Creating 'death-defying' insulin-producing islets for transplantation

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Australian scientists have identified one way of making a frustratingly tricky transplant – of insulin-producing 'islets of Langerhans' into patients with Type 1 diabetes – more successful.

A Sydney team, part of the Commonwealth-funded Australian Islet Transplant Consortium formed in 2006, has found that islets are severely handicapped from the outset. Before they ever reach their mark, they are full of inflammatory molecules, much like stressed or damaged tissue.

Associate Professor Shane Grey and Drs Mark Cowley and Anita Weinberg, from Sydney's Garvan Institute of Medical Research, detailed the 'molecular signatures' of islets that were transplanted into 15 recipients as part of a 5-year clinical trial spanning Sydney, Melbourne and Adelaide. Their findings, published online in Cell Transplantation, used the latest sequencing technologies to identify inflammatory signatures.

A very large initiative overall, the Sydney arm of the Consortium alone has operated with 5 teams: one team isolated islets; a second undertook transplants; a third monitored the patients' quality of life afterwards; a fourth monitored the liver; and the Garvan group compared gene signatures of grafts with patient outcomes, seeing what constituted a 'good' or a 'poor' graft.

"The importance of our finding in the context of the whole process of transplantation – which is very complex – is that it tells us the grafts we are using are not at ground zero," said Associate Professor Grey.

"They're like little smoking guns we're sending into patients, either doomed to fail, or have only partial success."

"Islets are easier to manipulate than the immune systems of patients, and this finding will help us establish targets for therapy. In other words, we have the potential to treat islets with anti-inflammatory compounds prior to transplantation."

"This should have a marked effect on the success of transplants – currently at 80% survival after a year and 10-15 % survival after 5 years – not nearly the same success rates as other organ transplants."

Since the 1960s, when pioneering anatomist Dr. Paul Lacy first implanted islets into rodents, islet transplantation has offered a compelling, yet elusive, treatment for diabetes.

Decades of work led to very limited success, until a great leap forward a Canadian team brought to transplantation practices in 2000 – known as the 'Edmonton Protocol'.

The work of the Edmonton team showed that recipients need many islets for the procedure to be effective – normally the islets from up to 3

whole human pancreases. This compounds the difficulty as donors are in limited supply, the pancreas has to be removed quickly after death, islets must be isolated within a matter of hours after that, and they happen to be intrinsically fragile.

“Until now, the state of islets used in transplantation has not been well understood, and this gives us better insight into what has been happening,” said Grey.

“And while progress has been a little slow, at least those patients who are prone to lethal glycaemic unawareness – in other words likely to lapse into hypoglycaemic comas and die – have been helped by transplants. Even when the grafts appear to fail, in that they stop producing insulin, for some unknown reason the patients appear to remain protected against these lethal comas.”

In order to show the importance of their findings, the group compared the difference between transplanting ‘pristine’ islets into mice, and transplanting islets with an ‘inflammatory signature’. As expected, the mice fared much better with the ‘good’ grafts.

Clinical islet transplantation involves the isolation of pancreatic islets of Langerhans from the pancreases of deceased organ donors, and deceased organ donors are in extremely short supply.

There are only 200-230 donor pancreases available in Australia each year. Up to 35 of these are used for islet transplantation. The majority of pancreases are used in whole-pancreas transplants, and some donors are deemed unsuitable for either whole-pancreas transplant or islet isolation as their pancreas is damaged in some way – from trauma or from diabetes.

For islet transplantations, the donor pancreas is collected by an organ

donor team, and then transported to an isolation facility. There is a very limited time window between removal of a pancreas and commencement of the isolation process (less than 10 hours).

Isolation of islets takes between 6 and 8 hours, after which they are placed in culture for approximately 24 to 48 hours before transplantation into a patient.

Islets are infused into the liver of a recipient via the portal vein. Islets from two or three donor pancreases are needed to achieve insulin independence - so the procedure is repeated two to three times.

Provided by Garvan Institute