Xenotransplantation as a therapy for type 1 diabetes: Pig beta cells show great promise in an animal model

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Transplantation of a whole pancreas or isolated insulin-producing beta cells are the only therapy to cure type I diabetes. However, the shortage of organ donors limits this approach to only few patients. LMU researchers have now shown that beta cells from genetically modified pigs can effectively restore pancreas function and can protect porcine beta cells from immune rejection in animal models.

Type 1 diabetes is caused by autoimmune destruction of the insulin-producing beta cells. Over 250,000 patients suffer from type 1 diabetes in Germany who are treated with daily insulin injections to maintain glucose metabolism. Replacement of the destroyed beta cells by transplantation of either a complete pancreas organ or isolated human beta cells is the only effective way to cure the disease. However, due to the shortage of organ donors this method can be offered to only few patients. As an alternative approach researchers are exploring xenotransplantation, i.e. transplantation of the organ from another species. The most obvious barrier in xenotransplantation is the strong immune rejection against the transplant. A research team led by LMU's Professor Eckhard Wolf and Professor Jochen Seissler has now generated a genetically modified strain of pigs whose beta-cells restores glucose homeostasis and inhibit human-anti-pig immune reaction. So far, the efficacy of this approach has been demonstrated only in an experimental mouse model. "Whether the strategy will work in humans remains to be demonstrated," says Professor Wolf. "Nevertheless, we

consider the approach as very promising and plan to test it further in other settings."

Type 1 diabetes is caused by an autoimmune reaction which ultimately leads to the destruction of the insulin-producing cells in the pancreas, and usually becomes manifest during adolescence. Thereafter, insulin must be administered by regular insulin injections. Since insulin therapy cannot reproduce the complex pattern of physiologically controlled insulin secretion, patients are at risk of hypoglycemia and many patients develop severe vascular complications such as myocardial infarction or stroke.

Transplantation of a healthy pancreas or pancreatic beta cells that synthesize insulin may represent the best treatment option. Unfortunately, the availability of donor organs falls far short of requirements. Over the course of the last several years, fewer than 200 pancreas transplantations have been carried out. "Pigs represent a possible alternative source, because glucose metabolism in this species is very similar to that in human beings," Professor Seissler points out.

Pig insulin differs from its counterpart in humans at only a single amino acid, and has been used successfully in the treatment of diabetic patients for decades. However, pig cells inevitably provoke an immune reaction leading to the destruction of the transplanted tissue. One way of avoiding this difficulty is to encapsulate the foreign tissue in a biologically inert material that is permeable to insulin but not to cells of the immune system. However, the drawback of this approach is the restricted supply of oxygen and essential nutrients to the transplanted cells, thereby reducing its lifespan.

Wolf and his team chose a different route. For the first time they generated genetically modified pigs that express the protein LEA29Y specifically in beta cells. LEA29Y effectively inhibits the activation of a

class of immune cells that are required to initiate a rejection reaction. The researchers then transplanted these cells into a diabetic mouse strain that has a humanized immune system. Seissler's group showed that these mice were able to restore glucose metabolism and were protected form human-anti-pig rejection. As Wolf is quick to point out, "It is not yet clear whether this will also work in humans. However, we will now attempt to validate the effects of this very promising approach using beta-cells expressing immune modulators in other transplantation models." (suwe)

More information: Paper: *Diabetes* online, 20. April 2012 diabetes.diabetesjournals.org/ … abstract/db11-1325v1

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