



Xenotransplantation of Islets: Can We Bring Home the Bacon?

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One of the holy grails of diabetes research is a safe and effective way to transplant new insulin-producing beta cells. While there are many ways to accomplish this feat in theory, few attempts have had any lasting success. Whole pancreas transplantation has been used successfully, but a severe shortage of organs, combined with the need for lifelong immune suppression, has restricted the use of this technique. Pancreas transplantation is also a difficult operation, and there is still a significant amount of morbidity associated with the surgery itself.

Transplanting just the pancreatic islets, however, can be performed with a minimally invasive procedure, involving infusion of the cells directly into a large vein called the portal vein, almost like a blood transfusion. The injected islets then take up residence in the liver, where they secrete insulin in response to ingested carbohydrates. This approach has worked in some animal experiments, and has been partially successful in a few limited human trials, but there are still numerous obstacles to overcome. Many of the best results have been achieved, for example, using two to four human donors per each recipient, making the chronic shortage of donor organs even worse. Furthermore, immunosuppressive regimens are still required to prevent rejection, and expose patients to numerous complications.

Because of these limitations, current research is focused on more easily attainable or renewable sources of islets, including islets transplanted from animals (known as "xenotransplantation"), the use of islets derived from stem cells, or gene therapy. While the latter two approaches may be the ultimate goal, they are both a very long way from clinical readiness. Xenotransplantation, however, offers the promise of a virtually unlimited supply of islets, and various immunological tricks may reduce the need for dangerous immunosuppression.

The source of xenotransplanted islets is likely to be the pig. Pig insulin is virtually identical to human insulin. In fact, insulin obtained from pigs was used to treat diabetes for decades, until biotechnology advances led to the advent of recombinant human insulin. There are two major problems with pig islets, or islets from any non-human species: rejection and the introduction of porcine viruses into humans. Let's discuss these problems and their possible solutions separately.

Our immune systems are extremely effective at rejecting cells that are not originally our own, whether they be from human donors, or another species like pigs. Rejection can occur early after transplantation, or after a significant delay. This reflects two very different immunological processes, and therefore different strategies are necessary to prevent each form of rejection. In xenotransplantation, the early form of rejection is primarily the result of a reaction against a carbohydrate (galactose alpha-1-3galactose) found on the surface of pig cells, but not human cells. Our bodies recognize this carbohydrate as a foreign invader, and attack it. Interestingly, researchers have generated a strain of pig that lacks the enzyme necessary to make galactose alpha-1-3galactose, which may prove to be a terrific source of islets that cannot be rejected hyperacutely, although this remains to be studied.

Another strategy to prevent rejection is called microencapsulation: coating transplanted islets with substances that allow nutrients and oxygen to get into the islet (and insulin to get out) while blocking the ability of antibodies and immune cells to attach to and destroy the islets. Several compounds have been tested, and a few have shown promise. In one report, microencapsulated pig islets maintained normal blood sugar levels in a diabetic monkey for more than two years without any immunosuppression. A similar result has been reported in a human patient with type 1 diabetes, who did take immunosuppressive drugs.

What about the risk of transmitting a porcine virus into the human population? The threat is not entirely theoretical, as there are potentially nasty viruses called “porcine endogenous retroviruses” (given the unfortunate acronym PERVs) that have been shown to infect human cells in the laboratory. Despite extensive searching, however, the transmission of PERVs has never been documented in humans exposed to living porcine tissue.

These promising indicators have encouraged at least one researcher to move directly into human trials with a significant numbers of patients— a move that has incited controversy in the diabetes and xenotransplantation communities. An investigator in Mexico announced recently that he had implanted porcine islets into twelve adolescents with type 1 diabetes. Success was variable, with one child able to stop taking insulin and five others able to reduce their dose of insulin. Amazingly, these results were obtained without the use of immunosuppressant drugs, a feat never before accomplished in diabetic humans. The controversy relates to the fact that many researchers feel that not enough groundwork was performed on monkeys and other animals before proceeding to humans, coupled with the fact that subjects chosen were too young to have given proper informed consent. In addition, despite the encouraging early results that PERVs and other pig viruses don't seem to be a major problem in humans, the Mexican studies have been taken to task for exposing children to the risk of serious infection.

My own view is that discretion is the better part of valor, and I wish that more studies had been performed in diabetic monkeys or other animal models before proceeding to humans. This would help establish both the effectiveness of the procedure, as well as provide more data about the risks of infection with pig viruses. Nonetheless, the diabetes community will be watching the results of these studies carefully. Eventually, I hope (and believe) that stem cell technology will advance to the point that xenotransplantation is no longer necessary, but for the near-to-midterm future, we may be getting more from our porcine friends than bacon and ham.

References:

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