



Beta-cells in sort 2 diabetes: a deficiency of capacity and mass

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EDITORIAL NOTE

Type 1 diabetes (T1D), which is typically caused by the autoimmune destruction of insulin-producing pancreatic islets, is affecting more than 1 million people in North America according to the National Diabetes Fact Sheet 2011. The key of treating T1D is to replenish the lost beta cells or their products, insulin. Insulin is commonly used for treating T1D. The occasional hypoglycemia post injection and the complications associated with long-term insulin administration may pose potential risks during a life-long insulin administration. Islet transplantation, as an experimental treatment for T1D, has the potential to maintain insulin-independence for a longer duration, but has failed to maintain normoglycemia for more than five years as per many studies. During the last two decades, much effort has been made into exploring beta cell regeneration so that the new insulin-producing cells can replenish the lost beta cells caused by autoimmune destruction. Taking advantage of the progresses in protein sciences and regenerative medicine, beta cell regeneration may be promising for treating type 1 diabetes in future.

It is commonly accepted that the total number of islets remains constant in the life time while the size of islet increases with age. Moreover, pancreatic beta cells which have longer life-span do not undergo proliferation frequently. However, many preclinical studies revealed that given proper stimulation some beta cells may regain the potential to proliferate. Proliferation of beta cells is a dynamic process of which the intrinsic pathways have not been thoroughly understood. For example, though pancreatic beta cells which originated from the same ancestor showed no differences in gene expression profile. It was recently revealed that only a small group of specialized beta cells will regain the potential to proliferate under certain conditions. On the other hand, the majority of islets is replication-refractory beta cells which do not react to mitogenic stimulation.

Luckily, the recent discovery made by Douglas Melton's group of Harvard University may shed some lights into this area. This group developed a novel insulin resistance mouse model to induce pathologic beta cell replication which typically happened in an early stage of type 2 diabetes. Then, they identified betatrophin, a hormone produced by liver and fat, worked specifically on pancreatic beta cells to promote replication. Most importantly, they demonstrated that the injection of betatrophin expression plasmids via tail vein led to a 17-fold increase in beta cell proliferation in just 8 days compared to the control.

Unlike previous factors, betatrophin showed both specificity and efficacy. Although the mechanisms underlying betatrophin induced beta cell proliferation is unclear, this study opens a new door to eliminate traditional insulin injection. It was reported that Evotec and Johnson & Johnson who have the rights to the molecule planned to turn it into a preclinical type 2 diabetes candidate this year.

Stem cell-based regenerative medicine is another term frequently associated with the beta cell regeneration. Stem cells with proliferation capacity and transdifferentiation potential have been

explored in depth to repair the bone defect and heart infarct. It was lately discovered that the same mechanism of stem cells, especially bone marrow mesenchymal stem cells can be used to reverse hyperglycemia in T1D animals and promoted the beta cell regeneration. The phenomenon can be explained by two distinct hypotheses: 1) stem cells produce soluble factors to promote the proliferation of preexisting beta cells and/or 2) stem cells can transdifferentiate to replenish the lost beta cells.