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Cover Story

Functional enhancement of transplanted islets by Extendin-4

Controlling the blood glucose level for the diabetic patients is one of the most challenging problems in drug delivery. Delivery of insulin to the diabetic patients is different from delivery of other drugs to treat different diseases. Insulin has to be administered at the right time and at the right dose. For insulin administration, even minor changes in the time and dose, which usually do not cause any particular problem for other drugs, will result in serious consequences. Various insulin delivery systems, in particular self-regulated insulin delivery systems [1], have been studied, but they are far from being an ideal system which allows introduction of a right dose at the intended time in a reproducible way.

Because of the lack of suitable insulin delivery systems, other than the current, multiple daily injections, new approaches that can fundamentally change the way we treat diabetes have been developed. One approach of complete cure of Type I diabetes mellitus is successful transplantation of pancreatic islets [2]. There are many hurdles in making this approach clinically viable, such as the limited availability of cadaveric pancreas, shortage of islet donors, immune rejection and autoimmunity in diabetic patients [3,4]. Among the several alternatives proposed to resolve islet donor shortage are the use of porcine islet xenografts [5,6] and insulin-secreting stem cell therapy [7].

In this issue, Professor Byun et al. describe the use of Exendin-4 protein in an effort to cure diabetes [8]. Extendin-4 is a glucagon-like peptide-1 analog currently employed in the treatment of type II diabetes mellitus. It provides a key to finding an enhancing effector that strongly stimulates insulin biosynthesis and secretion from islet allografts. The idea is that the viability and capacity of insulin secretion of Exendin-4 expressing islets could be improved, thereby reducing the marginal islet mass for curing diabetes. Professor Byun's team found no evidence of a significantly greater cumulative incidence of lymphocyte infiltration in or around the Exendin-4 gene transduced islets relative to that observed in the untransduced islets (the left column of the cover figure). A highly secretable Exendin-4 delivery in pancreatic islets that use lentiviral vector system was designed using a secretion signal peptide, which was fused with Exendin-4 at the furin cleavage site (the middle column). The required number of islets for the transplantation was reduced by up to 30% with Exendin-4 gene transduced islets. Furthermore, the Exendin-4 gene transduced islets showed a better outcome of prolonged islet survival time in the immunocompetent diabetic C57BL/6 mice since locally secreted Exendin-4 effectively inhibited apoptosis. TUNEL positive cells in the control islet transplanted group were present around the transplanted site. On the other hand, no TUNEL-positive cells were observed in the Exendin-4 gene transduced islets (the right column).

The work by Professor Byun et al. is one of the few studies that clearly highlight the potent insulinotropic action of Exendin-4 gene transduction on islets as a major mechanism for enhancing insulin secretion. These genetically engineered islets could contribute profoundly to the efficiency of transplanted islets by reducing the number of transplanted islets. Additionally, unlike the systemic injection of the Exendin-4, this new technology can attenuate the adverse effects of Exendin-4, as it can be locally secreted at the site of islet transplantation. As concluded in the article, it is important to support islet grafts in terms of functionality and viability for resolving the limited islet mass problem.

The approach of enhancing the function of transplanted islets by Extendin-4 still requires more extensive study before it can be translated into clinical applications, but such improvement in islet function can add up as we make a number of incremental enhancements. Finding a cure for diabetes is an incredibly challenging problem, but the solution can be found with many small advances which collectively will make a quantum advance in treatment, hopefully in the near future.

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