A 1-2 punch: Embryonic cell and adult pig islet transplants cure diabetes in rats

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In a step toward curing diabetes in humans, scientists at Washington University School of Medicine in St. Louis have alleviated the disease in rats using transplants from both embryonic and adult pigs.

The rats adopted the pig transplants as their own and produced enough insulin to control their blood sugar - all without the need for anti-rejection drugs. The researchers report their findings online in the American Journal of Pathology.

Using a two-step approach, the researchers first transplanted a cluster of embryonic pig pancreatic cells into diabetic rats. These cells grow to become the pancreas, which houses the islet cells that produce insulin. The embryonic cells primed the rats' immune system to accept a second implant of islets from adult pigs several weeks later.

The new research - the first long-term, successful cross-species transplant of pig islets without immune suppression - raises the prospect that it may one day be possible to cure diabetes in humans using a similar strategy. Pig cells could overcome the shortage of human islets available from deceased donors and the need for transplant patients to take anti-rejection drugs for life.

"While human islet transplants have cured diabetes in some people, there are so few donors that only a small percentage of patients get transplants," says senior author Marc Hammerman MD, the Chromalloy Professor of Renal Diseases in Medicine. "Moreover, those who receive

human islet transplants must take anti-rejection drugs for the rest of their lives, so essentially they are trading daily insulin shots for immune-suppression drugs, which carry their own risks. Our research paves the way for a new approach to treating diabetes, one that features a virtually unlimited supply of islets and no need for immune suppression."

Pig insulin has been used to treat diabetes in humans, making the animals potentially good islet donors for humans with the disease. Insulin from pigs was routinely given to patients with diabetes until the 1980s, when DNA technology enabled pharmaceutical companies to manufacture human insulin.

In the new study, the researchers transplanted clusters of embryonic pig pancreatic cells into 10 diabetic rats that could not produce any insulin on their own and had very high glucose levels. The cells were retrieved from the pig embryos early in their development, which is believed to make them "invisible" to the rats' immune system or induce a state of immune tolerance.

As the immature pancreatic cells developed, they began to produce insulin, significantly lowering blood glucose in the rats, though not to normal levels. Then, eight weeks later, some of the rats underwent a second transplant of islet cells from adult pigs. Other diabetic rats in a control group did not receive any embryonic pancreatic cells but only adult pig islets.

After 12 weeks and for the several months that followed, the rats that got both the embryonic pig pancreatic cells and the islets had normal blood glucose levels, a strong indicator that the pig islet cells were producing ample insulin. The rats in the control group that received only embryonic pancreatic cells continued to have higher-than-normal glucose levels.

The researchers determined by multiple methods that the successfully

transplanted pig islets had become established in the rats that had earlier received embryonic pancreatic cell transplants. In contrast, the pig islet cells underwent immune rejection in the rats that did not get the embryonic pancreatic cell transplants.

"This is a major advance and a completely new way to employ pig islets for the treatment of diabetes," Hammerman says. "In essence, first transplanting embryonic pig pancreatic cells enables adult pig islet implants to cure diabetes in rats without immune suppression drugs. We are now carrying out experiments to test whether the same transplant strategy works in diabetic non-human primates without using immune suppression drugs. If it does, we hope to evaluate pig cell transplants in people with diabetes."

In earlier research, Hammerman and his colleagues demonstrated they could cure diabetes in rats using larger quantities of embryonic pig pancreatic cell clusters alone, without the need for immune suppression drugs. But they hit a roadblock when they attempted the same transplant procedure in non-human primates. The embryonic pig pancreatic cells engrafted in the primates and lowered their blood sugar levels but not enough to wean the animals completely off insulin injections.

"Primates are much larger than rats, and we learned we would need to give them massive amounts of embryonic pig pancreatic tissues, which is not practical," Hammerman says. "Adult pig islets provide a more concentrated source of insulin and are easier to obtain. We are hopeful their ability to effectively control blood sugar levels in rats without an immune suppression requirement will carry over to non-human primates and eventually to humans."

Hammerman and lead author Sharon Rogers, research instructor of medicine, are leaders in the emerging field of organogenesis, which focuses on growing organs from stem cells and other embryonic cell

clusters known as organ primordia. Unlike stem cells, which can become virtually any cell type, primordia are locked into becoming a particular cell type or set of cell types that make up an organ.

More information: Rogers SA, Mohanakumar T, Liapis H, Hammerman MR. Engraftment of cells from porcine islets of Langerhans and normalization of glucose tolerance following transplantation of pig pancreatic primordia in non-immune suppressed diabetic rats. American Journal of Pathology. DOI:10.2353/ajpath.2010.091193 June 2010.

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