Major Advance for Diabetes Stem Cell Therapy?

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Last month, two papers reported successful transformation of human stem cells into insulin-producing beta cells that worked when they were implanted into diabetic mice. Both protocols aim to forge a significant population of beta cells in vitro, instead of transplanting cells that are not yet fully transformed, as is the case with one technology by ViaCyte currently headed to clinical trials.

Juan Dominguez-Bendala, PhD, of the Diabetes Research Institute at the University of Miami, is also working on solutions to create fully mature beta cells in vitro. In this contributed report, he provides context on the two papers and on the general landscape of stem cells in diabetes therapy.

The Papers

The two papers are very similar. The Melton protocol (Generation of Functional Human Pancreatic Beta Cells in Vitro) is slightly simpler than the Kieffer one (Reversal of Diabetes with Insulin-Producing Cells Derived in Vitro from Human Pluripotent Stem Cells), although both take about the same amount of time to complete. With regard to "major steps forward," it is important to keep in mind that both papers address the supply issue of type 1 diabetes: to replenish the lost beta-cell mass. The autoimmunity part remains to be tackled.

Viacyte and others are looking at immunoisolation strategies to bridge that gap and provide treatments in the meantime.

Two Papers in Context

The differentiation of human embryonic stem cells (hESc) to beta cells is difficult due to their natural resistance to adopt that fate. The first breakthrough was reported by Viacyte back in 2006, when they showed for the first time that the process is doable. The resulting beta cells, however, were scarce (5% to 7% of the total population) and did not respond to glucose stimulation. They did not correct hyperglycemia in diabetic mice either.

Seemingly accepting defeat at getting functional maturation of beta cells, Viacyte adopted in 2008 the strategy that is now heading to clinical trials -- the transplantation of hESc at the progenitor stage (prior to expression of insulin). The microenvironment found by these cells in the host was indeed conducive to their maturation. The process took a long time (3 to 4 months) and, at least at the beginning, was not devoid of complications such as the appearance of tumors (teratomas). Further refinements of the method, however, dampened this concern.

While generally accepting that the first-generation hESc-based therapy will be that spearheaded by Viacyte, other labs have been working at the conditions to improve functional maturation in vitro. The advantages would be obvious: we'd have a product that is functionally characterized prior to transplantation and that works right away, like transplanted islets do (no need to wait several months).

In the Race

We are also in this race. Earlier this year, our lab published that by simply manipulating the oxygenation of hESc-derived pancreatic progenitors (mimicking what beta cells "see" in their natural environment), much better differentiation outcomes were observed.

Using high-throughput screening techniques, Betalogics and Dr. Kieffer at the University of British Columbia came up with several refinements of their original protocol that eventually led to their breakthrough publication on Sept. 11 (Rezania et al., Nature Biotechnology, 2014). There they showed for the first time that fully functional, beta-like cells could be generated in vitro and were able to permanently reverse hyperglycemia when transplanted into diabetic mice. However, the results were not immediate, as it took about 40 days for this to happen.

Islets, in contrast, work right away. Still, it was 3 to 4 times shorter than what it currently takes with the Viacyte method, which uses progenitors and not fully differentiated beta cells.

Melton's paper came a bit later but follows a very similar protocol to that of Kieffer's, with common elements but slightly simpler. It takes up to 5 weeks, which is in line with Kieffer's and substantially longer than the progenitor cell protocol by Viacyte. They also showed functional beta-cell maturation in vitro, but their cells DID NOT reverse diabetes when transplanted into diabetic mice.

They used a different mouse model -- the immunodeficient Akita, which develops progressive hyperglycemia as a result of a defective insulin gene. At the time of transplantation, these animals were not diabetic. However, they report that the transplanted cells prevented the development of hyperglycemia. While interesting, one can only wonder why they didn't use the standard model of immunodeficient, streptozotocin-treated diabetic mice, so that we could do an "apples to apples" comparison to what has been published (and, more importantly, show that they can reverse diabetes, rather than preventing it).

They also report that their cells secrete less insulin than true beta cells, which may require larger numbers to achieve insulin-independence. However, as hESc can be grown in unlimited numbers, as long as there is space to put them, it should not be a concern.

Both of these protocols try to address a concern that still hovers over the Viacyte approach, namely, whether hESc-derived progenitors will mature in a diabetic HUMAN host as they do in a mouse (we will know this soon enough). However, the Kieffer protocol still falls short (some degree of maturation still has to happen within the host, since it takes 40 days for the cells to achieve competence); and the Melton one does not even attempt to reverse already established diabetes. In short, there are still a lot of questions to answer, and room for improvement.

Dominguez-Bendala holds stock in Ophysio, a biotechnology company dedicated to the development of oxygen-enhancing culture ware.

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