



Islet Transplantation for Type 1 Diabetes: Trying to Get More Bang For the Buck

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One of the more exciting therapeutic ideas for type 1 diabetes is *islet transplantation*. In this procedure, islet cells, which produce insulin in healthy non-diabetics but are damaged in type 1 diabetes, are surgically transplanted into diabetic patients. While this technology is significantly more advanced than other strategies (such as stem cell therapy or gene therapy), the results to date have been largely disappointing. Less than 10% of patients in most trials have been able to stop taking insulin injections. Moreover, the strict regimen of anti-rejection drugs patients must take after islet transplantation is burdensome and, in some cases, dangerous.

Recently, a group of Canadian researchers demonstrated that they could achieve much higher success rates in human islet transplantation (where success is defined as the ability to stop taking insulin injections) using a steroid-free regimen that has come to be called the "Edmonton Protocol." The publication of this report in 2000 re-energized the islet transplantation field, and since then other groups have been trying to replicate the Canadian feat in their own hospitals, with variable success.

Even in the most encouraging reports from the Canadian group, there are serious problems with the procedure. For example, multiple transplants from several different donors have to be performed to successfully treat a single recipient. Even successful cases are estimated to have only 20% or so of the islet function of a healthy, non-diabetic person. This makes large-scale adoption of islet transplantation infeasible, since there are not nearly enough donors to provide islets for all the type 1 diabetics who are candidates for the procedure.

So what's the problem? Why do so many transplanted islets die, or cease to function properly? Well, certainly there is often an inflammatory response to the islets, which the recipient's immune system treats as an invader. Even in the absence of full-blown "rejection," this inflammatory reaction can destroy some of the transplanted islets and prevent the rest from acting with maximal efficiency. Other factors are almost certainly afoot, as well. For example, there is evidence that islets exposed to human blood in test tubes cause an abnormal clotting reaction that traps the islet cells and disrupts their function. This clotting reaction seems to occur in human recipients of transplanted islets as well, where it may contribute to poor function of the transplant. There have also been cases

reported of massive clotting in the livers of such patients (which is where the transplanted islets go), with serious clinical consequences.

Now, a new article shows that a protein called *Tissue Factor* (TF) may be behind this abnormal clotting reaction. People have known about TF and its role in blood clotting for a long time, but the new work shows that TF is actually present in human islets, where previously it had not been suspected to occur. These researchers went on to show that if the TF on the islets is “inactivated” by blocking it with an antibody, the transplanted islets won’t trigger the abnormal blood clot formation. This opens the door for therapies designed to pre-treat islets with agents to decrease TF activity before they are transplanted. The hope would be that such islets would be less likely to induce the rare, severe clotting reactions as well as the more common islet dysfunction that one sees after transplantation.

This is all well and good, but I should raise the following concerns. First, it has not been proven that blocking TF or the clotting reaction will necessarily lead to more islet survival in transplant patients. Second, any attempt to block TF action in patients will almost certainly lead to general blood clotting problems, including a serious risk of hemorrhage. TF is there for a reason, after all. There will need to be anti-TF treatments that act directly on the islet cells for this to be a viable strategy in patients. The simplest way that I can conceive of this happening depends on how quickly stem cell technology advances for islet replacement. It should be relatively easy to “knock out” TF in stem cells using standard molecular tricks that we already have. Islets generated from these “TF-less” cells could then be used for transplantation. The problem, of course, is that we are still a long way from having viable stem cell protocols for islet transplantation, and the current political climate in this country does not afford much to be hopeful for in the way of a dramatic change.

There are other strategies on the horizon that could boost the efficiency of islet transplantation as well. For example, it’s been known for some time that specific hormonal factors can induce the insulin-producing cells of the islet to grow, thus increasing the size (and presumably the potency) of the islet. These factors include a molecule known as *hepatocyte growth factor*, or HGF. HGF has been shown to increase the size and function of islets in genetically engineered mice. A new report on HGF in mice shows that if HGF is added to islets before they are transplanted into diabetic mice, the survival of the transplanted islets is much higher, and the amount of insulin released is better able to keep sugar levels under control. In part, the effect of HGF seems to be controlled by proliferation of the insulin-producing cells, as well as a reduction in islet death. This was an unexpected finding, and the authors speculate that if the results translate to people, there could be a reduction in the number of islets needed to treat patients with diabetes by as much as 50%.

These are studies in mice, to be sure, but HGF has already been shown to stimulate the growth of human islets in the laboratory, and it may not be

unreasonable to anticipate good results from this approach. Again, the problem will be to specifically target the islets, as HGF could have unintended adverse consequences on the body as a whole. As with tissue factor, the further refinements that must take place will also delay the entry of this approach into the clinical arena.

References:

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