movies reveal the specific behaviors of various cells. "We're able to see how the beta cells eventually die and how the immune T cells access the pancreas from the blood stream," he said. Among the many insights gained, the researchers were able to identify the specific blood vessels where the T cells (normally none of these reside in the pancreas) enter the pancreas, how the T cells launch an attack and the time sequence of events.

The movies also illuminated particularly interesting information

regarding the beta cell destruction process. "The T cells move randomly throughout the pancreas until they encounter the beta cells, where they slow down and release toxic substances that eventually kill the beta cells. What was most surprising is that this 'kiss of death' takes quite a while, elaborate calculations indicated a timeline in the order of hours (to kill a few beta cells)," said Dr. Coppieters.

The scientists also found remarkable the large numbers of T cells needed in the mice – tens of millions -- to produce massive beta cell destruction. "These factors may help to explain the long pre-clinical stage in type 1 diabetes," said Dr. von Herrath, since T cell numbers in the human pancreas are thought to be significantly lower than in mice.

"This means that the autoimmune attack is already ongoing for years before the number of beta cells drops below a critical threshold, resulting in clinical diagnosis," he said, noting that 90 percent of beta cells are destroyed in humans before the disease is usually recognized. "From a therapeutic perspective, these studies suggest that we may need to find a way to prevent the T cells from accessing the pancreas in the first place, since once they do, they have the ability to destroy several beta cells at a time."

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