stem cell research&therapy

COMMENTARY

Human fetal pancreatic islet-like structures as source material to treat type 1 diabetes

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See related research by Zhang *et al.*, http://stemcellres.com/content/4/6/141

Abstract

The incidence of type 1 diabetes is increasing worldwide. Current therapy continues to be suboptimal. An exciting therapeutic advance in the short term is closed loop technology development and application. However, cell and tissue therapy continues to be an unmet need for the disorder. Human islets isolated from deceased donors will be clinically available to treat type 1 diabetes within the next 1 to 2 years. Other approaches such as xenotransplantation and islet products derived from human embryonic stem cells and induced pluripotent stem cells are currently being pursued. The current commentary provides context and discusses future endeavors for transplantation of islet-like structures derived from fetal pancreas.

Introduction

In this issue of *Stem Cell Research and Therapy*, Zhang and colleagues report results of their attempts to isolate, culture and transplant islet-like structures from human fetal pancreatic progenitor cells seeking to develop such therapy for type 1 diabetes (T1D) [1]. T1D is characterized by severe insulin deficiency [2] - although its most common and dramatic manifestation is in childhood, it can occur at any age. Currently, the disorder is treated with insulin replacement using multiple daily insulin injections, an insulin pump or an insulin pump with continuous glucose sensor augmentation. The recent approval of the first closed loop therapy for the disorder in the US by the Food and Drug Administration, following the publication of its efficacy, represents a major step forward in treatment of the disorder [3]. However, further improvements in closed loop therapy and additional options continue to be required for adequate treatment of the disorder. Such options include glucose responsive cell or tissue therapy. Currently, whole organ pancreas transplantation is available and islet product from deceased donor pancreata will likely be approved within the next 1 to 2 years as clinical therapy for T1D associated with frequent, severe hypoglycemia. Both therapies are associated with the need for chronic immunosuppression and shortage of donor organs.

With consent from research subjects and approval of the local Ethics committee, Zhang and colleagues obtained pancreata from several fetuses at 10 to 12 weeks gestational age [1]. They isolated islet-like structures using standard collagenase-based separation techniques from these pancreata and subsequently expanded and differentiated them *in vitro*. Various appropriate markers were evaluated *in vitro* after differentiation. The islet like structures reversed hyperglycemia when transplanted under the renal capsule of nude mice rendered chemically diabetic. Nephrectomy of the kidney bearing the islet-like structure transplants restored hyperglycemia, providing proof for function of the transplanted islet-like structures.

Research with human fetal tissues needs to be conducted with appropriate checks and balances. The current work was done working within such regulations. These checks and balances, as well as ethical concerns, may make research involving human fetal tissues very difficult and this is a likely explanation for the lack of or limited number of studies starting with such source material to date. Fetal tissue was clinically used for patients with Parkinson's disease about 20 years ago by three independent research groups [4-6]. An Editorial in the same issue comprehensively addressed ethical, societal and political issues associated with such work [7]. To date, work using such tissue continues to be limited in extent. Recently, human fetal pancreatic bud-derived cells from 7- to 11-week-old fetuses were used to establish a genetically engineered human pancreatic beta cell

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line, which reversed chemically induced diabetes in mice [8]. The current study represents the first of its kind attempting work with fetal islet-like structures as source material to generate transplantable material without transformation of the tissue. Many centers have, over the past 15 years, worked with alternative source material, such as human embryonic stem cells (ESCs) or, more recently, induced pluripotent stem cells (iPSCs) [9], with the latter offering the great advantage of being autologous. Each of these exciting areas of research needs to be pursued further to make more treatment choices available for patients with diseases such as T1D.

As such exciting work continues, laboratory and experimental challenges lie ahead. The current manuscript, being the first of its kind, used techniques based on experimental protocols from ESC and iPSC culture. Important areas for future research involving fetal pancreas tissue as source material include: (i) definition of source material, including minimum characteristics, such as proportion of cells that are CD133-positive (used by Zhang and colleagues); (ii) culture media and growth factors required for expanding islet-like structures; (iii) molecular/staining criteria to identify islet-like structures suitable for starting differentiation protocols; and (iv) culture media, stages and duration of each stage to induce differentiation. It is also important to monitor the glucose-responsiveness of the fetal tissue-derived islets, as neonatal beta cells generally show immature beta cell phenotypes with limited glucose-responsiveness [10-14]. Future clinical applications also require (i) release criteria for the islet product, (ii) appropriate animal models to evaluate the efficacy of the islet product, (iii) efficacy and safety data from animal experiments, and (iv) identification of appropriate human subjects for phase 1 and 2 studies. We realize that several of these challenges also apply to ESC and iPSC studies. Expansion of work in each of these fields offers great opportunity for cross-fertilization and acceleration of therapy development.

Conclusion

It is concerning that the incidence of T1D is increasing globally even as we approach 100 years since the discovery and subsequent therapeutic use of insulin to treat the disorder [15]. As we approach the centennial landmark, the progress in 'closed loop' therapy development is heartening. Efficient testing of alternative therapies, such as transplantation of various cell products from allo and auto sources, will require team efforts across disciplines and clinical centers on the one hand and patients and families on the other. The study reported by Zhang and colleagues expands the source material available to develop new therapies. Advancing this work will require scientific and clinical teams to innovate while conforming to appropriate regulatory boundaries.

Abbreviations

ESC: Embryonic stem cell; iPSC: induced pluripotent stem cell; T1D: Type 1 diabetes.

Competing interests

The authors declare that they have no competing interests.

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